

LATE NEUROPSYCHIATRIC CONSEQUENCES OF STROKE IN THE ELDERLY

THOMAS LINDEN

GÖTEBORG 2006



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*To my mother, Doris Lindén, lost in the clouds of dementia and
my father, Gösta Lindén, who succumbed in the efforts of caring for her.*

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Abstract

Cognitive impairments and depression have considerable impacts on rehabilitation, quality of life and mortality after stroke. The understanding of cognitive and mood impairments in old and, in particular, very old stroke patients is not sufficient. The knowledge of the frequency of neglect and its relation to other cognitive impairments is meager, especially in the elderly and late after stroke despite its known effect on rehabilitation.

As the economic burden of stroke is likely to increase, we need more information on the use of health care resources in elderly stroke patients in relation to cognitive impairments to be able to plan health care resources in society.

Our study was designed to analyze 1) the epidemiology of cognitive impairments and depression in relation to a normal population; 2) the epidemiology of visual neglect in relation to cognitive impairments; 3) the impact of cognitive impairments on ability in activities of daily life (ADL) and 4) the utilization and costs of health care during the first year in relation to ADL and cognitive impairments in a cohort of elderly stroke patients after one and a half years.

Two-hundred and forty-three stroke patients were recruited to the study. We collected data on the use of resources in health care during the first year, assessed ADL at 3 days, 3 weeks, 3 months and 12 months. A neurological and neuropsychiatric assessment and a semi-structured psychiatric interview were done after 1½ years. Data from the Gerontological and Geriatric Population Studies in Göteborg and the Prospective Population Study on Women, was used as reference populations.

The risks for cognitive and emotional impairments were increased in the stroke patients compared to controls: for dementia almost five times, for cognitive impairment over eight times and for depression four times in stroke patients compared to controls. The risk increase was higher in younger patients. Fifteen percent of the patients had visual neglect, mostly lateralised. They all had more cognitive impairments and those with severe neglect also more dementia. Health care costs were independently influenced by stroke severity at three days and cognitive impairment at follow-up.

In conclusion, neuropsychiatric consequences are common in the elderly late after stroke. Higher risk increase is seen in patients below the age of 80. Dementia is an insufficient marker for cognitive impairment. Dependence in daily life activities is associated with cognitive impairments. The costs of care are much higher in stroke patients with cognitive impairments, regardless of the stroke severity. Neglect is associated to cognitive impairment. Carers should be alert for attention inabilities when investigating stroke patients with cognitive impairments. A stronger focus on cognitive, perceptual and emotional components is needed in rehabilitation and research programs after stroke.

The thesis is based on the following original papers:

1. Linden T, Skoog I, Fagerberg B, Steen B, Blomstrand C
Cognitive impairment and dementia 20 months after stroke.
Neuroepidemiology, 2004. 23(1-2): p. 45-52
2. Linden T, Samuelsson H, Skoog I, Blomstrand C.
Visual neglect and cognitive impairment in elderly patients late after stroke.
Acta Neurol Scand 2005; 111: 163–168.
3. Claesson L, Linden T, Skoog I, Blomstrand C;
Cognitive Impairment after Stroke – Impact on Activities of Daily Living and Costs of Care for Elderly People. The Göteborg 70+ Stroke Study
Cerebrovasc Dis 2005;19:102–109
4. Linden T, Blomstrand C, Skoog I.
Depressive disorders after 20 months in elderly stroke patients. A case-control study.
Stroke. Accepted with minor revision.

Key words: Epidemiology, Cerebrovascular disorders, Rehabilitation, Dementia, Perceptual disorders, Depression, Depressive disorders, Activities of daily living, Health care costs

Table of contents

I.	LATE NEUROPSYCHIATRIC CONSEQUENCES OF STROKE.....	11
A.	THE EPIDEMIOLOGY OF STROKE.....	11
1.	<i>Incidence and prevalence of stroke</i>	11
2.	<i>Stroke risk factors</i>	12
a)	Depression as a risk factor for stroke	13
B.	CONSEQUENCES OF STROKE.....	15
1.	<i>Neuropsychiatric impairments</i>	15
a)	Cognitive impairments and dementia.....	15
b)	Visual neglect	18
2.	<i>Depression</i>	19
3.	<i>Health care resource utilisation</i>	21
C.	OBJECTIVES OF THE GÖTEBORG NEURO70+ STUDY	23
D.	METHODS	24
1.	<i>Subjects</i>	24
a)	Patients.....	24
b)	Controls	26
c)	Population reference	27
2.	<i>Examinations</i>	27
a)	Stroke severity	27
b)	Activities of daily life	27
c)	Comorbidity	28
d)	Resource utilisation.....	28
e)	Neuropsychological examinations	30
f)	Psychiatric examinations.....	30
g)	Medical records.....	30
3.	<i>Outcome measures</i>	30
a)	Dementia diagnosis.....	30
b)	Cognitive Impairments.....	31
c)	Neglect.....	31
d)	Depressive disorders	32
4.	<i>Blinding</i>	32
5.	<i>Statistical methods</i>	32
a)	Algorithms and software.....	32
b)	Selection of controls	33
E.	RESULTS.....	34
1.	<i>Characteristics of the subjects</i>	34
a)	Participants and non-participants	34
b)	Stroke subtypes	34
c)	Background morbidity	34
d)	Comorbidity	34
e)	Previous stroke.....	34

2.	<i>Activities of daily life</i>	34
3.	<i>Dementia</i>	35
4.	<i>Cognitive impairment</i>	36
5.	<i>Visual neglect</i>	39
6.	<i>Health care resource utilisation</i>	42
7.	<i>Depression</i>	45
F.	DISCUSSION	47
1.	<i>Remarks on the study</i>	47
a)	Originality of our study	47
b)	The use of Population-based controls	47
2.	<i>The Star Cancellation Test</i>	48
3.	<i>Remarks on the results</i>	48
a)	Activities of daily life	48
b)	Prevalence of dementia	49
c)	Prevalence of depressive disorders	49
d)	The association of the side of the stroke to depression	50
e)	Prevalence of visual neglect	50
f)	Visual neglect and cognitive impairments	50
g)	Visual fields and neglect	50
h)	Neglect long-term after stroke	50
i)	Lateralised neglect	51
j)	Resource utilization	52
4.	<i>Remarks on methods and research criteria</i>	53
a)	Dementia diagnosis	53
b)	Patients with aphasia	53
c)	Mortality before follow-up	54
d)	Exclusion of institutionalized patients at baseline	54
e)	No baseline cognition data	54
f)	Assessment of cognitive impairment	55
g)	Assessment of depressive disorders	56
5.	<i>Emerging therapies</i>	57
G.	CONCLUSIONS	58
H.	SAMMANFATTNING PÅ SVENSKA	60
II.	ACKNOWLEDGEMENTS	62
III.	REFERENCES	64
IV.	APPENDICES	73

I. Late Neuropsychiatric Consequences of Stroke

A. The epidemiology of stroke

1. Incidence and prevalence of stroke

According to the World Health Organisation (Sarti, Rastenyte et al. 2000; WHO 2004), stroke is worldwide the second most common cause of death, the second most common cause of dementia and a major and costly cause of long-term disability (Foulkes, Wolf et al. 1988; Claesson, Gosman-Hedstrom et al. 2000), with large variations of incidence between age groups (Feigin, Lawes et al. 2003) and between countries and regions (Thorvaldsen, Asplund et al. 1995; Ingall, Asplund et al. 2000; Truelsen, Piechowski-Jozwiak et al. 2006).

In Sweden, one in 310 per 100,000 or about 30,000 patients suffer a first stroke every year with a first-month lethality rate of about 20% or 60/100,000, making stroke the third cause of death (Appelros, Nydevik et al. 2002; Stegmayr and Asplund 2003). First strokes constitute about 70% of all strokes. During the last decades, the incidence has been fairly constant, but mortality and lethality, often called case fatality rate, has dropped, both internationally (Feigin, Lawes et al. 2003; Truelsen, Piechowski-Jozwiak et al. 2006) and in Sweden (Harmsen, Tsipogianni et al. 1992; Stegmayr and Asplund 2003). The pattern shows little variation between countries (Feigin, Lawes et al. 2003; Truelsen, Piechowski-Jozwiak et al. 2006), except for increasing incidences in Ukraine, Russia and Japan and high prevalences in Italy and UK.

The prevalence of stroke survivors is dependant on incidence, lethality and age structure in society. In an age-standardised international comparison, estimates of prevalence for people aged 65 years or more ranged from 46 to 73 and between 2 and 10 per 1000 for the whole population (Feigin, Lawes et al. 2003; Truelsen, Piechowski-Jozwiak et al. 2006). Reports from the Swedish MONICA project estimate the Swedish stroke prevalence to about 9 per 1000, which means about 80,000 stroke survivors.

Stroke epidemiology figures largely depend on a country's population's age

structure. The stroke lethality is diminishing, and both absolute and relative numbers of elderly in society is increasing. The number of stroke survivors, many of whom disabled, will thus probably increase during the next decades.

2. Stroke risk factors

A risk factor in an individual is a characteristic that predicts the risk of stroke in that individual. Some are casual, i.e. do themselves contribute to the risk of stroke (hypertension, smoking, and atrial fibrillation). Others are indicative, i.e. point out that the individual is at risk, but do not themselves constitute that risk as age, sex, heredity (Table 1)

Table 1. Strong and weak risk factors for stroke (Bousser 2004)

Risk factors for stroke		
Major RR>4	Moderate RR 2-4	Weak or debated RR<2
Age	Tobacco	Cholesterol
Hypertension	Diabetes	Fibrinogen, FVII
High dose alcohol	Homocysteine	HRT
	OC use	Migraine
	Infections, CRP	Obesity
	Male sex	Physical inactivity
	Family history	
	Snoring, sleep apnea	

Old age and hypertension are the strongest current established risk factors. Much debated is the influence of serum cholesterol and hormone replacement therapy on the risk of stroke (Makino, Kawano et al. 2000; Stegmayr, Vinogradova et al. 2000; McCarron, Greenwood et al. 2001; Sacco 2001; Whisnant, Wiebers et al. 2002). Obesity as measured with high BMI is a risk factor with high actuality (Jood, Jern et al. 2004). Effective prevention measures exist for many established risk factors, including hypertension, smoking, hypercholesterolemia, diabetes and high alcohol intake.

a) Depression as a risk factor for stroke

Of special interest in the context of this thesis is depressive symptoms or depression as a risk factor for subsequent stroke and it has been investigated by several studies. In 1992, a prospective study (Colantonio, Kasi et al. 1992) on 2604 elderly subjects followed for seven years demonstrated an elevated risk for stroke in those scoring above 16 on the Center for Epidemiological Studies Depression Scale (CES-D). Other studies have later confirmed this finding; In 3461 hypertensive subjects followed for six years (Simonsick, Wallace et al. 1995), a more than two-fold risk for stroke was seen in the half with the highest CES-D scores. Later, a study on 4367 hypertensive elderly followed for 4½ years (Wassertheil-Smoller, Applegate et al. 1996) showed that a five-point CES-D increase is associated to increased risk for stroke in women, but not in men. Following 6676 subjects aged 17 to 94 for 29 years (Everson, Roberts et al. 1998) showed a 50% stroke risk increase in those with more than five depressive symptoms at baseline. A prospective study on 6095 subjects found a low score on the General Well-Being Scale for Depression being a stronger risk factor for stroke in blacks than in whites and also stronger in men than in women. Most studies have examined depressive symptoms rather than clinically diagnosed depressive disorder, but one study (Larson, Owens et al. 2001) reported a relative risk for stroke of almost three times in individuals followed for 13 years diagnosed at baseline with depressive disorder by a diagnostic interview.

An overview of the relation between depression and vascular disease (Thomas, Kalaria et al. 2004) finds depressive illness and depression an independent risk factor as well for coronary artery disease as for stroke. Most studies on depressive symptoms (Wassertheil-Smoller, Applegate et al. 1996; Simons, McCallum et al. 1998; Jonas and Mussolino 2000; Ohira, Iso et al. 2001) report up to double risks. One study (Jonas and Mussolino 2000) found an association of score on a depression scale to subsequent stroke in men, but not in women. Another study (Wassertheil-Smoller, Applegate et al. 1996) however found an increase in CES-D score between two assessments incurring a higher risk for subsequent stroke in women than in men.

Comparing results from different studies is complicated by a vast variety in

setting, study base, selection of controls and diagnostic criteria/instruments. The lack of inclusion of depression or depressive symptoms in compilations of risk factors for stroke (Goldstein, Adams et al. 2006) may be a result of this disparity. Many studies used number of depressive symptoms or cut-off values on depression scales, most commonly the CES-D, for assessing depressive symptoms. Depression scale scores are considered less accurate than structured or semi-structured diagnostic interviews in reflecting depressive disorders even though the CES-D has been shown to have advantages over other instruments in assessing depressiveness in a stroke population (Parikh, Eden et al. 1988). However, even when assessed with a validated instrument, depressive symptomatology is not equivalent to clinical depression (Fechner-Bates, Coyne et al. 1994) and the results should not without caution be extrapolated to patients with depressive disorders.

Several mechanisms have been suggested to associate depressive symptoms or depression to subsequent stroke. First, depressive symptoms may merely be markers of mild cerebrovascular disease. In that case, there are one or several clinically silent infarcts already before an obvious stroke and the depressive symptoms that seem associated to subsequent stroke is rather a depression after a clinically silent stroke, which is well documented (Hackett, Yapa et al. 2005). Most studies have corrected for baseline vascular diseases, but not used Doppler or imaging techniques to rule out asymptomatic atherosclerosis or signs of silent cerebral infarcts. Second, subjects with depressive symptoms may experience more psychological distress, which may increase the risk of stroke by leading to hypertension, hypercholesterolemia, and glucose intolerance (May, McCarron et al. 2002). A third possible mechanism is self-neglect and medical non-compliance in depressed patients. Increased platelet activation in depression is a fourth proposed (Musselman, Tomer et al. 1996; Laghrissi-Thode, Wagner et al. 1997) mechanism for stroke being increased in the depressed.

All aspects of depressive symptoms or depression as a risk factor for stroke are not clear. What seems to be conflicting results regarding different risks in women and men need to be further explored.

B. Consequences of stroke

1. Neuropsychiatric impairments

a) Cognitive impairments and dementia

It is a far from recent finding that the rehabilitation prospects of patients suffering from cognitive impairment after a stroke are reduced (Adams GF 1963). Yet advice and support for carers of cognitively impaired stroke patients and appropriate resettlement for badly affected patients are often neglected (Ebrahim, Barer et al. 1987). Several studies of cognitive impairment after stroke have already been reported and the syndrome of dementia is often used to describe it. (Kotila, Waltimo et al. 1986; Wade, Parker et al. 1986; Tatemichi, Foulkes et al. 1990; Tatemichi, Desmond et al. 1992; Pongvarin, Prayoonwiwat et al. 1995; Andersen 1996; Censori, Manara et al. 1996; Kokmen, Whisnant et al. 1996; Inzitari, Di Carlo et al. 1998; Kase, Wolf et al. 1998; Pohjasvaara, Erkinjuntti et al. 1998; Zhu, Fratiglioni et al. 1998; Barba, Martinez-Espinosa et al. 2000; Desmond, Moroney et al. 2000; Henon, Durieu et al. 2001; Madureira, Guerreiro et al. 2001; Lin, Lin et al. 2003; Mok, Wong et al. 2004; Rasquin, Lodder et al. 2004; Tang, Chan et al. 2004; Zhou, Wang et al. 2004; Appelros and Andersson 2006) The prevalence of dementia increases with age, both in stroke patients and in the general population, but frequencies are consistently reported to be higher in stroke survivors than in society as a whole (Tatemichi, Desmond et al. 1992; Censori, Manara et al. 1996; Pohjasvaara, Erkinjuntti et al. 1998).

The prevalence of dementia was found to be about 25% shortly after stroke in patients aged above 55 or 60 (Tatemichi, Desmond et al. 1992) years, resulting in an odds ratio nine times that of a control population. Prevalence rates of dementia in studies of stroke patients have varied between 14% (Censori, Manara et al. 1996) and 32% (Pohjasvaara, Erkinjuntti et al. 1998) at 3 months. One study reported a prevalence rate of 32% after 5 years (Bornstein 1996). (Table 2)

Current diagnostic criteria for dementia, such as the DSM-III-R criteria (1987), are modelled on the profile of cognitive decline seen in Alzheimer's disease and are therefore heavily weighted towards memory dysfunction. Cognitive impairment

after stroke and in vascular dementia often has a more “patchy” distribution, and the memory dysfunction is often not as prominent as in Alzheimer’s disease (Rockwood, Parhad et al. 1994).

Therefore, severe cognitive impairments may be present even if the diagnostic criteria for dementia are not fulfilled (Kotila, Waltimo et al. 1986; Ritchie 1988). Thus, focusing on the diagnosis of dementia is likely to lead to underestimation of the occurrence of cognitive impairment after stroke (Bowler and Hachinski 1995). Such impairments, although falling short of the diagnosis of dementia, have a considerable impact on rehabilitation, quality of life and mortality (Hier, Foulkes et al. 1991; Galski, Bruno et al. 1993; Katzman, Hill et al. 1994; Brayne, Gill et al. 1998; Paykel, Huppert et al. 1998; Appelros, Karlsson et al. 2003). This may be especially relevant in the elderly, in whom both cognitive impairment and cerebrovascular disease are common. Unfortunately, our knowledge of cognitive impairment in old and, in particular, very old stroke patients has no solid scientific basis so far. Few studies have used matched population-based controls or have systematically assessed the occurrence of cognitive impairments apart from the dementia syndrome. Aphasic or otherwise cognitively impaired patients have sometimes been excluded, hence limiting the possibility of generalizing the results. Further, data have often been published after only a short follow-up period.

Table 2. Poststroke dementia prevalence studies

Author	Year	Ref	Delay (m)	Cases char's	Controls char's	Dementia criteria	P(%)	OR	Age			Sex			Exclusion criteria					
									Lowest	Highest	Mean	%F	Info from	Non-ischemic	Recurrent	Funct def	Prev TIA	non-small vessel cerebral disease	Baseline cognition deficit	Baseline dementia
Kotila	1986	48	52	Stroke register	nc	DSM III	5,8		65	49	40	Patient	Yes					Yes	Yes	
Wade	1986	3	138	Stroke register	Wechsler		14			72										
Tatemichi	1990	0	726	Hospital	Clinician		16		60		54	Patient	Yes							
Tatemichi	1992	3	251	Hospital	Relatives	DSM III R	26	9,4	60		72	55	Patient	Yes						
Poungvarin	1995	24	212	Hospital	Community	Thai MSE	33		63		35								Yes	
Andersen	1996	1	220	Hospital	Community	Mattis DRS	32		60	80		Patient	Yes						Yes	
Andersen	1996	6	220	Hospital	Community	Mattis DRS	26		60	80		Patient	Yes						Yes	
Censori	1996	3	110	Hospital	nc	N-A	14		40	65	35	Patient	Yes						Yes	
Inzitari	1998	12	339	Hospital	nc	ICD-10	17		76	71	48	Proxy							Yes	
Kase	1998	6	74	Community	Community	DSM III					54	Patient							Yes	
Zhu	1998		153	Hospital	Community	DSM III R	32	3,6	75	82	76	Register							Yes	
Pohjasvaara	1998	3	337	Hospital	nc	DSM III	32		55	70	50	Patient	Yes							
Barba	2000	3	251	Hospital	nc	DSM IV	22		20	98	69	47	Patient							
Desmond	2000	3	453	Hospital	nc	DSM III R	26		60	72	53	Patient	Yes							
Henon	2001	6	99	Hospital	nc	ICD-10	23		40		47	Patient								
Henon	2001	12	85	Hospital	nc	ICD-10	21		40		47	Patient								
Henon	2001	24	65	Hospital	nc	ICD-10	22		40		47	Patient								
Henon	2001	36	69	Hospital	nc	ICD-10	19		40		47	Patient								
Madureira	2001	3	237	Hospital	nc	N-A	5,9		59	45	45	Patient		Yes					Yes	
Lin	2003	3	283	Hospital	nc	ICD-10	9,2		64	34	34	Patient	Yes		Yes				Yes	
Lindén	2004	18	149	Hospital	Community	DSM III R	28	4,7	70		81	65	Patient						Yes	
Mok	2004	3	75	Hospital	Relatives	Clinical DRS	13		70	52	52	Patient	Yes			Yes			Yes	
Rasquin	2004	1	196	Hospital	nc	N-A	11		40		68	45	Patient	Yes					Yes	
Rasquin	2004	6	172	Hospital	nc	N-A	7,7		40		68	45	Patient	Yes					Yes	
Rasquin	2004	12	159	Hospital	nc	N-A	7,7		40		68	45	Patient	Yes					Yes	
Tang	2004	3	280	Hospital	nc	DSM IV	20		50	71	46	Patient							Yes	
Zhou	2004	0	434	Hospital	nc	DSM IV	27		55	68	47	Patient	Yes						Dysphasia	
Zhou	2004	3	434	Hospital	nc	DSM IV	27		55	68	47	Patient	Yes						Yes	

b) Visual neglect

In clinical practice, a diagnosis of visuospatial neglect is typically based on either a visual neglect or an asymmetric distribution of the inattentive behaviour or on both these aspects (Halligan, Cockburn et al. 1991). Several terms have been used for this phenomenon. In this thesis, the term visual neglect or simply neglect is used. The assessment of neglect includes tests such as target cancellation, figure copying and freehand drawing, reading and writing, and the line bisection test (Halligan, Cockburn et al. 1991). Although many studies have focused on the incidence of neglect after hemispheric stroke (Hier, Mondlock et al. 1983; Stone, Halligan et al. 1993; Pedersen, Jorgensen et al. 1997; Cassidy, Lewis et al. 1998; Appelros, Karlsson et al. 2002), most have been carried out during the acute or post-acute stage after stroke and little is known about the prevalence of visual neglect in the longer perspective after stroke (Sunderland, Wade et al. 1987; Zoccolotti, Antonucci et al. 1989; Halligan, Burn et al. 1992).

Levine et al (Levine, Warach et al. 1986) carried out a follow-up study of 29 patients ten to 20 weeks after a right cerebral infarction. Only 12 patients exhibiting moderate to severe neglect at the initial assessment were re-examined. Although all patients showed less severe neglect, persisting neglect was found in ten of the 12 patients. A relationship was reported for the severity of neglect at the follow-up and the degree of cortical atrophy. It was suggested that pre-stroke cortical atrophy probably plays an important role in determining the severity and prevalence of neglect in the late stage following stroke. This finding implies that patients suffering from cortical dementia may show poor recovery from neglect and that patients with a pre-stroke cortical atrophy in addition to a focal brain damage may show a higher frequency of persisting symptoms of neglect.

However, in spite of the theoretical and practical importance of the correlation indicated between dementia and frequency of neglect, little is known about this relationship. To our knowledge, no epidemiologic study has been done on this subject late after stroke and only a few such studies have been undertaken at an early stage following brain injury (Freedman and Dexter 1991). One group studied the incidence of neglect in 14 patients with cortical dementia and 14 patients with acute right hemisphere injury. At this early stage post injury, no significant

differences of the frequency of neglect were found. The presence of lateralised neglect, in terms of a lateralised spatial position preference, was observed in 86% in the right hemisphere group and in 79% in the dementia group. But the type of neglect symptoms in the two groups differed. The patients without dementia showed neglect only toward the left side, while the patients with dementia showed right- and left-sided neglect to a similar extent. Furthermore, some of the patients with dementia showed non-lateralised neglect.

Another group (Ishiai, Seki et al. 1996) studied a patient with a left-sided neglect following moderate symptoms of Alzheimer's disease. It was suggested that patients with mild to moderate dementia in the early stage of the disease may show disproportionate hemispheric damage or dysfunction and thus may show symptoms of lateralised neglect more frequently relative to a later stage in the process. That is, at the later stage, the cerebral dysfunction may be more bilateral and may consequently result in general visuospatial dysfunction but not lateralised symptoms of neglect.

The presence of neglect is associated with poor recovery, poor response to rehabilitation and increased dependence (Denes, Semenza et al. 1982; Katz, Hartman-Maeir et al. 1999; Paolucci, Antonucci et al. 2001). Thus, chronic neglect is a serious clinical problem to consider in rehabilitation and when assessing prognosis after stroke. Knowledge of the prevalence of neglect and its effect in these respects is still too meager, especially in elderly patients and late after the injury.

2. Depression

Among the unresolved issues regarding stroke patients' recovery and rehabilitation is post-stroke depression. Since the finding 30 years ago (Folstein, Maiberger et al. 1977) that stroke patients were more depressed than a control group of equally disabled orthopaedic patients, a number of research groups have shown that depression is common in stroke patients both in the acute, subacute, and long-term perspective (Feibel and Springer 1982; Finklestein, Benowitz et al. 1982; Robinson and Price 1982; Sinyor, Amato et al. 1986; Ebrahim, Barer et al. 1987; Eastwood, Rifat et al. 1989; Morris, Robinson et al. 1990; House 1991;

Schubert, Taylor et al. 1992; Burvill, Johnson et al. 1995; Ng, Chan et al. 1995; Pohjasvaara, Leppavuori et al. 1998; Kauhanen, Korpelainen et al. 1999; Rao, Jackson et al. 2001; Appelros and Viitanen 2004; Eriksson, Asplund et al. 2004); (Collin, Tinson et al. 1987; Wade, Legh-Smith et al. 1987; Astrom, Adolfsson et al. 1993; Kauhanen, Korpelainen et al. 2000). The prevalence estimates of depression in stroke patients varies from 25-48 percent in the acute stage, 14-50 percent in one to twelve months after stroke and 12-42 percent after a year or more following stroke.

Furthermore, many different instruments and criteria have been used to diagnose depression (Provinciali and Coccia 2002; Robinson 2006) making prevalence figures difficult to compare. A systematic review from fifty-one observational studies (Hackett and Anderson 2005) found a pooled estimate of 33 percent of stroke patients being depressed. Time from stroke, assessment instruments and diagnostic systems were, however, far from uniform between the studies, making the results hard to interpret. There are also differences in study-base and selection of patients (Rao 2000; Provinciali and Coccia 2002). Patients in stroke studies are often younger and although it is generally recognized that depression is common after stroke, few studies have examined whether depression prevalence is increased in elderly stroke patients compared to age- and sex-matched controls. Only a few studies have used population-based control groups. One study (House 1991) uses general practitioner records for selecting controls, but these were not sex-matched. A Danish study (Andersen, Vestergaard et al. 1994), that made diagnosis by cut-off values, used population-based controls, but did not publish risk estimates.

The recognition and diagnosis of depression in stroke patients is important, as it has been associated with worse outcome in numerous studies (Ebrahim, Barer et al. 1987; Eastwood, Rifat et al. 1989; Burvill, Johnson et al. 1997; Herrmann, Black et al. 1998; Ramasubbu, Robinson et al. 1998; Schulz, Beach et al. 2000; House, Knapp et al. 2001; Paolucci, Antonucci et al. 2001; Pohjasvaara, Vataja et al. 2001) Nevertheless, depression after stroke is often underdiagnosed (Schubert, Taylor et al. 1992) despite that effective treatment exists (Gill and Hatcher 2000; Paolucci, Antonucci et al. 2001).

Depressed stroke patients have more cognitive impairments (Pohjasvaara, Leppavuori et al. 1998), more days in hospital (Schubert, Taylor et al. 1992), utilise more care and are more often institutionalised than the non-depressed (Kotila, Numminen et al. 1999), but no quantitative estimation of the magnitude of how this impacts the health care delivery systems has so far been made (Provinciali and Coccia 2002).

The aetiology of depression after stroke is debated as some authors put focus on biological factors, i.e. disruption of tracts, such as aminergic cortico-striatal (Robinson, Starkstein et al. 1988; Alexopoulos, Meyers et al. 1997), fronto-striatal (Beblo, Wallesch et al. 1999) and left-sided prefronto-subcortical pathways (Vataja, Pohjasvaara et al. 2001) or infarcts in strategic locations, such as right hemisphere strokes (Folstein, Maiberger et al. 1977; Starkstein, Robinson et al. 1989), left anterior lesions (Robinson, Kubos et al. 1984), left-sided basal ganglia lesions (Starkstein, Robinson et al. 1988) and inferior frontal lesions (Singh, Black et al. 2000). Other studies emphasize the impact of sudden disability and loss of autonomy as a cause of reactive depression after stroke (House 1996; Kneebone and Dunmore 2000) and yet others try to join the two perspectives (Engel 1977; Katz 1996).

3. Health care resource utilisation

As stroke is a major cause of mortality and morbidity, stroke care consumes a substantial portion of total health care resources and costs. As stroke is a heterogeneous and complex disease it is difficult to make economic evaluations because of the complexity of the costs. Economic evaluations in stroke have calculated lifetime (Taylor, Davis et al. 1996), annual (Terent, Marke et al. 1994) and national costs (Isard and Forbes 1992) and have made economic comparisons between different treatment programs (Beech, Rudd et al. 1999) and developed models for calculation of costs (Caro and Huybrechts 1999). The majority of costs and resources are related to hospital inpatient services (Beech, Ratcliffe et al. 1996; Caro, Huybrechts et al. 2000), institutionalised living (Taylor, Davis et al. 1996) and home care assistance (Terent, Marke et al. 1994). Patients' age (Taylor, Davis et al. 1996), stroke severity (Caro, Huybrechts et al. 2000), stroke sub-type

(Currie, Morgan et al. 1997) and the presence of comorbidity (Caro, Huybrechts et al. 2000) influence the needs of health care resources and thus cost.

Follow-up studies of stroke survivors describe high proportions of cognitive impairment and dementia in elderly patients (Pohjasvaara, Erkinjuntti et al. 1997; Kase, Wolf et al. 1998; Pohjasvaara, Erkinjuntti et al. 1998; Desmond, Moroney et al. 2000). The occurrence of cognitive impairments and dementia increases with age (Pohjasvaara, Erkinjuntti et al. 1998; Desmond, Moroney et al. 2000). Cognitive impairment is a predictor of length of hospital stay (Galski, Bruno et al. 1993). Long-term follow-up studies show that the costs increase with increasing age and that they are highest in the age groups in which stroke is most common (Taylor, Davis et al. 1996). The economic burden of stroke is substantial and is likely to increase with the increasing number of elderly individuals in the population (Palmer, Valentine et al. 2005). There is thus a need for more information on the use of health care resources and costs among these elderly stroke patients to be able to plan health care resources in society.

C. Objectives of the Göteborg Neuro70+ Study

The objects of this study were to:

- Analyse the epidemiology of cognitive impairments and depression in a cohort of elderly patients one and a half years after acute stroke and in a normal population (Papers 1 and 4)
- Analyse the epidemiology of visual neglect in relation to cognitive impairments in a cohort of elderly patients one and a half years after acute stroke (Paper 2)
- Analyse the impact of cognitive impairments on activities of daily life (ADL) and the utilization and costs of health care in a cohort of elderly stroke patients (Paper 3)

D. Methods

1. Subjects

We followed a group of patients one and a half years after stroke. Two matched control groups were used for comparison. The characteristics of the different groups are described in Table 3. In Paper 2, a subset of 138 patients participated and no control group was used.

Table 3. Characteristics of study group, controls and population reference.

	Stroke patients N=149		Control group N=745		OR with 95% Confidence interval	Population reference
Age, years (SD)	81.0	(5.3)	81.3	(5.7)		81,3 (5.7)
Women, %	65.1		65.1			65.1
History of stroke, %	13.4		9.1		1.56 [0.90 , 2.6]	13.5
Living in institution, %	-		-			15.1
DSM-III-R dementia, %	27.5		7.4		4.7 [3.0 , 7.5]	14.7
History of Cardiac infarction, %	15.4		9.0		1.8 [1.1 , 3.1]	10.5
History of Angina pectoris, %	22.8		18.6		1.3 [0.84 , 2.0]	18.2
Diabetes, %	12.8		9.9		1.3 [0.78 , 2.3]	10.3
Cronic Obstructive Pulmonary Disease, %	7.0		11.1		0.60 [0.30 , 1.2]	11.9
Current smokers, %	12.6		10.4		1.2 [0.65 , 2.4]	11.0

a) Patients

The patients were recruited between February 1, 1993 and April 20, 1994 as part of the Göteborg 70+ Stroke Study, a randomised, naturalistic study designed to analyse the effect on outcome of stroke unit organisation in a hospital. The Göteborg 70+ study has been described in detail elsewhere (Fagerberg, Claesson et al. 2000).

We screened patients admitted to the emergency room at Sahlgrenska University Hospital in Göteborg, Sweden, which is a secondary care as well as a regional hospital. Patients were eligible for inclusion in the study if they were resident in the catchment area and presented with an acute focal neurological deficit of no other apparent cause than cerebrovascular, were aged 70 years or more, and were willing to participate in the study. Exclusion criteria were onset of symptoms more than seven days before admission, known cerebral lesion with recognised need of care, extracerebral or subarachnoid haemorrhage or cerebral tumour, coma,

indication for specialized neurological care, residence in a nursing home, and no available bed in the stroke units. The physician on call diagnosed the stroke, and the diagnosis was supported by routine investigations including an acute computerized tomography.

All patients were contacted by letter one year after the stroke. This was followed by a telephone call to arrange a hospital appointment. If the patient was not able to or declined to come to the hospital, the investigation took place in his/her place of residence (N=15, 10%).

At the hospital follow-up appointment, a nurse first met with each patient. That meeting included an interview regarding medication, measurement of weight, height and blood pressure, and drawing of blood samples. Then the patient was examined by a neurologist/psychiatrist (T.L.). This examination included a semi-structured diagnostic psychiatric interview, neuropsychological tests, including the Star Cancellation Test (Wilson, Cockburn et al. 1987)(Figure 1), and a neurological examination.

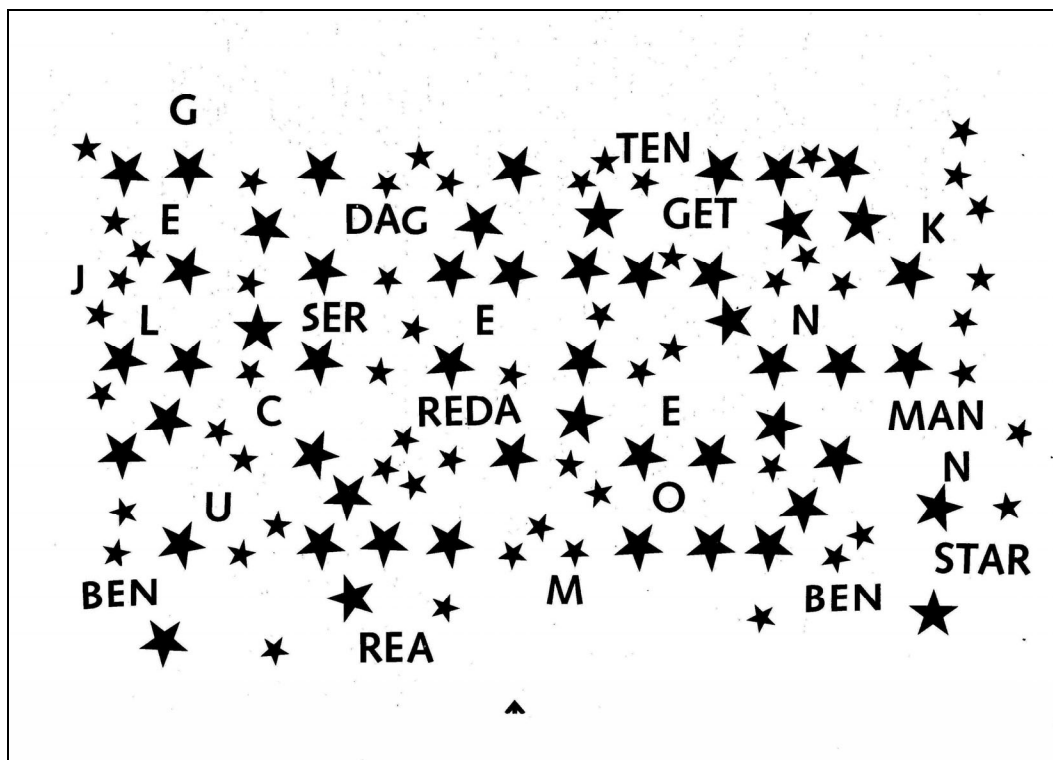


Figure 1. The adaptation of the Star Cancellation Test used in this study

The logistics of the study are shown in Figure 2. We included 243 patients in the study. Their mean age was 79.4 years (SD 5.3) and 65% (N=151) were women. By the time of follow-up, 32% (N=77) had died and 7% (N=17) refused to participate further, leaving 149 patients. 138 were tested with the Star Cancellation Test. A computerized tomography of the brain was done in 98% (N=146) of the cases. The mean time from inclusion to follow-up was 1.7 (SD 0.41) years, and the mean age at the time of examination was 81.0 (SD 5.3) years.

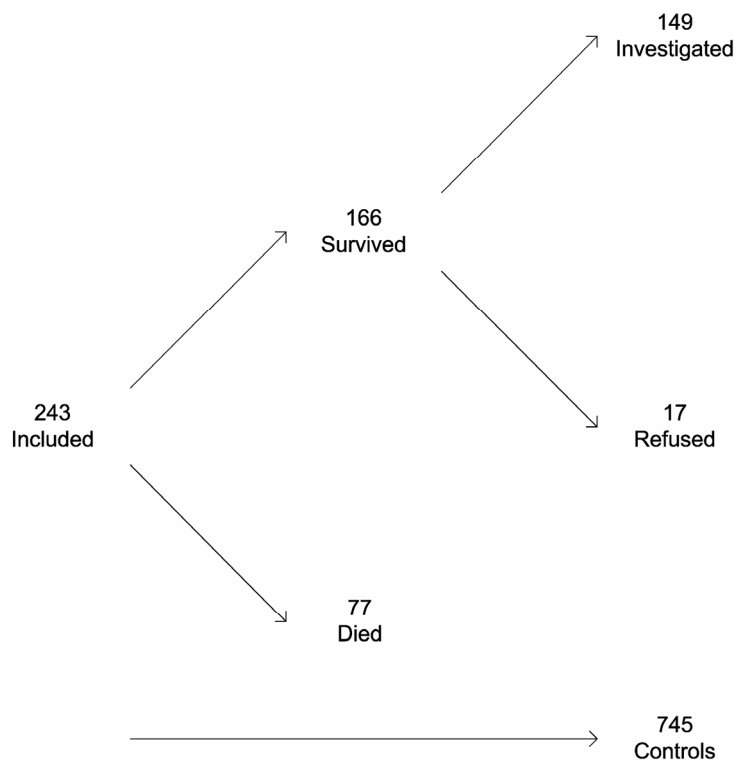


Figure 2. Study Design

b) Controls

Controls were selected from the Gerontological and Geriatric Population Studies in Göteborg, Sweden (Steen and Djurfeldt 1993) and the Göteborg Women's Health Study (Palsson, Larsson et al. 2001; Skoog, Nilsson et al. 1993), based on samples that are representative of the general population of Göteborg. The same exclusion criteria were applied to the sex- and age-matched control group as to the stroke patients. We used five controls for each stroke patient, giving a group of 745 controls in all.

c) Population reference

To estimate how the exclusion criteria affected patients and controls compared to the general population regarding risk factors and baseline characteristics, we also selected a population reference of 745 probands, matched for age and sex in the same way as the controls, but without applying the exclusion criteria. The characteristics of the different groups are shown in Table 3.

All subjects (or their nearest relatives) gave their informed consent to participation after receiving oral and written information. The Ethics Committee for Medical Research at the Göteborg University approved the study.

2. Examinations

a) Stroke severity

Severity of stroke was classified as mild, moderate or severe on the basis of the Barthel Index score within the first three days after randomisation. Mild, moderate and severe stroke were defined as Barthel scores 50-100, 15-45 and 0-10, respectively (1997).

b) Activities of daily life

Two senior occupational therapists (OT) not involved in the design of the study or in the treatment of the patients assessed ability in activities of daily living (Barthel Index and Sunnaas Index of ADL) and data collected on the use of resources in health care (Claesson, Gosman-Hedstrom et al. 2000; Fagerberg, Claesson et al. 2000). The assessments of ADL were performed within 3 days, 3 weeks, 3 months and 12 months after acute stroke.

The Barthel Index (Mahoney and Barthel 1965) and Sunnaas Index of ADL (SI) (Vardeberg K 1991) were used to assess the patient's level of independence in activities of daily living. The SI comprises 12 items in personal and instrumental activities: eating, continence, indoor mobility, toilet management, transfer, dressing and undressing, grooming, cooking, bathing/showering, housework, outdoor mobility and communication. The SI includes both the wordings "can" and "does" in its definition of the categories, but the raters in the present study evaluated whether the person performed (did) the activities. Independence was

defined as independent activity performance with or without the use of assistive devices, and dependence was defined as a need of personal assistance.

c) Comorbidity

Comorbidity was assessed by vascular risk factors including earlier cerebrovascular and cardiovascular disease and further by the Charlson's comorbidity index (Charlson, Pompei et al. 1987). This index is a weighted index of comorbidity that takes into account the number and seriousness of concurrent diseases, which may alter the risk of death. Medical data were collected from medical records by a physician not participating in the study (Fagerberg, Claesson et al. 2000).

d) Resource utilisation

Information on the use of health care resources was collected from the time of randomisation to the end of the 12-month follow-up. Information on length of hospital stay (acute hospital, geriatric wards, post-care unit) according to index stroke and any later re-admissions and the number of days of institutionalised living (nursing home, home for the elderly and assisted living) were obtained from hospital records. A structured interview questionnaire was used to collect data concerning the use of outpatient care and different kinds of support. Outpatient care included visits to physicians, nurses, occupational therapists, physiotherapists and/or speech therapists, outpatient rehabilitation, visits for anticoagulation treatment and use of prescription drugs. Different kinds of support included hours of home assistance, the number of one-way taxi trips for disabled people, use of safety alarms and assistive devices and housing adaptations required following stroke. The number of hours of informal care was also noted (Claesson, Gosman-Hedstrom et al. 2000).

All costs (Table 4) were estimated from the time of randomisation to the end of the 12-month follow-up. The total cost was obtained by taking the sum of all separate units and multiplying them by their costs. All costs were estimated in 1996 prices in Swedish Crowns (SEK). The costs for length of hospital stay were collected from hospital records. Unit costs per day of institutionalised, outpatient care and different kinds of support were taken from estimates made by the civic administration of the city of Göteborg. Official Swedish retail prices were used to

Table 4. Unit costs in resource utilisation analysis

Item	Cost per item
Initial hospitalisation for index stroke:	(SEK, 1996)
Stroke unit, "hotel cost" per day	2 987
General ward, "hotel cost" per day	2 671
Geriatric ward, per day	1 900
Acute hospitalisations after initial hospitalisation to 12 months:	
Medicine ward, "hotel cost" per day	2 473
Cardiology ward, "hotel cost" per day	3 279
Orthopaedic ward, "hotel cost" per day	2 432
Surgery ward, "hotel cost" per day	3 324
Neurology ward, "hotel cost" per day	2 659
Audiology ward, "hotel cost" per day	2 985
Oncology ward, "hotel cost" per day	2 432
Gynecology ward, "hotel cost" per day	2 245
Non-acute hospitalisations from discharge to 12 months:	
Geriatric ward, per day	1 900
Post-care unit, per day	1 021
Institutionalised living from discharge to 12 months:	
Nursing home, per day	898
Home for the elderly, per day	668
Assisted living, per day	441
Outpatient care from discharge to 12 months:	
Physician visit, per visit	500
Other medical visit, per visit**	320
Outpatient rehabilitation, per day	444
Anticoagulation treatment, per visit	142
Different kinds of support from discharge to 12 months:	
Home assistance, per hour	187
Taxi service for the disabled, per one-way trip	69
Safety alarm, per months	220
Other costs from discharge to 12 months:	
Informal care, per hour	38

estimate the cost of prescription drugs. SEK 38 per hour was used as the unit cost of informal care (Claesson, Gosman-Hedstrom et al. 2000)

e) Neuropsychological examinations

The examinations were carried out by a neurologist/psychiatrist (T.L.) and were similar to those in the Gerontological and Geriatric Population Studies and the Prospective Population Study on Women. (Steen and Djurfeldt 1993; Palsson, Larsson et al. 2001; Skoog, 1993 #19677). They included ratings of cognitive symptoms such as recent and remote memory, aphasia, items on knowledge of general information, motor/face apraxia, agraphia, alexia, acalculia, ability to understand proverbs, right-left disorientation, and judgment. Items from the Alzheimer's Disease Assessment Scale (Rosen, Sweet et al. 1994) that targeted spoken language ability, comprehension of spoken language, recall of instructions, word-finding difficulty in spontaneous speech, following commands, finger agnosia and ideational praxis were also included. Constructional apraxia was assessed by getting the patients to copy geometric figures.

f) Psychiatric examinations

The examinations were carried out by a neurologist/psychiatrist (T.L.) and were similar to those in the Gerontological and Geriatric Population Studies and the Prospective Population Study on Women. (Steen and Djurfeldt 1993; Palsson, Larsson et al. 2001; Skoog, 1993 #19677). They included a semi-structured psychiatric diagnostic interview designed for the Comprehensive Psychopathological Rating Scale (Asberg, Montgomery et al. 1978).

g) Medical records

The patients' medical records from hospitals and outpatient departments in the catchment area were reviewed.

3. Outcome measures

a) Dementia diagnosis

The diagnosis of dementia was made according to the criteria in the DSM III-R (1987) using an algorithm based on the neuropsychiatric examination. A DSM-III-R dementia diagnosis requires A) impairment in short- and long-term memory and B) at least one of B1) impairment in abstract thinking, B2) impaired judgment, B3)

impaired cortical functions or B4) personality change. This must C) significantly interfere with work, social activities and relationships and D) not exclusively be present during delirium. The cortical functions implied in the diagnosis are 1) aphasia, 2) apraxia and 3) agnosia.

b) Cognitive Impairments

The specific elements of cognitive impairment included in the algorithm were also studied separately. Classification of memory dysfunction required a moderate or severe impairment in short-, intermediate- or long-term memory or inability to remember both the name of the present and previous Prime Minister. A classification of aphasia required a moderate to severe expressive or impulsive aphasia, a moderate to severe disturbance in the ability to use or comprehend language or to find words, as judged by the investigator, or a moderate to severe inability to name demonstrated objects (missing two or more objects out of twelve). A classification of agnosia required moderate to severe inability to point at named fingers (missing two or more fingers). A classification of apraxia required moderate to severe inability to use tools from daily life (use knife and fork, light a match, brush teeth); to make a letter from an envelope, a sheet of paper and a stamp; to follow a spoken command, or to copy geometric figures. A classification of impaired abstract thinking required wrong interpretation of at least two out of four proverbs. The procedures have been described in more detail elsewhere (Skoog, Nilsson et al. 1993).

c) Neglect

Visual neglect was assessed with a Swedish adaptation of the Star Cancellation Test, using a sheet with 56 small stars arranged pseudorandomly across the test sheet with two in the midline and 27 at each side of the middle. Among these are dispersed 52 large stars, 13 letters and ten words. The words are translated into common words in the patients' native language. The patients were asked to cancel out all small stars on the test sheet with a pen. The two small stars in the middle were used once for demonstration. The number of correctly and incorrectly cancelled stars was registered. Cut-off points of 44 (Halligan, Burn et al. 1992) and 38 (Stone, Halligan et al. 1991) correctly cancelled stars were used to classify moderate neglect and severe neglect.

Lateralised neglect was assessed by measuring the asymmetry in the number of detected targets. The number of detections made at the left side in the test was divided by the total number of detected targets and expressed in percent. Cut-off levels were 45% for left bias and 55% for right bias (Friedman 1992).

d) Depressive disorders

The diagnosis of Major Depressive Episode (MDE), dysthymia (DT), depressive disorder not otherwise specified (DNOS) and dementia were made according to the criteria in the DSM III-R (1987). We used algorithms based on the psychiatric interview and the neuropsychiatric examination respectively. For practical reasons we did not require evidence of two years duration for diagnosis of DT. DT and DNOS criteria were pooled and presented as “Mild Depression”. Montgomery-Åsberg Depression Rating Scale (MADRS) scores (Montgomery and Åsberg 1979) were also derived from items in the psychiatric interview.

4. Blinding

The investigator, a neurologist/psychiatrist (T.L.), did not take part of previously recorded information of the type, size and location of the index stroke at the time of the investigation as well as throughout the diagnostic procedure.

5. Statistical methods

a) Algorithms and software

The SPSS version 10 and 11 packages were used for statistical analysis. Differences in group means of continuous variables and proportions of categorical data between groups were quantified using 95% confidence intervals. Relative occurrences between groups were compared using odds ratios with 95% confidence intervals. The Kruskal-Wallis test was done to determine whether the costs differed between mild, moderate and severe stroke. The Chi-square test was used for comparing proportions (dichotomised SI score and cognitive impairment). To study the association between the patient’s ability to perform activities of daily life and cognitive impairment, Spearman’s rank correlation coefficient was calculated. A multivariate analysis was performed to explore if cognitive impairment and stroke severity had independent effect on total health care costs. In

this analysis the total health care cost was the dependent variable and cognitive impairment and stroke severity were predictors.

b) Selection of controls

For each stroke patient, we used five controls of the same sex. The controls were age-matched by selecting persons as close as possible in age (measured in years). This was done so as to minimize the difference between the age of the patient and the mean age of the controls. If no control had the same age as the stroke patient, the closest younger control was chosen, if the mean age of the previously selected controls was higher than the age of the patient, or vice versa if the mean age of the previously selected controls was lower. Once selected, the control was removed from the set of available controls so that it would not be selected twice. This procedure was repeated for each of the patients, without replacement of the controls within the procedure for each patient but with replacement of the controls between different patients, until five referents had been sampled for each of the 149 studied patients.

E. Results

1. Characteristics of the subjects

a) Participants and non-participants

The patients who died or refused to participate did not differ significantly regarding age or risk factors from the participating patients (data not shown).

b) Stroke subtypes

The computerized tomography of the brain showed a hemorrhagic stroke in 5.5% (N=8), while 94% (N=138) were classified as ischemic strokes with either a normal CT scan or signs of relevant acute brain infarction. Three patients had no CT scan.

c) Background morbidity

The baseline characteristics of the stroke patients, controls and the population reference are shown in Table 3. A history of myocardial infarction was more common in the stroke patients.

d) Comorbidity

There were no differences between the groups regarding baseline data such as atrial fibrillation, myocardial infarction, hypertension, diabetes or smoking. The Charlson's comorbidity score was 1.57 in the group of patients without cognitive impairment and 1.92 among patients with cognitive impairment (ns).

e) Previous stroke

Twenty-seven percent (N=39) had signs of previous infarcts on CT, of which only half were clinically known (N=20). The prevalence of known stroke was 9.1% in the control group and 14% in the population reference, compared to known previous strokes in 13% of the stroke patients. Among the institutionalized probands in the population reference group, 36% had a history of stroke, compared to 10% among the non-institutionalized.

2. Activities of daily life

Significantly higher proportions of the patients with cognitive impairment were more dependent at twelve months after their stroke in ten of 12 items in Sunnaas Index of ADL (Figure 3). Formal and/or informal care in carrying out activities of

daily life was more common among patients with cognitive impairment ($p=0.005$). A combination of formal and informal care was common. The most common activities in which help was needed were cleaning, shopping and personal care. There was an association between cognitive impairment and activities of daily living according to Sunnaas Index ($r_s =0.48$, $p=0.01$) and the Barthel Index (r_s 0.49, $p= 0.01$). The cognitive domains associated to reduce activities of daily living according to Sunnaas index of ADL were amnesia (r_s -0.39 $p<0.001$), apraxia (r_s -0.60 $p<0.001$), abstract thinking (r_s -0.21 $p=0.13$) and aphasia (r_s - 0.38 $p<0.001$).

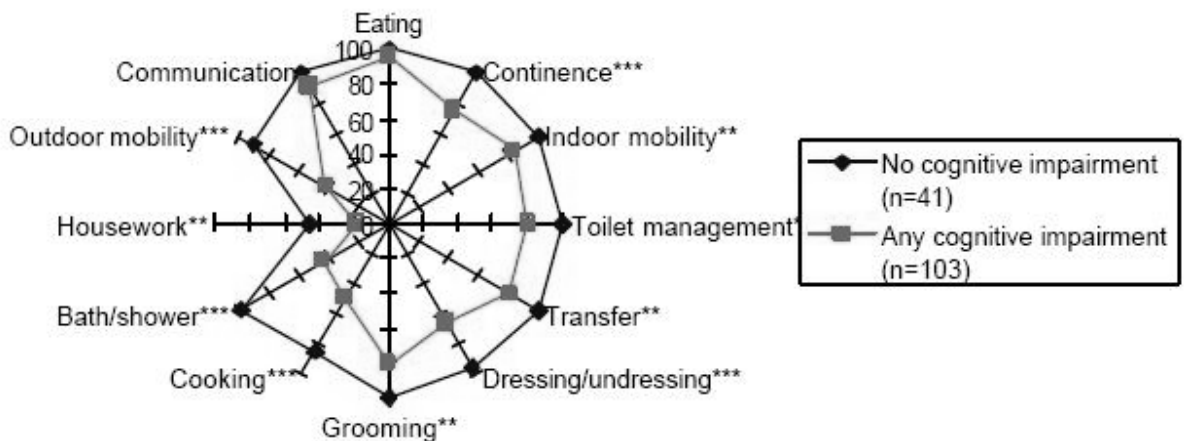


Figure 3. Percentage of patients independent in different items in the Sunnaas Index of ADL at 12 months after acute stroke (* $p<0.05$, ** $p<0.01$, *** $p<0.001$).

Institutionalisation

The exclusion criteria ensured that none of the stroke patients at the time of inclusion or the controls was institutionalized. In the population reference group, 15% were institutionalized. Among these, 61% had dementia, compared to 7.0% among the non-institutionalized.

3. Dementia

The prevalence of dementia was 28% in the stroke patients compared to 7.4% in the controls, giving an odds ratio for dementia of 4.7 (95% CI 3.0 to 7.5). The prevalence of dementia in the population reference group, which also contained

institutionalized probands, was 15%, reflecting the prevalence in the general population at this age. Below age 80, the prevalence of dementia was 18% in stroke patients and 3.2% in the controls, giving an odds ratio for dementia of 6.7 (95% CI 2.6 to 17). Above age 80, the prevalence of dementia was 34% in the stroke patients and 9.5% in the controls, giving an odds ratio for dementia of 4.8 (95%CI 2.8 to 8.2). The prevalence of dementia was higher in women than in men, both in the patients and in the controls, but the ratio for dementia in stroke patients was similar between the sexes with a five-fold increase in both groups.

4. Cognitive impairment

Cognitive impairments were common after stroke 72% vs. 36% in the controls; OR 4.5 (95% CI 3.0 to 6.6) The frequency of impairments in individual dimensions of cognitive dysfunction was also more common in stroke patients than in controls (Table 5).

There was no difference between stroke patients and controls classified as demented, but among those classified as non-demented, the prevalence of cognitive impairments was higher in stroke patients than in controls; 61% vs. 31%, OR 3.5 (95% CI 2.3 to 5.3) for any cognitive impairment, 36% vs. 21%, OR 2.1 (95% CI 1.3 to 3.2) for apraxia, 20% vs. 5.1%, OR 4.8 (95% CI 2.7 to 8.5) for agnosia and 16% vs. 1.3%, OR 13.8 (95% CI 6.0 to 32) for aphasia.

The increases in the risk of any cognitive impairment were highest for patients below the age of 80. For this group, the odds ratio for any cognitive disorder was 8.5 compared to 3.9 in the older group (Table 6).

Table 5. Frequencies of cognitive impairments

	Stroke patients 149		Controls 742		OR with 95% Confidence interval
	n	%	n	%	
All					
Amnesia	47	31.5	70	9.4	4.4 [2.9, 6.8]
Aphasia	38	25.5	31	4.2	7.7 [4.6, 12.9]
Apraxia	74	49.7	193	26.2	2.8 [1.9, 4.0]
Agnosia	35	23.5	50	6.8	4.2 [2.6, 6.8]
Abstract thinking	35	23.5	92	12.5	2.2 [1.4, 3.3]
Any cognitive impairment	107	71.8	267	36.2	4.5 [3.0, 6.6]
Demented	41		55		
Amnesia	41	100	55	100	-
Aphasia	21	51	22	40	1.6 [0.70, 3.6]
Apraxia	35	85	47	87	0.87 [0.27, 2.8]
Agnosia	13	32	14	27	1.3 [0.51, 3.1]
Abstract thinking	17	42	31	58	0.50 [0.22, 1.2]
Any cognitive impairment	41	100	55	100	-
Non-demented	108		687		
Amnesia	6	5.6	15	2.2	2.6 [1.0, 7.0]
Aphasia	17	16	9	1.3	13.8 [6.0, 32]
Apraxia	39	36.1	146	21.4	2.1 [1.3, 3.2]
Agnosia	22	20.4	35	5.1	4.8 [2.7, 8.5]
Abstract thinking	18	16.7	61	8.9	2.0 [1.2, 3.6]
Any cognitive impairment	66	61.1	211	31.0	3.5 [2.3, 5.3]

Table 6. Frequencies of cognitive impairments in age groups

	Stroke patients 149		Controls 742		OR with 95% Confidence interval
	n	%	n	%	
Age below 80	60		378		
Amnesia	13	21.7	11	4.5	5.9 [2.5 , 14.0]
Aphasia	13	21.7	6	2.4	11.0 [4.0 , 30.5]
Apraxia	26	43.3	29	11.8	5.7 [3.0 , 10.9]
Agnosia	16	26.7	7	2.8	12.5 [4.8 , 32.1]
Abstract thinking	12	20.0	17	6.9	3.4 [1.5 , 7.6]
Any cognitive impairment	39	65.0	44	17.9	8.5 [4.6 , 15.9]
Age 80 and above	89		364		
Amnesia	34	38.2	59	11.9	4.6 [2.8 , 7.6]
Aphasia	25	28.1	25	5.1	7.2 [3.9 , 13.3]
Apraxia	48	53.9	164	33.5	2.3 [1.5 , 3.7]
Agnosia	19	21.3	43	8.7	2.8 [1.6 , 5.2]
Abstract thinking	23	25.8	75	15.2	1.9 [1.1 , 3.3]
Any cognitive impairment	68	76.4	223	45.4	3.9 [2.3 , 6.6]

5. Visual neglect

Figure 4 describes the study design and the proportion of patients with different types of neglect. It shows that 15% (21/138) of the patients had neglect, in 12 of whom it was lateralised. The investigation was made in a natural setting without selecting patients, neither on the basis of localisation or extent of the damage nor on the basis of attendance at a specific rehabilitation procedure.

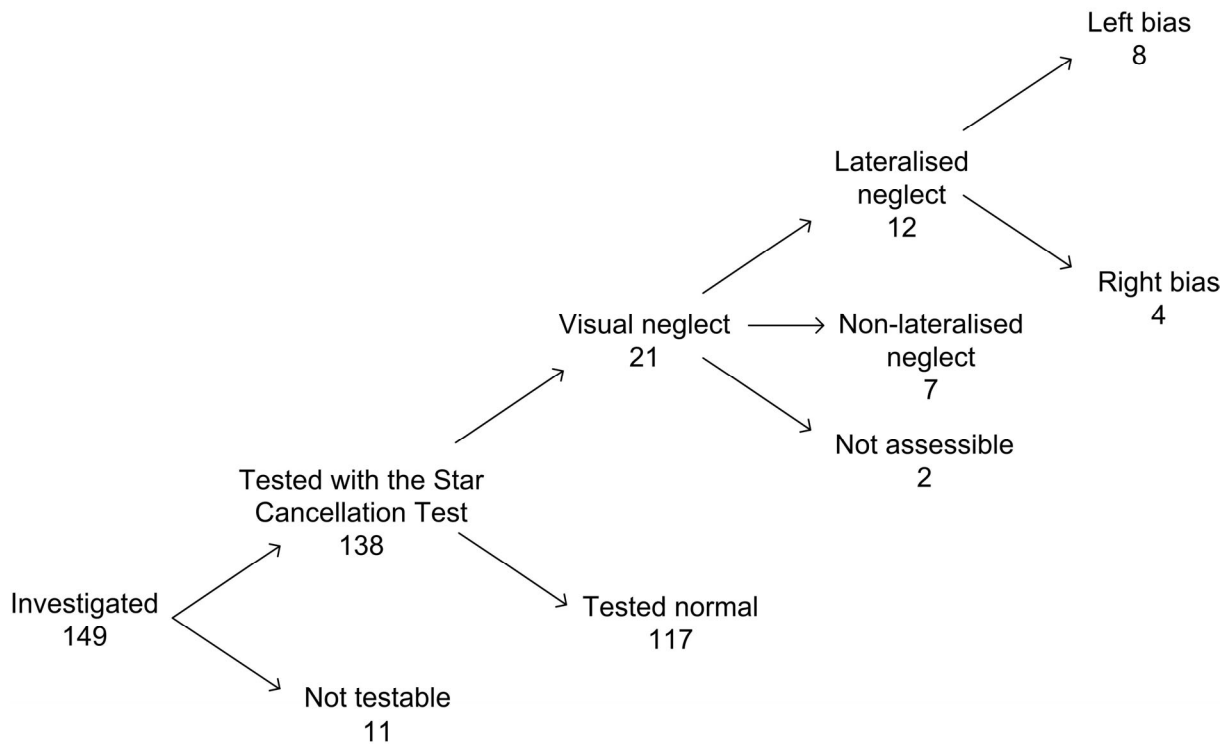


Figure 4. The design of the neglect study and categories of visual neglect

Characteristics of patients with and without neglect are shown in Table 7. No significant differences were found regarding medical history and demographic variables, with the exception of previous stroke, which was more common in patients with neglect. That may reflect that this group is elderly and already burdened with previous injuries.

Table 7. Characteristics of patients with neglect compared to those without

N	Normal		Visual neglect		difference in means	95% CI
	117		21			
Age at follow-up, years (<i>M, SD</i>)	80.7	5.4	82.2	5.2	1.6	0.9 - 4.1
No of impaired cognitive domains	1.3	1.3	2.4	1.4	1.0	0.4 - 1.7
					OR	95% CI
Female (<i>N, %</i>)	78	67%	10	48%	0.45	0.18 - 1.1
Previous stroke	12	10%	6	29%	3.5	1.1 - 11
Right-sided symptoms	49	42%	7	33%	0.69	0.26 - 1.8
Left sided symptoms	60	51%	15	71%	2.4	0.86 - 6.5
Impaired visual field	10	9%	9	39%	7.6	2.6 - 22
Amnesia	34	29%	10	48%	2.2	0.86 - 5.7
Aphasia	22	19%	7	33%	2.2	0.78 - 6.0
Apraxia	48	41%	19	90%	14	3.0 - 61
Agnosia	27	23%	6	29%	1.3	0.47 - 3.8
Impaired abstraction	25	21%	8	38%	2.3	0.85 - 6.1
Any cognitive impairment	77	66%	20	95%	10	1.3 - 80
Dementia diagnosis (DSM-III-R)	29	25%	10	48%	2.8	1.1 - 7.2

The group with neglect differed significantly from those with no neglect by showing a significantly higher proportion of visual field impairments and dementia (Table 7). Apraxia was the most common cognitive impairment in this group. A tendency, although not statistically significant (OR 2.4; 95%CI 0.86 – 6.5), towards more left-sided neurological symptoms was also observed in this group.

Patients with severe neglect (< 38 correctly cancelled stars on the SCT) were compared (Table 8) to patients showing moderate neglect (38 - 43 correctly cancelled stars). Visual field impairments, cognitive impairments and dementia were significantly more common in the patients with severe neglect. The profile of cognitive impairment differed in that amnesia was significantly more common in the “severe” than in the “moderate” group.

Patients with lateralised neglect were compared to those with non-lateralised neglect (data not shown). Overall, the groups were too small to show any statistically significant differences. A tendency toward more left-sided neurological symptoms in patients with lateralised neglect (83%, N=10 compared to 43%, N=3) was observed but no such trend in relation to right-sided symptoms.

Table 8. Characteristics of patients with moderate vs severe neglect

Visual neglect N	Moderate (38-43)		Severe (<38)		difference	
	9		12		in means	95% CI
Age at follow-up, years (<i>M, SD</i>)	80.9	5.8	83.3	4.7	2.4	-2.4 - 7.2
No of impaired cognitive domains	1.7	1.4	2.9	1.1	1.2	0.11 - 2.4
					OR	95% CI
Female (<i>N, %</i>)	2	22%	8	67%	7.1	0.97 - 50
Right-sided symptoms	3	33%	4	33%	1.0	0.16 - 6.2
Left sided symptoms	6	67%	9	75%	1.5	0.22 - 10
Impaired visual field	1	11%	8	67%	16	1.5 - 176
Amnesia	1	11%	9	75%	24	2.1 - 280
Aphasia	2	22%	5	42%	2.5	0.36 - 18
Apraxia	7	78%	12	100%	*	*
Agnosia	2	22%	4	33%	1.8	0.24 - 13
Impaired abstraction	3	33%	5	42%	1.4	0.24 - 8.6
Any cognitive impairment	8	89%	12	100%	*	*
Dementia diagnosis by DSM-III-R	1	11%	9	75%	24	2.1 - 280

The spatial orientation of the neglect was compared with the side of the neurological symptoms. Lateralised neglect toward the left side was found exclusively in patients with left-sided neurological symptoms (N=8). Neglect toward the right (N=4) was observed in two patients with neurological symptoms on the right side, one subject with symptoms on both sides and another patient with symptoms on the left side. Non-lateralised neglect was found in four patients with symptoms on the right and three patients with symptoms on the left.

An interesting observation was made on the laterality of the neglect and presence of dementia (Table 9). Of those with lateralised neglect, four out of five patients without dementia had neglect towards the left, while patients with dementia had neglect towards both sides equally much. It is not possible, however, to draw any conclusions at all from groups with numbers this small.

Table 9. Laterality of visual inattention in relation to dementia

	Side-biased neglect			Total
	No bias	Right bias	Left bias	
Neglect, no dementia	5	1	4	10
Neglect and dementia	2	3	4	9
Total	7	4	8	19

6. Health care resource utilisation

A multivariate analysis (Figure 5) shows that cognitive impairment and stroke severity at 3 days independently influenced the health care costs.

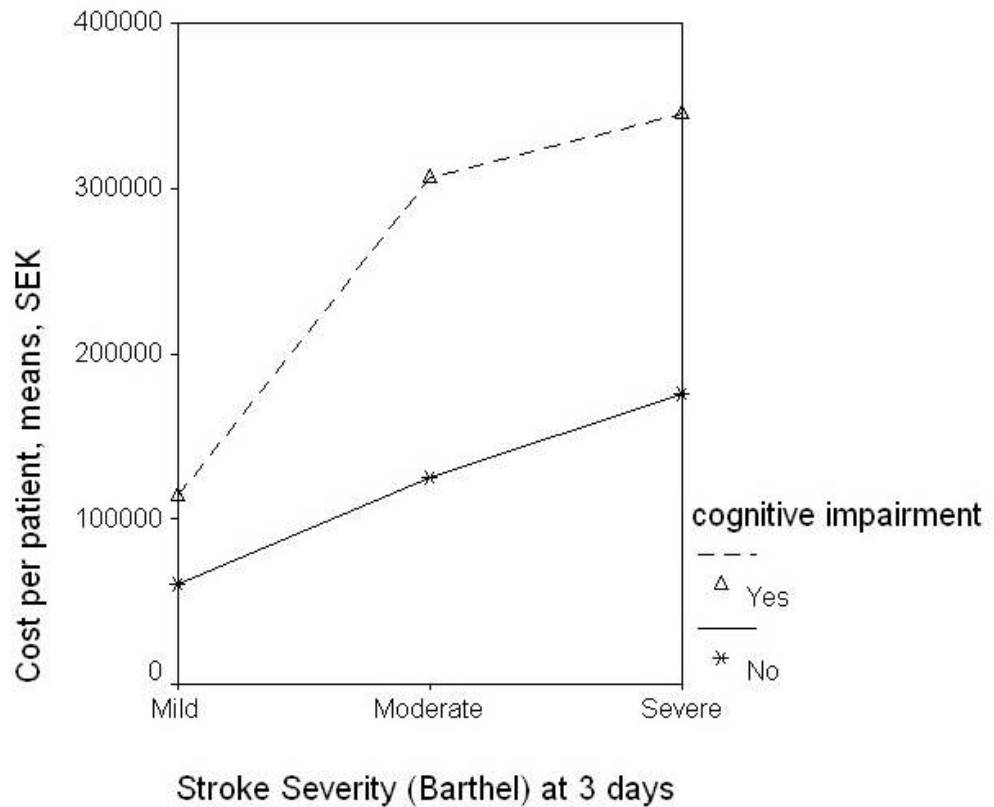


Figure 5. Stroke severity, comorbidity and cognitive impairment at 1½ years

The use of resources in health care service during the first year after acute stroke is shown in (Table 10) and costs per patient during the study are shown in (Table 11).

The mean total costs for different kinds of support (home assistance, safety alarm, taxi service for the disabled, assistive devices and house modifications) were significantly higher ($p < 0.001$) among patients with cognitive impairment.

Table 10. Resource utilisation during the first year versus cognitive impairments

Item	No cognitive impairment n=42		Any cognitive impairment n=107		p-value		
	Mean	Median	25 th -75 th	Mean		Median	25 th -75 th
Initial hospitalisation for index stroke:							
Days per patient	11.4	7.0	4.8-14.3	41.6	17.0	5.0-62.0	<0.001
Rehospitalisation from discharge to 12 months							
Days per patient	3.2	0	0-1.3	14.2	0	7.0-21.0	0.02
Institutionalised living from discharge to 12							
Nursing Home, days per patient	0	0	0	26.3	0	0-0	
Home for the elderly, days per patient	0	0	0	11.0	0	0-0	
Assisted living, days per patient	0	0	0	10.6	0	0-0	
Outpatient care from discharge to 12 months:							
Physician visits per patient	5.8	4.5	2.8-9.0	4.2	3.0	2.0-6.0	0.01
Other medical visits per patient	10.4	2.0	0-14.3	13.4	4.0	0-14.0	0.73
Outpatient rehabilitation, days per patients	0.5	0	0-0	4.9	0	0-0	0.02
Anticoagulation treatment, visit per patient	6.2	0	0-4.5	1.6	0	0-0	0.05
Different kinds of support from discharge to 12							
Home assistant, hours per patient	27.3	0	0-9.0	133.8	0	0-106.0	0.03
Safety alarm, months per patient	1.4	0	0-00	3.7	0	0-9.0	0.02
Taxi service for the disabled, one-way trip per	37.3	0	0-4.0	44.8	18.0	2.0-41.0	0.02
Assistive devices, number of devices per patient	2.2	1.0		4.3	3.0	1.0-7.0	0.001
House modification, % of patients with	0			10			
Other costs from discharge to 12 months:							
Informal care, hours per patient	356.1	56	0-194.5	638.3	103.0	7.0-479.0	0.15

Table 11. Cost per patient during the first year versus cognitive impairment

Item	No cognitive impairment n=42			Any cognitive impairment n=107			p-value
	Mean	Median	P25-P75	Mean	Median	P25-P75	
Initial hosp for index stroke: Total (SEK, 1996 prices)	33 566	24 600	14 861 - 46	93 367	50 702	21 918 - 139	<0.001
Rehosp from discharge to 12 months: Total	7 175	0	0 - 10236	31 917	0	0 - 41 892	0.018
Instit living from discharge to 12 mo: Total	0			35 626	0	0 - 0	
Output care from discharge to 12 mo: Total	10 632	8 548	3 433 - 16 638	12 951	9 098	4 355 - 14 833	0.846
Support from discharge to 12 months Total	8 874	717	113 - 16 810	38 306	12 647	3 771 - 40 212	<0.001
Other costs, discharge to 12 months Informal care	13 557	2 123	0 - 7 394	24 258	3 898	277 - 18 202	0.154
Total costs	73 805	57 770	32 127 - 98	236 425	193 420	79 145 - 395	<0.001

Among patients with cognitive impairment, the mean total cost was 236 425 SEK (\$35 287) as compared to 73 804 SEK (\$11 016) in patients with no cognitive impairment ($p<0.001$). Patients with cognitive impairment spent significantly more time in the hospital for the index stroke ($p<0.001$) and at re-admissions ($p=0.018$).

The mean total costs for patients with mild, moderate and severe stroke were 90 880 SEK (\$13 564), 273 880 SEK (\$40 878) and 339 885 SEK (\$50 729), respectively ($p=0.001$) (data not shown). During the first year after acute stroke the mean total cost for the use of health care resources was significantly higher ($p<0.001$) among patients with dementia (282 719 SEK, \$42 197) than in patients without dementia (155 609 SEK, \$23 225)

7. Depression

All categories of depressive disorders were more common in stroke patients than in controls. About one third of the patients ($N=50$, 34%) had any depressive disorder, almost three times as many as in the control group ($N=97$, 13%). Half of these ($N=25$, 16%) were diagnosed with MDE which was double the prevalence of the control group ($N=61$, 8.2%). Also the load of depressive symptoms, as assessed by the MADRS score was increased in the stroke patients compared to controls (Table 12)

Table 12. Depression in stroke patients and controls

	Stroke patients		Controls		OR [95% confidence interval]	
	N=149	%	N=745	%	lower	upper
Major Depressive Episode	25	17	61	8.2	2.3	[1.4 , 3.7] *
Mild depression	25	17	36	4.8	4.0	[2.3 , 6.8] *
Any Depressive disorder	50	34	97	13	3.4	[2.3 , 5.0] *
	score	SD	score	SD	Mean score difference	
MADRS score	12	11	6.8	7.7	5.2	[3.8 , 6.7] *
MMSE score	24	3.7	27	4.3	2.7	[1.9 , 3.5] *

Depression was increased compared to controls in both women (OR 3.2, 95%CI 2.0 to 5.2) and men (OR 4.0, 95%CI 1.9 to 8.3). The prevalences of both major and mild depression were higher in women than in men both in stroke patients and in controls (Table 13).

Table 13. Depression in women and men

	Stroke patients		Controls		OR [95% confidence interval]	
	N=97	%	N=485	%	lower	upper
Women						
Major Depressive Episode	17	18	48	9,9	1,9	[1,1 , 3,5] *
Mild depression	18	19	25	5,2	4,2	[2,2 , 8,0] *
Any Depressive disorder	35	36	73	15	3,2	[2,0 , 5,2] *
Men	N=52		N=260			
Major Depressive Episode	8	15	13	5,0	3,5	[1,4 , 8,8] *
Mild depression	7	14	11	4,2	3,5	[1,3 , 9,6] *
Any Depressive disorder	15	29	24	9,2	4,0	[1,9 , 8,3] *

MDE was more prevalent in both stroke patients and controls over 80 years of age than in the younger group. For the controls, but not the stroke patients, this was also the case for mild depression. However, because of the strong association of age and prevalence of depression in the controls, the odds ratio for depression after stroke was, despite roughly the same prevalence of depression after stroke in both groups, higher in the younger patients (OR 5.3, 95%CI 2.7 to 11) vs (OR 2.7, 95%CI 1.7 to 4.5). (Table 14)

Table 14. Depression in stroke patients and controls above and below 80 years of age

	Stroke patients		Controls		OR [95% confidence interval]	
	N=89	%	N=435	%	lower	upper
Age over 80 years						
Major Depressive Episode	17	19	44	10	2,1	[1,1 , 3,9] *
Mild depression	15	17	30	6,9	2,7	[1,4 , 5,3] *
Any Depressive disorder	32	36	74	17	2,7	[1,7 , 4,5] *
Age 80 years or less	N=60		N=310			
Major Depressive Episode	8	13	17	5,5	2,7	[1,4 , 5,3] *
Mild depression	10	17	6	1,9	10,1	[3,5 , 29] *
Any Depressive disorder	18	30	23	7,4	5,3	[2,7 , 11] *

No difference in prevalence of depression was seen between patients with and without predominantly left- and right-sided symptoms in the acute stage following the stroke.

F. Discussion

1. Remarks on the study

a) Originality of our study

We examined a consecutive series of elderly stroke patients, including ones with aphasia one and a half years after their index stroke, and used a representative control group for comparison.

(1) Cognitive impairment

To our knowledge, this is the first clinical study that compares cognitive impairment and dementia in a group of elderly stroke patients beyond the acute and subacute periods and an age- and sex-matched control group from the same background population, investigated with the same instruments.

(2) Depression

We are also, to our knowledge, the first study using structured diagnostic instruments to present risk estimates for depression after stroke, based on a population-based control group.

(3) Long-term follow-up of neglect

To our knowledge, no group study has been done on visual neglect at the late stage following stroke. Only one such study has been undertaken at the early stage following brain injury.

b) The use of Population-based controls

We found a markedly increased risk of cognitive impairment in stroke patients, particularly among those below the age of 80. Some studies of cognitive impairment after stroke have either used controls from volunteers, spouses and neighbours (Tatemichi, Desmond et al. 1992), from proxy interviews (Inzitari, Di Carlo et al. 1998) from population studies, or have been uncontrolled (Censori, Manara et al. 1996; Henon, Pasquier et al. 1997). Two studies have used population-based controls: the Framingham Study, which reported only results from the Mini-Mental-State Examination (Kase, Wolf et al. 1998), and the Kungsholmen Study (Kase, Wolf et al. 1998), which selected index stroke patients from a national in-patient registry.

In our study, we included only patients who were hospitalized for their stroke, which might account for the higher frequency of severe strokes in the study. However, in Sweden most cases of mild stroke are also treated in hospitals. We therefore believe that our sample reflects the population of elderly stroke patients fairly well. The group of stroke patients is comparable to the group of controls according to baseline characteristics. Differences were statistically significant only for previous myocardial infarction, which reflects that stroke patients are also at risk for other vascular disease (Naver, Blomstrand et al. 1996). Patients with severe dysfunction already requiring institutional care before the index stroke were not included in the study. This probably led to underestimation of cognitive impairments, as may be seen by comparing the control group from the population reference.

2. The Star Cancellation Test

The test has the advantage of being straightforward and easy to administer. Among conventional tests, Star cancellation is among the most sensitive for identification of visual neglect (Halligan, Marshall et al. 1989). This is also shown in elderly stroke patients (Bailey, Riddoch et al. 2000). Furthermore, visual cancellation is a sensitive and reliable measure of attention in elderly subjects with dementing illness (Solfrizzi, Panza et al. 2002).

3. Remarks on the results

a) Activities of daily life

Stroke associated with cognitive impairment has a very high impact on everyday functioning and dependence in daily life activities (Tatemichi, Desmond et al. 1994). In our study the patients with cognitive impairments showed a higher dependency in instrumental activities (I-ADL) compared to personal activities, which was confirmed in two Scandinavian population studies of elderly persons (Steen, Sonn et al. 2001). I-ADL represents more complex tasks that are influenced by cultural and environmental factors and places more obvious demands upon cognitive function. These activities constitute a potential marker of frailty in older people (Nourhashemi, Andrieu et al. 2001). In this context it should

be mentioned that cognitive examinations and ADL assessments measure different consequences after stroke, and the examinations are made in different environments. Most of the ADL assessments were carried out in the patients' homes. The occupational therapists (OT) evaluated dependence in activities of daily life by interviews. There is a problem in using interviews to assess activities of daily living in stroke patients, especially in those with cognitive impairment, because the patients can over- or underestimate their ability to carry out these activities, particularly in the presence of cognitive weakness. This risk was reduced by performing most of the ADL assessments by the visit of the occupational therapist to the patients in their own familiar environment. Further the OTs clarified unclear points on the basis of information given by relatives and home help services. This allowed a more reliable interview and first-hand observations of how the patients acted in the environment.

b) Prevalence of dementia

Dementia was common in this stroke population, the prevalence being 28%. Results from other studies of dementia in stroke survivors in different hospital-based studies vary according to the follow-up time after stroke, age distribution of the patients, assessment methods and diagnostic criteria (Rockwood, Parhad et al. 1994; Erkinjuntti, Ostbye et al. 1997; Desmond, Moroney et al. 1998). Hence, data are often difficult to compare. Despite this, our results are similar to those of other studies. The prevalence of dementia was substantially higher in the stroke cohort than in the general population, in agreement with earlier findings. Our relative risk of dementia in the stroke patients is lower than the figures previously reported by others. This may be due to a lower mean age in previous studies and different selection of controls.

c) Prevalence of depressive disorders

The prevalence of depressive disorders after stroke was 34%, a figure similar to results from recent meta-analyses and systematic reviews (Robinson 2006), (Hackett and Anderson 2005) and the prevalence of depression for controls was similar to those found in population studies (Palsson and Skoog 1997).

d) The association of the side of the stroke to depression

We found no association between the patients' predominant side of symptoms at the time of the stroke and depressive syndromes. This adds to the evidence supporting no side effect (Singh, Herrmann et al. 1998; Carson, MacHale et al. 2000). Moreover, there is a possibility (Robinson 2006) of a temporally dynamic coupling between side of stroke and depression in the acute stage of stroke which might diminish in the long-term.

e) Prevalence of visual neglect

We found that visual neglect was common (15%) still one and a half years after stroke and that the severity of neglect was associated with presence of dementia and cognitive impairment. These findings were not related to age or gender.

f) Visual neglect and cognitive impairments

Most of the patients with visual neglect showed left-sided neurological symptoms (71%), indicating right-sided injuries. A large proportion of these patients (90%) also had apraxias. This finding was expected since a wide classification of apraxia was used in this study, including constructional apraxia as well as ideational instrumental apraxias. Impaired constructional abilities are often observed in patients showing visual neglect (Friedman 1990).

g) Visual fields and neglect

In our study, the presence of a visual field deficit was statistically associated with neglect. Relations between visual field deficits and visual neglect have also been reported in previous studies (Vallar and Perani 1986; Halligan, Marshall et al. 1990). This relationship may reflect that similar injuries are responsible for both syndromes, namely those in posterior locations, but also that the two syndromes are difficult to distinguish in clinical tests. Actually, the association between neglect and a visual field deficit in this study is open to discussion. The reason is that a double dissociation was a rather common finding. Ten patients showed visual field deficits but no neglect and 12 patients had neglect but no visual field deficits.

h) Neglect long-term after stroke

Twelve patients in this study still had severe visual neglect 1½ years post stroke. The severity of the neglect was associated with the presence of visual field deficit,

dementia and memory impairments. This combination of symptoms may be indicative of a large cortical dysfunction in the posterior brain. Both visual field deficits (Tant, Cornelissen et al. 2002) and cognitive impairment following cortical dementia (Rosler, Mapstone et al. 2000) can by themselves deteriorate the visual scanning ability and thereby contribute to neglect. Thus, it is possible that the combination of cognitive impairment following dementia and visual field impairment makes the attention ability difficult to restore. However, this tentative explanation is incomplete since four of the patients with severe neglect did not show either dementia or impaired visual fields in this study. Other components not investigated in this study may represent mechanisms involved in the inattentive performance. Memory impairment is heavily weighted in the DSM-III-R dementia diagnosis, and thus the classification of dementia and memory problems overlapped in the patients with severe neglect in this study.

i) Lateralised neglect

Among the neglect patients (N=19), a lateralised neglect was the most common observation (N=12) and neglect toward the left side was (N=8) more common than toward the right side (N=4). Patients showing neglect with bias toward the left side exhibited signs of right hemisphere involvement and patients showing neglect with bias toward the right exhibited signs of left hemisphere or bilateral involvement, except in one patient with signs of right hemisphere involvement. These observations seem to be in agreement with the expectations of lateralised symptoms following a hemispheric stroke.

No systematic relationship was observed between non-lateralised neglect and the side of neurological symptoms. This occurrence of non-lateralised neglect indicates a capacity to orient the visual attention toward both the left and right sides but an inability to detect the targets in spite of this ability. The patients with non-lateralised neglect may have had a relative intact system for orientation of visual attention but impairments in other systems connected to visual attention. The above findings illustrate the importance of including both a measure of the number of omissions and a measure of the asymmetry of the omissions when diagnosing neglect

We found that dementia constitutes only a small proportion of cognitive impairments after stroke. Dementia was seen in 28%, while some cognitive impairment was seen in as many as 72%. Another very specific type of cognitive impairment - although not part of the diagnostic criteria for dementia - is neglect. In patients with neglect in the present study, dementia was twice as common; in patients with severe neglect, dementia was three times as common as in the group of all stroke patients. Thus, our results show an association between neglect and cognitive decline, and we thus propose that high alertness should be maintained in order also to detect impaired attention abilities and spatial dysfunction when investigating stroke patients with dementia and other cognitive impairments.

j) Resource utilization

We found an association between cognitive impairment, dependence in daily life activities and costs for health care. The costs for health care resources were three times higher among patients with a cognitive impairment than among patients without cognitive impairment.

Stroke severity has a major impact on health care resources and costs (Diringer, Edwards et al. 1999; Claesson, Gosman-Hedstrom et al. 2000). In our study, days in hospital care, institutionalised living and different kinds of support from society, were associated with cognitive impairment, as were need for a longer initial rehabilitation period and greater dependence in daily life activities. Cognitive impairments were also associated with the highest costs. On the other hand, cognitive dysfunction has a strong impact on ADL dysfunction. Disability in daily life activities among demented patients has been shown to be an important predictor of health care costs (Taylor, Schenkman et al. 2001), but dependence in everyday functioning is not the only factor that predicts these costs. Functional ability in daily life activities combined with a chronic health condition, admission to continuous care accommodations and household structure has an impact on costs to society (McNamee, Gregson et al. 1998).

The consequences of cognitive impairments seem to have an independent effect of health care costs. A detailed estimation of costs and occurrence of cognitive dysfunction as performed in the present study shows differences between costs for

stroke patients with and without cognitive impairment and how these costs distribute among inpatient care and outpatient care. In a lifetime perspective, the costs and the distribution of the cost components change, and costs are highest during the first year after acute stroke (Taylor, Davis et al. 1996). Costs for hospital care dominate in the first year, as in our study, while costs during the second year are dominated by costs for institutionalised living and social service home care.

4. Remarks on methods and research criteria

a) Dementia diagnosis

Most present criteria for dementia are derived from the profile of cognitive decline seen in Alzheimer's disease (Bowler and Hachinski 1995), where impairment of memory is mandatory for a dementia diagnosis. Therefore, significant cognitive impairment may be underestimated in stroke patients when only dementia is assessed, as the picture of cognitive impairment after stroke may be heterogeneous, with a relatively preserved memory function (Bowler, Hadar et al. 1994; Bowler, Eliasziw et al. 1997). In our study, severe cognitive impairment was very common. It was present in 72% of the stroke patients and in 61% of those considered non-demented. The difference in the prevalence of cognitive impairments was even more pronounced when the non-demented stroke patients were compared to the non-demented controls, especially in the youngest age group. Indeed, the majority of stroke patients with significant cognitive impairment were classified as non-demented. This finding emphasizes that if the current criteria for dementia are used as a marker of cognitive impairment, cognitive impairment after stroke will be severely underestimated.

b) Patients with aphasia

We included patients with severe aphasia, a group excluded from several previous studies on both cognitive impairment after stroke and post-stroke depression (Bowler, Hadar et al. 1994; Tatemichi, Desmond et al. 1994; Pohjasvaara, Erkinjuntti et al. 1997). Aphasia was the single cognitive dimension that was relatively common in the stroke cohort. Exclusion of patients with aphasia may result in a selection bias towards left-sided damage and towards the more severely impaired patients. However, cognitive impairment may be difficult

to assess in patients with aphasia. Aphasic patients also show a high frequency of depression (65). However, in our study depressive disorders were not related to lateralized symptomatology, indicating that aphasia was not a strong predictor of depression. On the other hand, depressive disorders may be difficult to diagnose in patients with aphasia and we may therefore wrongly estimate the prevalence of depressive disorders in stroke patients.

c) Mortality before follow-up

One third of the patients had died by the time of the follow-up. These patients were probably more severely damaged than those who survived, as stroke severity is associated with increased mortality (Tatemichi, Paik et al. 1994). This might also have led to underestimation of the prevalence of cognitive impairments, depressive disorders, neglect and dementia in our study, as these conditions all are associated to stroke severity.

d) Exclusion of institutionalized patients at baseline

By protocol for the Göteborg 70+ study, patients that already at the time of their baseline stroke were living in an institution were not included in the study. This probably led to underestimation of depressive disorders and cognitive impairment as indicated by a higher prevalence of depression and dementia in the population sample before excluding the institutionalized [data not shown].

e) No baseline cognition data

Because we lack baseline data on cognitive function, we cannot determine whether the cognitive impairment was a direct consequence of the index stroke. Unrecognized pre-existing dementia may account for some cases (Henon, Pasquier et al. 1997; Henon, Durieu et al. 2001), and in one study cognitive decline was present prior to stroke in 32 to 36% of patients developing post-stroke dementia (Pohjasvaara, Erkinjuntti et al. 1997). A systematic evaluation of pre-existing dementia with a standardized questionnaire administered to a relative on admission suggested that one sixth of stroke patients had pre-existing dementia (Henon, Pasquier et al. 1997). It has also been shown that demented patients are half as likely to receive adequate preventive measures against recurrent strokes as non-demented patients (Moroney, Tseng et al. 1999). Although we believe that most cases of cognitive impairment were a consequence of stroke, others have reported

that individuals with cognitive impairment may be at increased risk of stroke (Ferrucci, Guralnik et al. 1997; Pasquier and Leys 1997; Snowdon, Greiner et al. 1997; Zhu, Fratiglioni et al. 2000). The exclusion of patients who were institutionalized before stroke has probably led to the lower frequency of pre-stroke dementia reported here. The population reference group might give an indication of the prevalence of cognitive impairment at baseline. However, the pre-stroke patients represent a greater vascular risk and probably exhibit a higher prevalence of cognitive impairment than the population reference. In some patients the index stroke may well have been a manifestation of a progressive cerebrovascular disease.

f) Assessment of cognitive impairment

(1) Depression and cognitive assessment

Depression is a condition that makes possible cognitive decline more difficult to evaluate but also a common consequence of stroke. The Framingham Study (Kase, Wolf et al. 1998) explored the association between depression and cognitive decline in stroke patients and found that cognitive decline in stroke patients is a phenomenon independent of depression. In our study, we found about the same stroke patient vs-controls MMSE difference odds ratio after excluding demented patients and controls from the analysis (Table 15) as in the total group (Table 12), supporting the conclusion that the frequency of cognitive impairment after stroke is not a phenomenon heavily related to depression.

Table 15. Depression in non-demented stroke patients and controls

Non-demented	Stroke patients		Controls		OR [95% confidence interval]
	N=108	%	N=687	%	
Major Depressive Episode	17	16	55	8.0	2.1 [1.2 , 3.9] *
Mild depression	20	18	33	4.8	4.5 [2.5 , 8.2] *
Any Depressive disorder	37	34	88	13	3.5 [2.2 , 5.6] *
	score	SD	score	SD	Mean score difference
MADRS	12	11	6.7	7.5	5.3 [3.7 , 7.0] *
MMSE	25	2.7	28	2.5	2.3 [1.8 , 2.9] *

(2) *Differences between DSM-III-R and DSM-IV*

We used the DSM-III-R criteria for dementia; the most frequently used diagnostic criteria at the time of the study. Most dementia studies today rely on these criteria. The DSM-IV criteria introduced later have added two exclusion criteria, making sure that the syndrome is not the result of a known somatic or psychiatric disorder. That addition would not have changed any of the dementia cases in our material. Therefore, the prevalence figures we report for dementia are also comparable to the ones in studies using DSM-IV criteria.

g) Assessment of depressive disorders

(1) *Measurement of outcome*

It has to be emphasized that the diagnosis of depression in our study was based on a semi-structured interview performed by a neurologist/psychiatrist in the stroke patients and a psychiatrist in the controls. This is probably a more reliable way of making diagnosis than using other types of professionals, lay interviewers or using cut-off values of rating scales or self-assessment forms. One recent review (Robinson 2006) of post-stroke depression concluded that consistent use of semi-structured or structured psychiatric interviews and standardised diagnostic criteria is important for improving comparability between studies.

Some common stroke symptoms are also part of the symptom profile in depression (Fedoroff, Starkstein et al. 1991; Spalletta, Bria et al. 2005) and there is thus a possibility that stroke symptoms might falsely be considered symptoms of depression, consequently overestimating depression in stroke patients.

(2) *Aphasia and depression*

Aphasic patients show a high frequency of depression (Robinson and Benson 1981). However, in our study depressive disorders were not related to lateralized symptomatology, indicating that aphasia was not a strong predictor of depression. On the other hand, depressive disorders may be difficult to diagnose in patients with aphasia and we may therefore wrongly estimate the prevalence of depressive disorders in stroke patients.

(3) *Cognitive impairment and depression*

Cognitive impairments are common, among others aphasia, agnosia, apraxia, amnesia and emotional disturbances, and therefore it may be difficult to use

standardised rating scales otherwise used in diagnosis of depression (Schramke, Stowe et al. 1998; Bruce 2001). One solution to this problem is simply excluding subjects with cognitive impairments from the study, which on the other side implies less generalisability of the findings to clinical practise. We therefore chose not to use cognitive impairment as an exclusion criterion. To analyse the possibility of an effect of cognitive impairment on the diagnosis of depression in our study, we also analysed prevalences in the patients and controls with demented subjects excluded (Table 15. This did however not change the results much.

Epidemiological trends in stroke

In Sweden, as in most of the world, the case fatality rate after stroke is diminishing, while the incidence is more or less unchanged. There is also a shift towards a diminishing share of severe strokes (Peltonen, Stegmayr et al. 1998). We can thus expect more people with apparently “minor stroke” and more survivors of major strokes, making the number of patients with persisting cognitive impairments more common. The impact of a shift towards more “minor stroke” on the frequency of post-stroke cognitive impairment is not clear, but the care burden of cognitive impairment after stroke will as an effect of increased number of stroke survivors probably increase and thus also the challenge to the health care system accordingly.

5. Emerging therapies

New therapeutic measures for stroke appear to be under way. An appropriate measure of early cognitive symptoms at the impairment level would therefore be a most useful tool for identifying a “brain at risk” so that preventive measures may be taken rather than waiting until severe brain damage is established. Cerebrovascular pathogenetic factors, including effects of hypertension, hyperlipidemia and diabetes, are increasingly discussed in dementing disease - not only vascular dementias but also in Alzheimer disease (Skoog, Kalaria et al. 1999). Using the dementia syndrome and established diagnostic criteria for dementia when describing impairment in cognitive functions after stroke will only partially describe the problem. We should therefore seek new ways of describing and classifying cognitive impairments in stroke patients.

G. Conclusions

We found a markedly increased risk of cognitive impairment in stroke patients, particularly among those below the age of 80. Dementia was common in this stroke population, the prevalence being 28%. Results from other studies of dementia in stroke survivors in different hospital-based studies vary according to the follow-up time after stroke, age distribution of the patients, assessment methods and diagnostic criteria. Hence, data are often difficult to compare. Despite this, the frequencies in our study are similar to those of others. The prevalence of dementia was substantially higher in the stroke cohort than in the general population, in agreement with earlier findings. Our relative risk of dementia in the stroke patients is lower than the figures previously reported by others. This may be due to a lower mean age in previous studies and different selection of controls.

The present criteria for dementia are derived from the profile of cognitive decline seen in Alzheimer's disease, where impairment of memory is mandatory for a dementia diagnosis. Therefore, significant cognitive impairment may be underestimated in stroke patients when only dementia is assessed, as the picture of cognitive impairment after stroke is often heterogeneous, with a relatively preserved memory function.

In our study, severe cognitive impairment was very common. It was present in 72% of the stroke patients and in 61% of those considered non-demented. The difference in the prevalence of cognitive impairments was even more pronounced when the non-demented stroke patients were compared to the non-demented controls, especially in the youngest age group. Indeed, the majority of stroke patients with significant cognitive impairment were classified as non-demented. This finding emphasizes that if the current criteria for dementia are used as a marker of cognitive impairment, cognitive impairment after stroke will be severely underestimated. We also found that depressive disorders were more common in elderly stroke patients than in age- and sex-matched population controls and have presented risk estimates for age- and sex-related subgroups. We did not find evidence for differences in post-stroke depression associated to gender, side of stroke symptoms or dementia. Since depressive disorders have an adverse effect

on rehabilitation, quality of life and survival after stroke, this urges stroke clinicians to systematically assess elderly stroke patients for depressive disorders - not only in the acute stage following stroke but also at long term follow-up. These conditions should be properly treated so as to optimize rehabilitation. Controlled treatment studies for post-stroke depression in the elderly should be performed to find the optimal regimens for this category of stroke patients. As the case fatality rate after stroke is diminishing, while the incidence is more or less unchanged, we can expect more people with apparently “minor stroke” and more survivors of major strokes, making the number of patients with persisting cognitive impairments more common. The care burden of cognitive impairment after stroke will therefore probably increase.

New therapeutic measures for stroke appear to be under way. An appropriate measure of early cognitive symptoms at the impairment level would therefore be a most useful tool for identifying a “brain at risk” so that prophylactic measures may be taken rather than waiting until severe brain damage is established. Using the dementia syndrome and established diagnostic criteria for dementia when describing decline in cognitive functions after stroke will only partially describe the problem. We should therefore be open to new ways of describing and classifying cognitive impairments in stroke patients

There is an association between visual neglect and cognitive impairment, and we conclude that high alertness should be maintained in order also to detect impaired attention abilities and spatial dysfunction when investigating stroke patients with dementia and other cognitive impairments.

Cognitive impairment is common in elderly stroke patients. Dependence in daily life activities seems to be associated with cognitive impairments. The costs of stroke care were three times higher for patients with cognitive impairments during the first year after stroke. A stronger focus on cognitive, perceptual and psychosocial components is needed in rehabilitation and research programs after stroke.

H. Sammanfattning på svenska

Stroke är globalt den tredje vanligaste dödsorsaken, den näst vanligaste orsaken till demens och den mest betydande och resurskrävande orsaken till långvariga funktionshinder. Strokevården tar en betydande del av de totala hälsovårdsresurserna i anspråk. Kognitiva funktionshinder och depression är vanligt efter stroke och har en avgörande påverkan på rehabilitering, livskvalitet och dödlighet. Detta är speciellt tydligt för patienter med visuell uppmärksamhetsstörning (neglekt). Allvarligt kognitivt funktionshinder är inte detsamma som demens och att beakta enbart de med demensdiagnos kommer att leda till en underskattning av förekomsten av kognitiva funktionshinder efter stroke.

Förståelsen av intellektuella och känslomässiga funktionshinder hos gamla, särskilt de riktigt gamla, strokepatienterna är inte tillräcklig. Få studier har använt matchade populationsbaserade kontroller eller har systematiskt uppskattat förekomsten av kognitiva funktionshinder skilt från demenssyndromet. Afatiska eller på annat vis kognitivt funktionshindrade patienter har ibland uteslutits och därmed har möjligheten att generellt tillämpa resultaten begränsats. Vidare har data ofta publicerats efter endast en kort uppföljningsperiod. Kunskapen om förekomst av neglekt, dess relation till andra kognitiva funktionshinder och depression samt dess effekt på rehabilitering är fortfarande alltför mager, speciellt rörande äldre och sent i förloppet efter stroke.

Eftersom stroke med det ökande antalet äldre och ökande andel överlevare förmodligen kommer att bli mer resurskrävande på samhällsnivå, behöver vi mer kunskap om användningen av hälsovårdsresurser till äldre strokepatienter i relation till kognitiva funktionshinder hos dem, för att väl kunna planera samhällets resurser.

Vår studie utformades för att, efter ett och ett halvt år i en kohort äldre strokepatienter, analysera 1) epidemiologiska data för kognitiva funktionshinder och depression i relation till en normalpopulation; 2) epidemiologi för neglekt i relation till kognitiva funktionshinder; 3) hur kognitiva funktionshinder påverkar

aktiviteter i dagliga livet (ADL) och 4) utnyttjandet av och kostnader för hälso- och sjukvårdsinsatser under det första året efter stroke i relation till ADL och kognitiva funktionshinder.

243 strokepatienter togs in i vår studie, som en delstudie av strokestudien Göteborg 70+. Vi registrerade användningen av hälso- och sjukvårdsresurser under det första året. ADL utvärderades dag 3, efter 3 veckor, 3 månader och 12 månader. En neurologisk och neuropsykiatrisk undersökning och en semistrukturerad psykiatrisk diagnostisk intervju gjordes efter 1½ år. Data från Gerontologiska och Geriatriska Befolkningsstudien i Göteborg, H70, och från Kvinnohälsostudien i Göteborg användes som referensmaterial.

Risken för intellektuella och känslomässiga funktionshinder var påtagligt förhöjd hos strokepatienterna jämfört med normalbefolkningen. Stroke ökade risken för att drabbas av demens nästan fem gånger, av intellektuellt funktionshinder över åtta gånger och för depression fyra gånger. Riskökningen var större hos de yngre patienterna. Femton procent av patienterna hade visuellt neglekt, de flesta lateraliserat. Alla hade mer kognitiva funktionshinder och de med kraftigt visuellt neglekt hade också mer demens. Kognitivt funktionshinder vid uppföljningen och svårighetsgrad av stroke vid 3 dagar var oberoende av varandra associerat till sjukvårdskostnaderna.

Risken för kognitiva funktionshinder och depression ökar efter stroke. Den största riskökningen drabbar patienter under 80 år. Demens är inte ett tillräckligt bra begrepp för att beskriva ett brett spektrum av kognitiva funktionsstörningar. Beroende i ADL är kopplat till kognitiva funktionshinder. Sjukvårdskostnaderna är mycket högre hos strokepatienter som får kognitiva funktionshinder, oavsett svårighetsgraden av stroke. Eftersom visuellt neglekt är relaterat till kognitiva funktionshinder och i sig innebär en belastning på aktivitetsförmåga och delaktighet bör man vara vaksam på brister i uppmärksamhet och spatials förmågor när man undersöker strokepatienter med kognitiva funktionshinder. Kognitiva, perceptuella och psykosociala faktorer behöver uppmärksammas mer i rehabiliterings- och forskningsprogram som riktar sig till strokepatienter.

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IV. Appendices

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Cognitive impairment and dementia 20 months after stroke.
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