Depression and its assessment among stroke patients and their caregivers

Anu Berg

Department of Psychology, University of Helsinki, Finland

Department of Neurology, Helsinki University Central Hospital, Finland

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Supervisors: Emeritus Professor Juhani Vilkki, PhD
Department of Psychology
University of Helsinki
Finland

Emeritus Professor Veijo Virsu, PhD
Department of Psychology
University of Helsinki
Finland

Emeritus Professor Markku Kaste, MD
Department of Neurology
University of Helsinki
Finland

Reviewers: Docent Mervi Jehkonen, PhD
Department of Psychology
University of Tampere
Finland

Professor Peter Langhorne, BSc, MBChB, PhD, FRCP
Faculty of Medicine
University of Glasgow
Scotland, UK

Opponent: Docent Tuomo Hänninen, PhD
Department of Neurology
University of Kuopio
and
Department of Health Sciences
University of Jyväskylä
Finland

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Abstract

Approximately one-third of stroke patients experience depression. Stroke also has a profound effect on the lives of caregivers of stroke survivors. However, depression in this latter population has received little attention. In this study the objectives were to determine which factors are associated with and can be used to predict depression at different points in time after stroke; to compare different depression assessment methods among stroke patients; and to determine the prevalence, course and associated factors of depression among the caregivers of stroke patients.

A total of 100 consecutive hospital-admitted patients no older than 70 years of age were followed for 18 months after having their first ischaemic stroke. Depression was assessed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R), Beck Depression Inventory (BDI), Hamilton Rating Scale (HRSD), Visual Analogue Mood Scale (VAMS), Clinical Global Impression (CGI) and caregiver ratings. Neurological assessments and a comprehensive neuropsychological test battery were performed. Depression in caregivers was assessed by BDI.

Depressive symptoms had early onsets in most cases. Mild depressive symptoms were often persistent with little change during the 18-month follow-up, although there was an increase in major depression over the same time interval. Stroke severity was associated with depression especially from 6 to 12 months post-stroke. At the acute phase, older patients were at higher risk of depression, and a higher proportion of men were depressed at 18 months post-stroke.

Of the various depression assessment methods, none stood clearly apart from the others. The feasibility of each did not differ greatly, but prevalence rates differed widely according to the different criteria. When compared against DSM-III-R criteria, sensitivity and specificity were acceptable for the CGI, BDI, and HRSD. The CGI and BDI had better sensitivity than the more specific HRSD. The VAMS seemed not to be a reliable method for assessing depression among stroke patients. The caregivers often rated patients' depression as more severe than did the patients themselves. Moreover, their ratings seemed to be influenced by their own depression.

Of the caregivers, 30-33% were depressed. At the acute phase, caregiver depression was associated with the severity of the stroke and the older age of the patient. The best predictor of caregiver depression at later follow-up was caregiver depression at the acute phase.

The results suggest that depression should be assessed during the early post-stroke period and that the follow-up of those at risk of poor emotional outcome should be extended beyond the first year post-stroke. Further, the assessment of well-being of the caregivers of stroke patients should be included as a part of a rehabilitation plan for stroke patients.

Tiivistelmä

Masennus on yleinen aivoinfarktin seuraus. Aivoinfarkti vaikuttaa usein merkittävästi myös sairastuneen läheisten elämään. Heidän masennustaan on kuitenkin tutkittu vain vähän. Tämän väitöskirjatyön tavoitteena oli selvittää masennuksen kulkua aivoinfarktin jälkeen ja masennukseen liittyviä ja sitä ennakoivia tekijöitä, arvioida erilaisten masennuksenarviointimenetelmien toimivuutta tällä potilasryhmällä ja tutkia omaisten masennuksen esiintyvyyttä, kulkua ja siihen liittyviä tekijöitä.

Tutkimukseen osallistui sata perättäistä ensimmäisen aivoinfarktinsa saanutta korkeintaan 70-vuotiasta osastohoitoon otettua potilasta. Heitä ja heidän omaisiaan seurattiin 1½ vuotta sairastumisen jälkeen. Masennusta arvioitiin DSM-III-R:llä (Diagnostic and Statistical Manual of Mental Disorders), Beckin masennuskyselyllä (BDI), Hamiltonin arviointiasteikolla (HRSD), visuaalisella asteikolla (VAMS), CGI:llä (Clinical Global Impression) ja omaisten arvioinnilla. Potilas tutkittiin neurologisesti ja kattavin neuropsykologisin menetelmin. Omaisten masennus arvioitiin BDI:llä.

Masennusoireet alkoivat tyypillisesti pian sairastumisen jälkeen ja jatkuivat noin puolella potilaista ainakin vielä vuoden päästä sairastumisesta. Lievän depression esiintyvyys (23-29%) ei juuri muuttunut seurannan aikana, mutta vakava masennus lisääntyi (6-16%). Neurologisen oireiston vaikea-asteisuus oli yhteydessä masennukseen erityisesti 6-12 kuukauden päästä sairastumisesta. Vanhemmat potilaat kärsivät masennusoireista nuoria useammin heti sairastumisen jälkeen, kun taas 1½ vuoden päästä miehet olivat naisia useammin masentuneita.

Arviot masennuksen esiintyvyydestä vaihtelivat suuresti käytetyn menetelmän mukaan. DSM-III-R:n mukaiseen vakavaan masennustilaan verrattuna sensitiivisyys ja spesifisyys olivat riittäviä CGI:llä, BDI:llä ja HRSD:lla. CGI ja BDI olivat herkempiä kuin HRSD, mutta HRSD oli näitä spesifimpi. VAMS ei ollut sen helpompi käyttää kuin muutkaan mittarit eikä se osoittautunut luotettavaksi tällä potilasryhmällä. Omaiset arvioivat potilaat masentuneemmiksi kuin nämä itse.

Omaisista 30-33% oli masentunut seurannan aikana. Potilaiden oireiden vaikea-asteisuus ja korkea ikä olivat yhteydessä omaisten masennukseen seurannan alkuvaiheessa. Omaisten myöhemmän masennuksen paras ennustaja oli alkuvaiheen masentuneisuus.

Aivoinfarktipotilaiden masennus tulisi arvioida pian sairastumista seuraavan akuuttivaiheen jälkeen, ja riskipotilaiden seuranta tulisi jatkua riittävän kauan. Lisäksi aivoinfarktipotilaiden omaisten hyvinvoinnin arvioinnin olisi hyvä kuulua aivoinfarktipotilaan kuntoutussuunnitelmaan.

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List of original publications

The thesis is based on the following original research papers, referred to in the text by Roman numerals (I-IV).

I Berg, A., Palomäki, H., Lehtihalmes, M., Lönnqvist, J., & Kaste, M. (2001). Poststroke depression in acute phase after stroke. *Cerebrovascular Diseases, 12,* 14-20.

II Berg, A., Palomäki, H., Lehtihalmes, M., Lönnqvist, J., & Kaste, M. (2003). Poststroke depression. An 18-month follow-up. *Stroke, 34,* 138-143.

III Berg, A., Lönnqvist, J., Palomäki, H., & Kaste, M. (2009). Assessment of depression after stroke. A comparison of different screening instruments. *Stroke, 40,* 523-529.

IV Berg, A., Palomäki, H., Lönnqvist, J., Lehtihalmes, M., & Kaste, M. (2005). Depression among caregivers of stroke survivors. *Stroke, 36,* 639-643.

Abbreviations

ADL	activities of daily living
ADRS	Aphasia Depression Rating Scale
ANOVA	analysis of variance
AQ	aphasia quotient
AUC	area under curve
BDI	Beck Depression Inventory
BI	Barthel Index
CES-D	Center for Epidemiological Studies Depression Scale
CGI	Clinical Global Impression
DSM-III	Diagnostic and Statistical Manual of Mental Disorders. 3rd edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders. 3rd edition - revised
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders. 4th edition - Text Revision
GDS	Geriatric Depression Scale
GHQ	General Health Questionnaire
HADS	Hospital Anxiety Depression Scale
HRSD	Hamilton Rating Scale for Depression
MADRS	Montgomery Åsberg Depression Rating Scale
MCA	middle cerebral artery
MMSE	Mini-Mental State Examination
PAS	Psychiatric Assessment Schedule
ROC	receiver operating characteristics
SAH	subarachnoid haemorrhage
SD	standard deviation
SSS	Scandinavian Stroke Scale
VAMS	visual analogue mood scale
WAB	Western Aphasia Battery
WAIS	Wechsler Adult Intelligence Scale
WMS-R	Wechsler Memory Scale - Revised

1 Introduction

Depression is a usual consequence of stroke. Approximately one third of stroke survivors experience significant symptoms of depression (Hackett et al. 2005). Post-stroke depression is associated with poor quality of life (Carod-Artal et al. 2000, Ones et al. 2005, Pan et al. 2008), greater disability and poor rehabilitation outcomes (Paolucci et al. 2001, Chemerinski et al. 2001, Pohjasvaara et al. 2001a, Brodaty et al. 2007), more healthcare use (Jia et al. 2006), mortality (House et al. 2001, Williams et al. 2004, Townend et al. 2007c), and suicidal ideation (Kishi et al. 2001, Pohjasvaara et al. 2001b). It is therefore highly important to find patients at risk of depression in order to be able to help them early enough and avoid its detrimental consequences.

Apart from the clinical importance, understanding depression that follows stroke could improve our theoretical understanding of the basis of mood regulation in general. An early study suggested that post-stroke depression might be associated with a specific brain location and be related to a focal disturbance of neurotransmitter pathways (Robinson et al. 1975), which gave rise to a vast number of studies on post-stroke depression. However, after three decades, the aetiology of post-stroke depression is not well understood and a consensus on the associating factors has not been reached. Post-stroke depression probably has a multifactorial aetiology involving both organic and reactive components. Most studies suggest an association between stroke severity and depression (Hackett & Anderson 2005). In addition to stroke-related factors, many patient-related factors, including age, sex, personality, coping abilities, and extent of social support received may be associated with post-stroke depression. The context of recovery and adaptation cannot be neglected. During recovery, a patient goes through a psychological process from acute phase crisis to the adaptation and integration with the remaining long-lasting disabilities.

The assessment of post-stroke depression is often complicated by several physical and cognitive impairments from which stroke patients typically suffer. First, vegetative symptoms such as fatigue, psychomotor retardation, or insomnia, may be the direct physical consequences of stroke. However, they also constitute some of the symptoms of depression. Second, neuropsychological impairments may produce alterations, among other things, in expression of emotions, and aphasia may make it impossible to

assess depression conventionally. In order to screen and diagnose post-stroke depression reliably, we need to know how different assessment methods are influenced by these factors.

Compared to the extensive research on post-stroke depression, little attention has been focused on the emotional outcome and depression of caregivers of stroke survivors. When the majority of stroke survivors continue to live at home and often need practical help and emotional support, it is understandable, that many caregivers may suffer considerable stress (Bugge et al. 1999, Jones et al. 2000). Very little is known of changes that occur in the depression experienced by caregivers and factors associated with it. Family support can significantly improve the psychosocial outcome of caregivers (Mant et al. 2000). Consequently, it is important to gain knowledge of the risk factors for caregiver depression in order to be able to provide support when most needed.

1.1 Stroke

Stroke is a major health problem in the whole of western society. In addition to being the third most common cause of deaths, stroke is the most important cause of physical disability of people over 60 years old (Kaste et al. 1998). The incidence rates of stroke rise steeply with increasing age. In the Finnish population the incidence of an individual's first-ever stroke was 303/100 000 in 2002, among men and 175/100 000 among women aged 35-75 years. These values increased by six- to nine fold for older populations of up to 84 years of age (Pajunen et al. 2005). Although the age-adjusted incidence and case-fatality of stroke have been declining since the 1980s (Sivenius et al. 2004, Pajunen et al. 2005), the number of stroke events in Europe is projected to increase by as much as 30 per cent over the 2000 to 2025 period, because of extended life expectancy and other demographic factors (Truelsen et al. 2006). Consequently, the numbers of stroke survivors living with their residual impairments will increase. Prevalence rate estimates vary between 5 and 12 per 1000 in the adult population, and 46 to 72 per 1000 in people aged 65 or over (Bonita et al. 1997, Feigin et al. 2003).

Stroke is caused by an ischaemic brain infarction in about 70-80 per cent of all cases (Feigin et al. 2003, Sivenius et al. 2004, Hallström et al. 2008), haemorrhagic strokes being less frequent. Of patients with ischaemic stroke, 82-90 per cent survive the first

month, and 67-81 per cent are still alive one year after the stroke (Kaste et al. 1998, Feigin et al. 2003, Pajunen et al. 2005). In clinical work and research, ischaemic strokes are commonly categorized by vascular territory. Internal carotid arteries that primarily supply the hemispheres are affected more often than the vertebral-basilar arteries that supply the posterior portion of the brain, including the brain stem and the cerebellum. The majority of all ischaemic strokes are localized in the area of the middle cerebral arteries (MCA), and often cause severe disability (Ng et al. 2007). Stroke is, inter alia, followed by various motor and cognitive symptoms the range and quality of which depend on the side, location and size of the infarction.

The major part of spontaneous recovery tends to occur within the first three months after stroke, and patients with cognitive deficits can continue to show gains for months or even years afterward (Cramer 2008). After the recovery period, long-term disability, of varying severity, often remains. The majority of stroke survivors continue to live at home (Hackett et al. 2000, Hankey et al. 2002), but, based on population studies, 20-50 per cent of stroke survivors need help in at least one aspect of daily living activities (Bonita et al. 1997, Hackett et al. 2000, Hankey et al. 2002, Hardie et al. 2004). It is understandable that stroke might have effects on survivors' and their carers' quality of life and mood.

1.2 Prevalence of post-stroke depression

Various studies report the prevalence of post-stroke depression as ranging from 9 per cent to 53 per cent. In their respective reviews, Robinson (2006) and Hackett et al. (2005) calculated the pooled means for prevalences, which ranged from 25 to 41 per cent. Table 1 summarizes the most representative prospective studies, of the prevalence of depression as assessed from the acute phase up to 12 months after stroke. This table includes studies using only well-known assessment methods and relatively large patient samples ($n > 80$). These data are not limited to the oldest age groups or to specific lesion location. Moreover, the times elapsed since stroke are well defined and without large variation. In the majority of these studies the assessment of depression was done 3 to 12 months after stroke, though depression is usual even years after stroke (Paul et al. 2006, Sharpe et al. 1994, Van de Port et al. 2007, Linden et al. 2007).

Table 1. Studies on the prevalence of depression after stroke

	N	Patient population	Time since stroke	Depression Criteria	Prevalence of depression
At the acute phase (0 - 1 month after stroke)					
Caeiro et al. 2006	178	hospital	≤ 4 days	MADRS ≥ 7 & DSM-IV-TR	46%
Townend et al. 2007	125	hospital	2 - 5 days	HADS > 8	5%
	112		1 month		16%
Ramasubbu et al. 1998	626	hospital	7 - 10 days	CES-D ≥ 16	26%
Robinson et al. 1983	103	hospital (no SAH)	2 weeks	DSM-III major	27%
				minor	20%
				total	47%
Gillen et al. 2001	243	rehabilitation hospital	2 weeks	GDS ≥ 15	13%
Wade et al. 1987	379	community	3 weeks	Wakefield > 14	33%
Andersen et al. 1994	285	hospital inpatient & outpatient (no SAH)	1 month	HRSD ≥ 18	10%
House et al. 1991	89	community (first-ever)	1 month	DSM-III major	11%
				minor	12%
				total	23%
	76			BDI ≥ 10	32%
				BDI ≥ 13	20%
				BDI ≥ 17	8%
After the acute phase up to 12 months after stroke					
Morris et al. 1990	99	hospital (no SAH)	2 months	DSM-III major	14%
				minor	21%
				total	35%
Townend et al. 2007	105	hospital	3 months	HADS > 8	21%
Pohjasvaara et al.1998	277	hospital ischaemic	3 - 4 months	DSM-III-R	
				major	26%
				minor	14%
				total	40%
				BDI ≥ 10	38%
Burvill et al. 1995	248	population based	4 months	DSM-III (PAS)	
				major	15%
				minor	8%
				total	23%

Dennis et al. 2000	251	hospital inpatient & oupatient (no SAH)	6 months	HADS > 6 > 8 > 10	31% 20% 12%
Ebrahim et al. 1987	149	hospital	6 months	GHQ ≥ 12	23%
Herrmann et al. 1998	150	hospital (no SAH, vertebral-basilar)	3 months	MADRS ≥ 7 Zung ≥ 50	27% 22%
	133		1 year	MADRS ≥ 7 Zung ≥ 50	22% 21%
Kauhanen et al. 1999	106	hospital (infarct, first-ever)	3 months	DSM-III-R major minor total	 9% 44% 53%
			12 months	DSM-III-R major minor total	 16% 26% 42%
Kotila et al. 1998	321	community (first-ever)	3 months	BDI ≥ 10	47%
	311		12 months		47%
House et al. 1991	119	community (first-ever)	6 months	DSM-III major minor total	9% 11% 20%
	107			BDI ≥ 10 BDI ≥ 13 BDI ≥ 17	32% 15% 6%
	112		12 months	DSM-III major minor total	8% 1% 9%
	88			BDI ≥ 10 BDI ≥ 13 BDI ≥ 17	16% 8% 1%
Wade et al. 1987	377	community	6 months	Wakefield > 14	32%
	348		12 months		31%
Appelros & Viitanen 2004	231	population-based (first-ever no SAH)	12 months	GDS ≥ 5 DSM-IV total	37% 27%
Verdelho et al. 2004	110	hospital	6 months	MADRS ≥ 7	43%
	71		12 months		36%

MADRS = Montgomery and Åsberg Depression Ratings Scale, DSM = Diagnostic and Statistical Manual of Mental Disorders, III refers to 3rd edition, III-R to 3rd edition - revised, and IV-TR to 4th edition - text revision, HADS = Hospital Anxiety Depression Scale, CES-D = Center for Epidemiological Studies Depression Scale, SAH = subarchnoid haemorrhage GDS = Geriatric Depression Scale, HRSD=Hamilton Rating Scale for Depression, BDI = Beck Depression Inventory, PAS = Psychiatric Assessment Schedule, GHQ = General Health Questionnaire.

The reported frequencies vary according to patient inclusion criteria, study settings, diagnostic criteria and time elapsed after stroke. Some studies reviewed have included all stroke survivors, whereas others have excluded those with subarachnoid haemorrhages. There are also some studies, e.g. Kauhanen et al. (1999) in which only a homogenous patient group with ischaemic strokes was recruited. This approach is reasonable because of the different types of recovery and prognoses in strokes of different aetiology. In addition to this, patients with recurrent strokes suffer depression more often than patients with first-ever strokes (Andersen et al. 1994). Community studies, which also include patients with very mild stroke symptoms, have reported somewhat lower rates than those studies involving hospital settings (Robinson 2006). However, in the review by Hackett et al. (2005) pooled frequencies from both the population based and hospital based studies overlapped. In Table 1, the prevalence of depression is higher in hospital settings than in community studies when depression is diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders criteria, Third edition (DSM-III, American Psychiatric Association 1980) or Third edition – revised (DSM-III-R, American Psychiatric Association 1987). However, when the Beck Depression Inventory (BDI) (Beck et al. 1961) is used as a depression rating scale, the results are more variable. Depression is assessed by a great number of different methods with different cutoff points, which apparently causes large variation in prevalence estimates. In the review by Hackett et al. (2005) the Hamilton Depression Rating Scale (HRSD) (Hamilton 1960) produced the lowest prevalences for depression, whereas the highest prevalences were found in studies that used the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg 1979). The different assessment methods make it difficult to compare results across studies and time points.

1.3 Course of depression

In a series of studies by Robinson et al. (1983, 1984b, 1987), depression of stroke patients was followed up to two years after stroke for the first time. These authors concluded that the prevalence of depression remains high and relatively stable during the first two years after stroke. However, when prevalence rates were compared across the different time points, subgroups of only 38 to 50 patients were assessed. The prevalence of major depression remained stable or, more often, increased from the acute phase. The prevalence of depression as measured by the BDI in larger patient samples also remained unchanged for up to 12-15 months in studies by Pohjasvaara et al. (2001) and Kotila et al. (1998). However, decreasing rates for depressive symptoms from 6 months onwards have also been reported by House et al. (1991) for the BDI and also by Verdelho et al. (2004) with regards to MADRS. Further, Åström et al. (1993) followed 80 hospital admitted patients for up to 3 years, and found a non-linear development in the prevalence rates: major depression decreased from 31 per cent at 3 months to 16 per cent at 12 months and thereafter increased to 19 per cent at 2 years and up to 29 per cent at 3 years. A recent study by Brodaty et al. (2007) found that the prevalence of both major and minor depression increased from 3 months to 15 months.

Post-stroke depression has an early onset in most cases. In the studies conducted by Andersen et al. (1994) and Aben et al. (2003), about 50 per cent of post-stroke depression cases were diagnosed during the first month after stroke. Paolucci et al. (2005) reported that for over 60 per cent of those patients who developed depression, the mood disorder had arisen during the first 6 weeks, and this proportion rose to 80 per cent within 3 months of having the stroke. The duration of depression varies widely (Morris et al. 1990). In the study by Åström et al. (1993) 60 per cent of the patients with early depression had recovered by 1 year. Similarly, according to the study by Burvill et al. (1995) 41 per cent of the patients who were depressed at 4 months after stroke were still depressed at 12 months follow-up. Based on the results of Åström et al. (1993) there seems to be a high risk of chronic depression, if a patient has not recovered during the first year after stroke.

From the literature, it is known that depressive symptoms often arise soon after stroke, but a consensus on the course of post-stroke depression has not been reached

yet. More longitudinal studies with sufficiently large and representative sample sizes and lasting longer than one year follow-up are needed.

1.4 The associated factors and predictors of post-stroke depression

1.4.1 Importance of lesion location

One of the oldest studies that investigated the role of brain damage per se as the cause of post-stroke depression, is that of Folstein et al. (1977). Stroke survivors had higher rate of depression compared to orthopaedic patients with similar levels of disability in activities of daily living (ADL). Although the patient groups were small and there were several methodological problems, this study began a series of studies, in which mood disorders were primarily attributed to structural brain damage. A series of studies (Robinson & Price 1982, Robinson et al. 1984a, Parikh et al. 1987) suggested that higher incidences of depression may be associated with left hemisphere strokes, and the severity of which may be inversely related to the distance of the lesion from the anterior pole of the left hemisphere. Furthermore, Starkstein et al. (1987) found that the prevalence of depression was similar for left cortical and left subcortical lesions. Later, the importance of subcortical lesions affecting the basal ganglia and frontal-subcortical circuits were highlighted as determinants of post-stroke depression (Vataja et al. 2004). A few investigators such as Åström et al. (1993) have been able to replicate the association between left hemispheric lesion and post-stroke depression. However, many others did not find such a relationship (Morris et al. 1990, House et al. 1990a, Herrmann et al. 1995, Burvill et al. 1996, Gainotti et al. 1997a, Pohjasvaara et al.1998, Andersen et al. 1995, Nys et al. 2005). Moreover, some studies even suggest an association between the right hemisphere lesions and depression (Dam et al. 1989, MacHale et al. 1998). In addition, a systematic review by Carson et al. (2000) did not support the hypothesis that lesion location is associated with depression. It is possible, that methodological differences, such as patient selection, time elapsed since stroke and differences in assessment of depression, gave conflicting results. Shimoda and Robinson (1999) proposed that only acute depression during the first weeks after stroke is associated with left anterior lesion location, though there are no hemisphere-related

differences in the frequency of depression 3 to 6 months after stroke. In a review Bhogal et al. (2004) found that the association between depression and left hemisphere stroke was predominantly found in studies of hospital inpatients early after stroke. In contrast, studies of community-based samples and with assessments which took place 6 months after stroke suggested depression after right hemisphere stroke. These associations need to be confirmed in follow-up studies.

1.4.2 Stroke severity and cognitive impairments

Stroke severity and physical and functional impairments are associated with post-stroke depression (Pohjasvaara et al. 1998, Kotila et al. 1998, Hermann et al. 1998, Ramasubbu et al. 1998, Singh et al. 2000, Kauhanen et al. 2000, Gainotti et al. 2001, Desmond et al. 2003, Verdelho et al. 2004, Nys et al. 2005, Townend et al. 2007c): the more the impairment the more severe depression. Of all variables studied, this association has the greatest consensus in study literature.

Knowledge of the associations between specific cognitive deficits and depression is still lacking. Depressed patients have been reported to be more cognitively impaired in some studies (Robinson et al. 1983, Wade et al. 1987, House et al. 1990b, Sharpe et al. 1994, Andersen et al. 1995), but other studies have not confirmed this association (Eastwood et al. 1989, Pohjasvaara et al. 1998). Furthermore, in a study by Brodaty et al. (2007), the time interval since the stroke seemed to have an effect on the association between stroke severity and cognitive impairment. Depressed patients had more impaired cognition than nondepressed 15 months after stroke, but not at 3 to 6 months after stroke. In all these studies, cognitive impairment was assessed by only a single score. The most commonly used assessment method was the Mini-Mental State Examination (MMSE) (Folstein et al. 1975), which is strongly sensitive to language deficits and is not optimal for assessing cognitive impairments of stroke patients. Visuoperceptual and inattention disorders, which are induced most often by right hemisphere lesions may be overlooked when using MMSE.

Of specific cognitive impairments, the association between aphasia and depression is supported by studies of Åström et al. (1993) and Kauhanen et al. (1999), but not by those of Dam et al. (1989) and Stern and Bachman (1991) and Spalletta et al. (2002). Herrmann et al. (1993) found that patients with non-fluent aphasia were more depressed

than those with fluent aphasia, but Damecour and Caplan (1991) did not get the same result. Because the assessment of depression is usually based on language, most studies have excluded patients with at least severe or moderate aphasia (Townend et al. 2007b), which makes conclusions based on different studies problematic.

Comprehensive neuropsychological examinations have very rarely been performed in studies on post-stroke depression. Detailed results have been reported by Nys et al. (2005) and Kauhanen et al. (1999). Nys et al. (2005) studied their patients during the first three weeks after stroke whereas Kauhanen et al. (1999) followed their patients from 3 months to 1 year. In the study conducted by Nys et al. (2005) deficits of visual perception, memory, and language were associated with depression. In the other study (Kauhanen et al. 1999) depressed patients performed more poorly than nondepressed patients in almost all cognitive functions studied, both at 3 and at 12 months follow-up. However, neither of these studies was based on comprehensive multivariate analyses. Both groups of authors did not take into account stroke severity or other underlying factors, which might have interactions with both depression and cognitive deficits.

1.4.3 Demographic risk factors for post-stroke depression

In addition to stroke-related factors, several demographic factors may also be associated with post-stroke depression. Females were more often depressed in several studies (Sharpe et al. 1994, Andersen et al. 1995, Herrmann et al. 1998, Desmond et al. 2003, Eriksson et al. 2004, Provinciali et al. 2008) but not in all (Morris et al. 1991, Åström et al. 1993, Pohjasvaara et al. 1998, Kauhanen et al. 1999, Aben et al. 2002a, Verdelho et al. 2004, Brodaty et al. 2007). Results on the association between age and depression are even more controversial. Some studies have found older patients to be more depressed (Kotila et al. 1998, Kauhanen et al. 1999), whereas other studies suggest younger stroke-patients are more susceptable to depression (Robinson et al. 1983, Eriksson et al. 2004, Verdelho et al. 2004). Despite these studies most often no significant association between age and depression has been found (Åström et al. 1993, Andersen et al. 1995, Herrman et al. 1998, Pohjasvaara et al. 1999, Aben et al. 2002a, Desmond et al. 2003, Appelros et al. 2004). Results on the association between educational level and post-stroke depression are also inconsistent (Pohjasvaara et al. 1998, Paolucci et al. 1999, Spalletta et al. 2002, Caeiro et al. 2006). Of social factors,

living alone (Åström et al. 1993, Andersen et al. 1995, Eriksson et al. 2004, Brodaty et al. 2007), missing social support and/or experiencing social isolation (Åström et al. 1993, Andersen et al. 1995, Townend et al. 2007c), having specific personality traits (Aben et al. 2002a) and a lack of adaptation or efficient coping strategies (King et al. 2002, Rochette et al. 2007) are potential risk factors for post-stroke depression, in addition to having a history of depression (Andersen et al. 1995, Herrmann et al. 1998, Caeiro et al. 2006).

We do not yet have enough knowledge for the accurate identification of stroke patients at high risk of depression. Some of the inconsistencies in the literature might be resolved with improvements in patient selection and in the definition and assessment of depression. Moreover, the time related changes in depression and its associates should especially be clarified with follow-up studies.

1.5 The aetiology of post-stroke depression

The question of the aetiology of post-stroke depression has been tackled by two major approaches: some propose that post-stroke depression results from the brain injury per se. In contrast, others assume that it is the psychological response to the impairments or loss. Many findings described earlier can be seen as evidence for both physiological and psychosocial mechanisms of post-stroke depression. Both are not mutually exclusive approaches, but instead reflect the complex and multifactorial disorder, with the interaction between physiological and environmental factors.

It has been suggested, that the disruption of biogenic amine pathways by stroke, that causes abnormalities in the production and metabolism of monoamine transmitters, may play an aetiological role in post-stroke depression (Bryer et al. 1992, Ramasubbu et al. 1999, Rocco et al. 2007). Endogenous depression has long been hypothesized to be due to neurotransmitter changes. The deficiency of the monoamine transmitters dopamine, serotonin and noradrenaline especially, or the malfunctioning of the entire monoaminergic neurotransmitter system in various brain circuits, may cause depression (Stahl 2008). In the study of both post-stroke depression and endogenous depression, the interest shifted from the monoamine neurotransmitters themselves, to their receptors and to the molecular events that these receptors trigger. These include downstream signal transduction and the regulation of gene expression. For example, it has been

proposed that under stress the gene for brain-derived neurotrophic factors may be repressed (Stahl 2008). New hypotheses for post-stroke depression are the increased production of proinflammatory cytokinenes (Spalletta et al. 2006), and the importance of specific high-risk genes (Ramasubbu et al. 2008).

As seen earlier (1.4.1), results on the association of the location of lesion and post-stroke depression are conflicting. Neuroimaging and neuropathological studies of endogenous mood disorders have most often identified structural and functional abnormalities in the prefrontal cortex and in the limbic system including the amygdala and the basal ganglia (Drevets 2001, Sheline 2003). These neuro-anatomical structures have special functions in modulating emotional behaviour in the different components and at various levels of the emotional system (Gainotti 2001). Abnormalities in these emotional processes may be contributors in the development of the cognitive-emotional manifestations of longer-lasting mood disorders. In addition to the general assessment of depression, there are a variety of symptoms characterizing depression. These symptoms vary from autonomic responses to subjective feelings and merit being studied together with cognitive abilities. Such approaches could give some light to the topic of hemispheric lateralization in depression, which as yet remains unsettled.

When post-stroke depression is seen as a natural psychological reaction to the stroke and its consequences, the time that has elapsed since stroke becomes especially important. It is widely accepted that psychological responses to different kinds of major losses involves a series of stages, a sequence of which occurs with predictable regularity. Denial and rejection are typical in the very acute phase, followed by anger or frustration, and weeks later by depression. In a study by Maciejewski (2007) on bereaved individuals, depression increased from 1 to 6 months, and after a peak at approximately 6 months after the bereavement decreased in intensity to 24 months after the event. Acceptance increases with time, and usually can not be reached earlier than a year after the loss. Among stroke patients there are at least two additional factors that complicate this process. First, stroke patients become aware of their impairments gradually. Typically this occurs in different ways with different symptoms. Second, the impairments caused by stroke, are relieved over time by spontaneous recovery and rehabilitation.

1.6 Assessing post-stroke depression

1.6.1 Various methods in assessing post-stroke depression

Considering the large quantity of research on post-stroke depression, little attention has been paid to the validation of assessment methods of depression used on stroke patients. The definition of depression and the methods used to measure depression may cause variations in the prevalence and consequently give differing results on associated factors for post-stroke depression. During recent years the majority of the studies have included a diagnostic definition of major depression. In some studies minor depression, dysthymic depression and adjustment disorder have also been used. In addition to this, numerous observer-rating and self-rating scales each with different cutoff points have been used either in combination with a diagnostic interview or as the only assessment scale. Several rating scales, commonly used in the assessment of post-stroke depression, are reviewed by Salter et al. (2007). One of the most often used interview-administered scales is the HRSD (Hamilton 1960). A common self-rating scale is the BDI (Beck et al. 1961).

The diagnosis of depression is based on psychiatric interview and needs specific criteria to be fulfilled. The DSM-III-R (American Psychiatric Association 1987) criteria for a major depression episode, are similar to those of the newer version DSM-IV TR (American Psychiatric Association 2000), and include nine different symptoms and signs. At least five of the symptoms should be present in major depression, and one of them must be either depressed mood, or loss of interest or pleasure. The other symptoms are significant weight loss or gain or changes in appetite; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue; feelings of worthlessness or excessive guilt; impaired concentration or indecisiveness; and recurrent thoughts of death or suicide. Dysthymic disorder is characterized by long-term but less severe symptoms than major depression. Adjustment disorder is a maladaptive reaction to an identifiable stressor that causes significant emotional and behavioural symptoms that do not meet the criteria for more specific disorders.

A variety of stroke patients' physical and cognitive impairments after having a stroke may interfere with the assessment of depression. First, vegetative symptoms such as fatigue, psychomotor retardation, or insomnia may be related directly to the stroke

without depression, though they are also included in the criteria for depression. Second, aphasia, among other cognitive problems, may even make it impossible to assess depression directly. These problems have to be considered both when using diagnostic DSM criteria and various rating scales.

1.6.2 The importance of various symptoms in post-stroke depression

Some authors consider that both psychological and somatic symptoms are associated with post-stroke depression and support the use of the DSM criteria, irrespective of the nature or origin of the symptoms (Spalletta et al. 2005, Fedoroff et al. 1991, Paradiso et al. 1997). In a study by Lipsey et al. (1986), patients with post-stroke major depression and patients with functional major depression had very similar depressive symptoms. Contrary to this, some other studies found that somatic symptoms are less specific than nonsomatic symptoms in respect to post-stroke depression (Stein et al. 1996) and stressed differences in symptom profiles between post-stroke and endogenous depression (Gainotti et al. 1997b, 1999 Beblo and Driessen 2002). Moreover, De Coster et al. (2005) suggested that instead of grouping symptoms into somatic and psychological symptoms, the different symptoms should be considered individually according to their sensitivity. Using discriminant analysis they found that "depressed mood" was the most sensitive symptom, but also that some somatic symptoms, such as "reduced appetite", "fatigue", and "psychomotor slowing" had high discriminative properties.

The few studies where both the time aspect and different symptoms were considered gave conflicting results. Gainotti et al. (1999) found that symptom profiles obtained from stroke patients with major depression were very similar at different time points after the stroke, but differed from those obtained from patients with endogenous major depression. Paradiso et al. (1997) found, that symptoms that characterize major depression after stroke appear to change during the first two years following stroke. Verdelho et al. (2004) studied patients who were rated as depressive on the basis of MADRS (Montgomery and Åsberg 1979) and found that time course of various symptoms differed.

Both the BDI and the HRSD were developed to measure the severity of depression primarily among psychiatric patients. The validity of these rating scales should be

studied when they are used for assessing depression of stroke patients. Somatic items are included in both scales, but with more emphasis in the HRSD. Self-rating scales require self-awareness of one's own mood states in addition to verbal abilities. A low response rate is a common problem when using self-rating scales, and among stroke patients this may be due to an inability more often than to an unwillingness to complete the form. In some earlier studies, both the BDI and the HRSD proved to be acceptable screening scales, but the specificity was too low to provide the basis for a diagnosis (House et al. 1989, Aben et al. 2002b, Lincoln et al. 2003).

In screening scales appropriate cutoff points are dependent on the sample, the sensitivity and the specificity needed. Aben et al. (2002) found that the optimum cutoff point for the BDI among stroke patients was a score of 10, a generally accepted score (Kendall et al. 1987). The study by House et al. (1989) is so far the only one in which the characteristics of the BDI with different cutoff points have been followed for up to 12 months. They found, that sensitivity and specificity may change over the elapse of time since the stroke. For instance, at 1 month post-stroke a cutoff point of 9 was the lowest at which the sensitivity exceeded 0.90, it had to be lowered to 7 to achieve the same sensitivity at 12 months post-stroke. Andersen et al. (1994) suggested raising the cutoff point of the HRSD score because of the somatic symptoms. More information on the discriminatory power of the depression assessment methods and the sensitivity and specificity of different symptoms over a longer follow-up period are needed. General validation studies do not reveal stroke-related and patient-related factors that influence the sensitivity and specificity of the assessment methods.

1.6.3 Use of nonverbal means to assess depression

When patients with aphasia are included in post-stroke depression studies, some kind of adaptation of conventional verbally-based methods of depression assessment is usually done. Most often informants are used to supplement the information obtained directly from the patients (Townend et al. 2007a). However, studies on the validity and reliability of using common verbal tools for the assessment of depression among aphasia patients are very rare (Laska et al. 2007), and the validity and reliability of these adaptations have not been established (Townend et al. 2007a).

The two main alternative means for the adaptation of conventional language based methods are the visual assessment methods and observational assessment by proxies or rehabilitation personnel. Visual analogue mood scales are based on schematic face emotion pictures joined by a line upon which patients are asked to indicate their mood by marking the most appropriate position on the line. Slightly different versions of visual analogue scales are reported in the literature (Stern and Bachman 1991, Stern 1997). Some studies have supported the use of these scales for stroke patients with impaired language function (Arruda et al. 1999, Stern et al. 1997, Bennett et al. 2006). However, validation studies with aphasic patients do not exist to the best of my knowledge.

Few studies have used nurses' or other rehabilitation personnels' observations and proxy ratings in the assessment of post-stroke depression. In studies by House et al. (1989) and Lightbody et al. (2007) nurses detected only about half of the patients with depression. More promising results were obtained in a study by Benaim et al. (2004) with the Aphasia Depression Rating Scale (ADRS), which they developed by deriving items of observable behaviour from existing depression scales. However, no other group has so far reported validity data on this assessment scale. Of separate items observed by nurses, crying and overt sadness at the acute phase (Carota et al. 2005) and agitation, restlessness or anxiousness (Lightbody et al. 2007) have been associated with depression.

Carers were reported to be valuable sources of information in the studies by House et al. (1989) and Lightbody et al. (2007). They could identify every or almost every patient with depression. Although the specificity was not high, the information from carers shows the potential to improve screening for depression. The major disadvantage was that there were so few carers available in these studies.

1.7 Depression among caregivers of stroke survivors

Caregivers of stroke survivors are required to cope with the stroke outcomes the survivor experiences and also with the sudden impact these have in their own lives. Considerable stress is experienced by many caregivers from the early post-stroke period (Bugge et al. 1999) to at least from 3 to 5 years after stroke (Greveson et al. 1991, Jones et al. 2000, Visser-Meily et al. 2008). Prolonged stress may result in exhaustion, a state

characterised by fatigue and a lack of energy (Appels 1997). Depressive symptoms are reported for between 11 and 51 per cent of caregivers (Wade et al. 1986, Carnwath and Johnson 1987, Anderson et al. 1995, Dennis et al. 1998, Kotila et al. 1998, Visser-Meily et al. 2008).

Depression in caregivers may be associated with several patient-related variables. Spouses or other caregivers of patients with severe stroke or high physical dependency were often more depressed than patients with milder impairments (Schulz et al. 1988, Kotila et al. 1998, Dennis et al. 1998, Chumbler et al. 2008). However, not all studies (Anderson et al. 1995, Smith et al. 2004, Visser-Meily et al. 2005) agree on these findings. The length of time elapsed since the stroke may explain this difference as the former studies were carried out from 3 to 9 months after stroke, and the latter about 1 year after stroke. This hypothesis is supported by the results of Wade et al. (1986), who found that caregiver depression was related to a patient's observed disability up to 1 year, but that this association was not apparent at 2 years. Patient depression was also found to be associated with caregiver depression 6 to 12 months after stroke (Wade et al. 1986, Dennis et al. 1998, Smith et al. 2004), but not at 2 years after stroke (Wade et al. 1986). The associations between patients' cognitive impairments and caregiver depression are not known. Some studies have found that a non-significant trend that a marked cognitive impairment or dementia is related to caregiver depression (Anderson et al. 1995, Visser-Meily et al. 2005). However cognitive abilities were assessed by only a single MMSE score. Dennis et al. (1998) failed to find significant associations between patients' dysphasia and visuospatial dysfunction and caregiver depression. In a study by Cameron et al. (2006) caregivers' depression was associated with patients' memory and comprehension problems rated by caregivers. However, to the best of my knowledge detailed studies of the impact of cognitive defects are missing. Patients' behavioural abnormalities may also increase caregiver depression (Anderson et al. 1995).

Of caregiver-related factors, the poorer physical health of the caregiver (Carnwath and Johnson 1987, Schulz et al. 1988, Hodgson et al. 1996, Grant et al. 2000, Chumbler et al. 2008), being female (van den Heuvel et al. 2001, Jönsson et al. 2005) and lack of social contacts or support (Carnwath and Johnson 1987, Smith et al. 2004) have been found to be associated with caregiver depression. Studies on the association between

caregiver's depression and caregiver's or patient's age give controversial results (van den Heuvel et al. 2001, Jönsson et al. 2004, Smith et al. 2004, Visser-Meily et al. 2008). The ability to respond to stress factors by the appropriate use of adaptive coping resources may alleviate the level of perceived stress and may be critical for the caregiver's well-being (Van den Heuvel et al. 2001, Visser-Meily et al. 2005, Chumbler et al. 2008).

Follow-up studies of caregiver depression are rare. Wade et al. (1986) and Schulz et al. (1988) found, that the severity of stroke is an important determinant of caregiver depression early after stroke but seems to become less important after some time has elapsed. In the study by Visser-Meily et al. (2008), the percentage of spouses with depressive symptoms remained stable from 1 to 3 years post-stroke. More studies on the changes occurring in caregiver depression and the factors associated with it are needed.

2 Aims of the study

The aims of the present study were:

1. To investigate which factors, including cognitive impairment, are associated with depressive symptoms at acute phase after having a stroke.

2. To investigate the course of post-stroke depression during an 18-month follow-up and to find out which factors are associated with and can be used to predict post-stroke depression at different time points after the stroke.

3. To compare the performance of the BDI, HRSD, visual analogue mood scale, proxy assessment, clinical global impression of nursing and study personnel, together with DSM-III-R –diagnosis in the assessment of depression after stroke by studying the feasibility of using these approaches, their accuracy in detection of depression, and factors related to the differences found at different stages after the stroke.

4. To assess the prevalence of depression and exhaustion among caregivers of stroke survivors during the 18-month recovery process and to determine, which patient- and stroke-related factors are associated with and can be used to predict caregiver depression and exhaustion.

3 Methods

3.1 Subjects

The present study included 100 consecutive patients who had had their first ischaemic stroke and who were admitted to the Department of Neurology, Helsinki University Central Hospital. Patients over 70 years of age and those with known histories of alcohol abuse, dementia, psychosis, current antidepressant treatment, or severe concomitant disease and confused patients who were unable to co-operate were excluded. Clinical diagnosis was confirmed by computed tomography and/or magnetic resonance imaging. The present study was a part of a larger project including a clinical drug study trial (Palomäki et al. 1999). Randomly selected patients were treated with mianserin or a placebo for up to 12 months. There was no difference in the prevalence of depression at any time point between the treatment groups. Thus all the patients were included in the present study.

For studies III and IV a person providing the closest contact with the patient was identified in 98 of the cases. We referred to this person as the caregiver, regardless of the level of handicap or the independence of the stroke patient. A total of 69 of the caregivers were spouses; in 17 cases the next of kin was a child of the patient, in six cases a sibling, five were friends or other relatives and one was a neighbour.

The study protocol was approved by the ethics committee of the Department of Neurology, University of Helsinki. Informed consent was obtained from the patients and/or the caregivers.

3.2 Procedure

Patients were studied at the acute phase after stroke (studies I-IV) and at 2, 6, 12, and 18 months after stroke (studies II, III and IV). The caregivers were interviewed at the acute phase and at 6 and 18 months after the stroke (studies III and IV). Patient depression assessment, neurological examination and functional outcome measures were completed at each time point. Neuropsychological examination was performed at the acute phase, and at 6 and 12 months. Aphasia battery was given at the acute phase, and at 6, 12, and 18 months after stroke.

3.3 Measurements

Major depression, dysthymic depression and adjustment disorder were diagnosed according to the DSM-III-R criteria (American Psychiatric Association 1987) by a neurologist. The patients completed a self-rating BDI scale (Beck et al. 1961), and were assisted in this task when needed. In the BDI, a score of 10 points was the threshold for mild depression (Kendall et al. 1987, Aben et al. 2002b). The HRSD (Hamilton 1960) was used as an observer-rated scale by a neuropsychologist. The patients were presented with a single item VAMS (Stern and Bachman 1991, Arruda et al. 1999), comprising a 100-mm continuous vertical line that connected two schematic faces, a happy face positioned at the top pole and a sad face at the bottom with the corresponding word. Patients were asked to assess their mood by placing a mark at an appropriate point on the line. The VAMS score was used as a continuous variable, but when categorical dichotomous choice was needed, patients who marked the line closer to the negative endpoint ($\geq$ 50 mm), were considered as depressed and vice versa. A neurologist, a neuropsychologist, and a study nurse rated patients according to the Clinical Global Impression (CGI) (Guy 1976). The mean of these CGI ratings was used in further analyses. At the acute phase, a ward nurse whose charge was caring for the particular patient rated that patient according to the CGI during routine clinical work. At six months and at 18 months, the caregivers were asked to assess patients' moods by completing the BDI scale.

In studies I and II, the BDI score was the main dependent variable. In study III, we compared all the assessment methods with each other and used the DSM-III-diagnosis as the reference. In study IV, caregiver depression was assessed using the BDI scale and also exhaustion on the basis of an interview.

Stroke severity was measured according to the Scandinavian Stroke Scale (SSS) (Scandinavian Stroke Study Group 1985). ADL was assessed by using Barthel Index (BI) (Mahoney 1965) and the Rankin Scale (Rankin 1957). Cognitive functions were assessed using the comprehensive neuropsychological battery including 8 subtests of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler 1955), the Wechsler Memory Scale – Revised (WMS-R) (Wechsler 1987), the Western Aphasia Battery (WAB) (Kertez 1982), and Albert's test for neglect (Albert 1973). Motor functions were

assessed by using the finger tapping task and Luria's hand sequencing, hand posture and reciprocal co-ordination tasks (Christensen 1979).

3.4 Statistical analyses

Studies I, II, and IV

Descriptive statistics were used to summarize data. In Study I, factor analysis was computed to reduce the number of cognitive test variables. When comparing patient groups, a chi-square test or the Fisher's exact test were used to analyse nominal variables. Student's t-tests, Mann-Whitney U test, and one-way or two-way analysis of variance (ANOVA) were used to analyse continuous variables. Pearson correlations and Spearman correlations were calculated to measure bivariate associations between variables. Multivariate linear regression analyses were used to identify factors independently associated with patient depression (Studies I-II) and caregiver depression (Study IV). A logistic regression analysis was used to identify factors associated with caregiver exhaustion (Study IV).

Study III

Response rates of each depression assessment method were calculated, and the percentages of depressed patients obtained for the different criteria were compared. The discriminatory power, sensitivity, and specificity of the scales were calculated with the DSM-III-R being used as the reference. To assess different cutoff points, receiver operating characteristic (ROC) curves were obtained, and the area under the curve was calculated. The internal consistencies of the BDI and HRSD were measured using Cronbach's alpha. The contribution of individual depression symptoms to the diagnosis of post-stroke depression was assessed by using discriminant analyses. Scores for each of the BDI items were assessed according to major depression (DSM-III-R) as the principal classification criterion, followed by other depression criteria used in the respective study. One-way ANOVA was used to compare different symptoms between various patient groups. Spearman correlations, multiple linear regression analyses, and logistic regression analyses were used to model some associations.

A value of $p < 0.05$ was considered significant in all studies. The data were analysed by using the BMDP (Dixon et al. 1990) (Studies I-II) and SPSS (SPSS 2000) (Studies II-IV) statistical packages.

4 Results

4.1 Characteristics of the patients

The group consisted of 68 men and 32 women, aged from 27 to 70 years (mean 55.2, SD 10.6). Of the patients, 38 had a right hemisphere infarct, 42 a left hemisphere infarct and 20 an infarct in the brain stem region or cerebellum. All of the 100 patients at acute phase, continued in the study at 2 months. The corresponding values at the other time points were 96 at 6 months, 93 at 12 months, and 92 at 18 months. At the acute phase the mean SSS score was 43.7 (SD 11.6) and the mean BI score 14.4 (SD 4.5). Of all the patients, 83 per cent needed at least some help in ADL functions (BI score < 20) and 31 per cent had aphasia (WAB aphasia quotient (AQ) $\leq$ 93.7). At the follow-up at 18 months, the mean SSS score was 51.4 (SD 7.3) and the mean BI score 19.1 (SD 2.2.), and 28.6 per cent of patients needed at least some help in ADL functions. Seventy-seven patients lived with a spouse, a relative, or a friend, and the remaining 23 lived alone.

4.2 Depression and its associated factors at the acute phase (Study I)

Five patients fulfilled the criteria for major depression: one patient had a right hemisphere lesion, two had a hemisphere lesion and two had a brainstem lesion. They did not differ significantly from those patients without major depression in stroke severity or background factors. Because so few patients had major depression, the use of advanced statistical analyses to find any associates was not appropriate. Of those 89 patients who could complete the BDI scale, 27 per cent were at least mildly depressed (BDI $\geq$ 10).

The location of the lesion had no significant effect on the BDI and HRSD scores as analysed by one-way ANOVA. Mean scores on the BDI and HRSD of the patients are presented by site of the lesion in Table 2.

Table 2. Beck Depression Inventory (BDI) and Hamilton Rating Scale for Depression (HRSD) mean scores and standard deviations by lesion locations, and percentages of patients with at least mild depression (BDI≥10). The numbers of patients in parentheses.

	All	Right hemisphere	Left hemisphere	Brain stem
BDI	8.4 ± 7.2 (89)	7.3 ± 5.7 (37)	9.7 ± 8.9 (32)	8.4 ± 6.5 (20)
HRSD	5.0 ± 3.8 (90)	4.6 ± 3.3 (37)	5.0 ± 3.8 (34)	5.7 ± 4.8 (20)
BDI≥10	27%	16%	34%	35%

The severity of neurological impairment (SSS) correlated significantly with the BDI (Spearman $r = -0.21$, $p < 0.05$): the severer the neurological impairment the worse were the symptoms for depression. With cutoff point of 38 (the first quartile) for the SSS, a two-way (2 x 3) ANOVA revealed a statistically non-significant trend for interaction between stroke severity and lesion site ($F = 3.0$, $p = 0.06$; Table 3). Among patients with lesions in the left hemisphere or in the brainstem/cerebellum, the severity of neurological impairment was associated with the severity of depression (BDI). In contrast, among those who had lesions in the right hemisphere, this relationship was inverse. A low statistically non-significant correlation was found between difficulties in ADL measured by the BI and depression (BDI) ($r = -0.18$, $p = 0.08$).

Table 3. Two-way analysis of variance for the effect of stroke severity (cutoff point of Scandinavian Stroke Scale (SSS) ≤ 38) and lesion location on the Beck Depression Inventory (BDI) score. Means and standard deviations, with the numbers of patients in parentheses.

	Severe disability	Mild disability
Right hemisphere	5.3 ± 3.2 (9)	8.0 ± 6.2 (28)
Left hemisphere	15.3 ± 11.6 (4)	9.0 ± 8.5 (28)
Brain stem	16.5 ± 5.0 (2)	7.5 ± 6.1 (18)

Location of lesion: F=3.57, p=0.03; severity of disability: F=3.27, p=0.07; interaction: F=3.00, p=0.06

The associations between demographic factors and the prevalence of depression are presented in Table 4. Of the patients older than 55 years (mean), 39 per cent were depressed compared with only 11 per cent of the younger patients. There was also a significant correlation between age and the BDI scores (Spearman $r = 0.24$, $p < 0.05$),

which still remained when the effect of stroke severity was removed (partial correlation $r = 0.27$, $p < 0.05$). Patients living alone and those with higher education had higher BDI scores, but these trends were not significant. Sex or marital status showed no association with the prevalence of depression.

Table 4. Prevalence of depression (with cutoff point at Beck Depression Inventory ≥ 10) according to demographic factors. Numbers of patients in parentheses.

	Prevalence of depression (%)	χ^2	p-value
Age			
55 or less (38)	11	9.1	<0.01
Over 55 (51)	39		
Sex			
Male (62)	24	0.8	ns
Female (27)	33		
Education			
8 years or less (46)	20	2.5	0.10
More than 8 (43)	34		
Living			
Alone (18)	44	3.5	0.06
With someone (71)	23		
Marital status			
Married (60)	27	0.01	ns
Not married (29)	28		

ns = nonsignificant

Principal-component varimax-rotated factor analyses were conducted on the WAIS scores, WMS subtests and praxis tasks. The three-factor solution, which accounted for a total of 75 per cent of the variance was selected. Factors were labelled verbal abilities (eigenvalue 5.9), visual abilities (eigenvalue 5.3) and practical abilities (eigenvalue 1.6). A linear regression analysis was computed using the BDI score as the dependent variable. Verbal abilities, visual abilities, practical abilities, the differences between right and left hand tapping score and age were chosen as independent factors. A significant model emerged [$F(5,81) = 3.23$, $p < 0.05$], that could predict 17 per cent of the BDI variance. Advanced age of patient ($\beta = 0.26$, $p < 0.05$) and poor verbal abilities ($\beta = -0.23$, $p < 0.05$) were associated with high BDI scores. The prevalence of

depression was not significantly higher among aphasic patients than non-aphasic patients (30% vs. 26%). Similarly the mean BDI scores of aphasic and non-aphasic patients did not differ significantly.

4.3 Prevalence and duration of depressive symptoms during an 18-month follow-up after stroke (Study II)

The prevalence of depressive symptoms measured by the BDI scores showed little or no change during the 18-month follow-up (Table 5). The number of patients with major depression increased from 6 per cent at acute phase to 16 per cent at 18 months. A total of 54 per cent of patients scored 10 points or more on the BDI scale at least once during the follow-up. In comparison, the proportion was 26 per cent for major depression.

Table 5. Percentages of patients with mild depression in the Beck Depression Inventory (BDI), and mean BDI scores with standard deviations (SD) at different time points after stroke.

	Prevalence of depression (%) BDI $\geq$ 10	Mean BDI $\pm$ SD
Acute phase	27	8.5 $\pm$ 7.2
2 months	29	7.2 $\pm$ 6.3
6 months	23	6.8 $\pm$ 5.9
12 months	24	7.0 $\pm$ 6.8
18 months	26	7.0 $\pm$ 6.4

Depressive symptoms usually had an early onset after stroke and often persisted. Of those patients who were found to be at least mildly depressed (BDI $\geq$ 10) in the acute phase or at two months, 46 per cent continued to be depressed at 12 and/or 18 months. Of male patients the corresponding rate was 54 per cent, and of female patients 27 per cent. Of those who were depressed at six months, 67 per cent remained depressed at 12 and/or 18 months. Most of those who did not score above the cutoff point at the acute phase or at two months were not depressed at later times. Only 12 per cent (5 patients) of all those patients who were found to be depressed (BDI > 10) at least once during the

follow-up scored above the cutoff point for the first time between 12 and 18 months. All of them were men.

4.4 Associated factors of depressive symptoms at different time points (Study II)

The associated factors of longitudinal change of depressive symptoms during the follow-up are reported next. These are followed by the associated factors for depressive symptoms at different time points. After these the acute predictors of later depression are presented.

4.4.1 Associates of change in depressive symptoms

A linear regression analysis was performed to determine the associated factors of change in depressive symptoms covering the period from the acute phase to 18 months. When the change in the BDI was a dependent variable and age, sex, living alone, SSS, and BI at acute phase were selected as independent variables a significant model emerged [$F(5,75) = 3.74$, $p < 0.01$]. It accounted for 15 per cent of the variance of the change that occurred from the acute phase to 18 months. Male gender ($p < 0.01$) and better initial ADL at the acute phase ($p < 0.05$) were significantly associated factors of a poorer outcome. No new associated factors were revealed, when the SSS and BI change scores were used instead of the acute phase scores, or when the most representative cognitive scores or their change during the follow-up were included in the analyses.

The effect of lesion site on the BDI changes was not significant throughout the follow-up. However, the change in the HRSD score from the acute phase to two months was significantly affected by the location of the lesion [ANOVA $F(2,88) = 4.24$, $p < 0.02$]; only the scores of brain stem lesion patients declined over time (Figure 1).

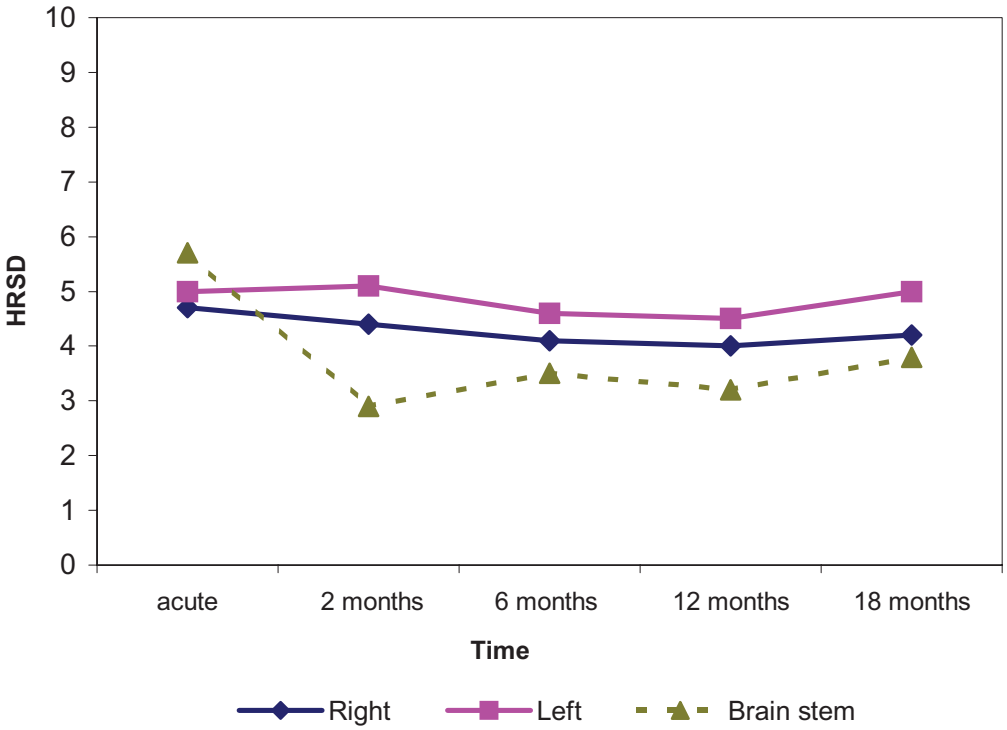

Figure 1. Hamilton Rating Scale for Depression (HRSD) scores for patients with lesions in one of three different locations during the 18-month follow-up period.

4.4.2 Associated variables of depressive symptoms at different time points

The significant associations between background and stroke related variables and the BDI at different time points are presented in Table 6. Of the background factors, age correlated with the BDI from the acute phase to six months, and male sex was associated with the BDI at 18 months. In all, 34 per cent of men versus only 8 per cent of women scored 10 points or more on the BDI scale at 18 months, (Pearson $\chi^2 = 6.5$, $p < 0.05$). Living alone and location of lesion were not associated with the BDI (ANOVA). Stroke severity (SSS) and functional impairment (BI) indices associated with the BDI from six months onward. Because the BI correlated strongly with the SSS, it was not included in further analysis. Depressed patients performed slightly more poorly in the neuropsychological tests. The correlations between the BDI and neuropsychological tests were mostly non-significant during the first 2 months after stroke. Nevertheless, at later time points several significant correlations were recorded. For further analyses only 3 representative tests we chosen: logical memory, block

design and right-hand tapping. Aphasic patients had no significantly higher BDI scores than non-aphasic patients at any phase of the follow-up.

Linear regression analyses were then performed to determine the strength of associations with those variables found to have significant correlations with the BDI scores used as the dependent variables. Age, sex, SSS, right-hand tapping and logical memory at each time points were independent variables. The results are presented in Table 6. The model accounted for 11 per cent of the variance at acute phase, but was not significant at two months. At six months and at 12 months, SSS was significant, and the model accounted for 9 and 20 per cent of the variance, respectively. At 18 months the male sex variable remained significant and the model accounted for 14 per cent of the variance. We verified the importance of medication by also including it in with independent variables in linear regression analyses. Medication had no significant effect at any time point throughout the 18 month study period.

Table 6. Associated factors of depression (BDI scores) at different time points after stroke: correlation coefficients (r) and beta values (β) of linear regression analyses.

	Acute		2 months		6 months		12 months		18 months	
	r	β	r	β	r	β	r	β	r	β
Age	0.27 *		0.24 *		0.18 *					
SSS					-0.30 **	-0.32 *	-0.47 **	-0.38 **	-0.23 *	
Sex (men)									0.30 **	0.32 **
Tapping, right	-0.34 **	-0.26 *	-0.25 *				-0.32 **			
Logical memory					-0.18 *		-0.31 **		-0.24 *	
Model	F(5,83) = 3.12		F(5,86) = 2.18		F(5,82) = 2.62		F(5,81) = 5.27		F(5,79) = 3.75	
p	0.05		ns		< 0.05		< 0.001		< 0.01	
Adjusted R^2	0.11		0.06		0.09		0.20		0.14	

BDI = Beck Depression Inventory, SSS = Scandinavian Stroke Scale.
ns = nonsignificant, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

4.4.3 Acute predictors of later depression

A series of linear regression analyses were performed to determine the acute predictors of later depression. With the same independent variables as used above (4.4.2), no significant model emerged to predict depression at six months. The models were significant at 12 months [$F(5,82) = 3.06$, $p < 0.05$] and at 18 months ([$F(5,79) = 3.19$, $p < 0.05$], and accounted 11-12 per cent of the variance. Initial SSS and male sex were the only significant predictors, respectively. When we added acute BDI to the predictors, the model accounted for 35 per cent of the variance at 12 months [$F(6,76) = 8.31$, $p < 0.001$] and acute BDI remained the only significant predictor. At 18 months, the model [$F(6,74) = 10.79$, $p < 0.001$] accounted for 42 per cent, and acute BDI and the male sex variable were significant predictors.

4.5 Differences in methods used in the assessment of post-stroke depression (Study III)

4.5.1 Response rates

Approximately 90 per cent of the patients included in the study could be assessed by the DSM-III-R, BDI, and HRSD at the acute phase (Table 7). The CGI achieved the highest feasibility level and the VAMS the lowest. After the acute phase, the feasibility rates of these assessment methods varied from 92 per cent to 100 per cent.

Table 7. Feasibility of various assessment instruments. Percentages of patients who could be assessed with each assessment method out of all patients participating at each time point.

	DSM-III-R	BDI	HRSD	VAMS	Caregiver BDI	CGI/ psne	CGI nurse
Acute	90	89	91	87		97	100
2 months	93	92	94	96		99	
6 months	95	94	95	99	89	100	
12 months	96	95	95	98		100	
18 months	96	92	93	99	86	100	

DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, 3rd edition - revised, BDI = Beck Depression Inventory, HRSD = Hamilton Rating Scale for Depression, VAMS = Visual Analogue Mood Scale, CGI = Clinical Global Impression, psne = by both psychologist and neurologist.

4.5.2 Prevalence of depression

The prevalence of depression during the follow-up according to the various assessment methods and with their different cutoff points are presented in Table 8. The DSM-III-R-based diagnoses produced the lowest prevalence rates: 6 to 16 per cent of patients had major depression. When a cutoff point of 10 in the BDI was used as the criterion, depression was found in 23-29 per cent of patients, and when the same cutoff point was used in the HRSD, the corresponding percentages were 10-14 per cent. According to the CGI ratings given by study personnel, between 22 and 27 per cent of patients were at least mildly depressed. The CGIs of the three raters, a neurologist, a neuropsychologist and a study nurse, correlated significantly with each other (Spearman $r = 0.6$ to 0.87, $p < 0.01$) during the whole follow-up. The highest prevalence rates were given by the respective ward nurse with CGI and by the patients' proxies with the BDI. Approximately half of the patients were found to be at least mildly depressed with these criteria.

Table 8. Prevalence of depression expressed as percentages according to various assessment instruments with different cutoff points.

	DSM-III-R		BDI	BDI	BDI	HRSD	HRSD	HRSD	VAMS	Caregiver		CGImean	CGInurse
	Major	Minor+	≥ 7	≥ 10	≥ 14	≥ 7	≥ 10	≥ 12	≥ 50 mm	BDI ≥ 10	≥ 14	≥ mild	≥ mild
Acute	6	11	56	27	16	31	11	7	26			27	49
2 mo	8	12	45	29	13	25	14	6	16			22	
6 mo	9	13	40	23	11	21	10	3	16	46	36	25	
12 mo	11	11	40	24	16	23	13	6	9			23	
18 mo	16	17	45	26	13	22	13	12	20	51	33	26	

The numbers are percentages of depressed patients of the total available at each time point. Major indicates major depression and Minor+ indicates major depression, dysthymic depression or adjustment disorder.

4.5.3 Discriminatory power of the methods with DSM-III-R as the reference

The percentages for correct classifications, sensitivity, specificity, and area under the curve (AUC) of each assessment method are presented in Table 9. The CGI ratings of the study personnel had a sensitivity of 0.80 and a specificity of 0.79 at the acute phase, and even higher (0.82-1.00) during the follow-up. Although the BDI (with a cutoff point of 10) appeared to be more sensitive (0.71-1.00) than the HRSD, the HRSD (with a cutoff point of 10) showed a higher degree of specificity (0.92-0.94). The BDI had its highest sensitivity and specificity at 12 months, and did not miss any patients with a diagnosis of major depression. The HRSD showed its highest sensitivity and specificity at two months, after which its sensitivity became poor.

The sensitivity and specificity of the BDI assessment by caregivers were poor. The respective ward nurse detected 80 per cent of depressive patients, but the specificity was only 54 per cent. The VAMS was not sensitive to depression, and the AUC of the VAMS was significant only at 18 months. The ROC of the VAMS was not analyzed in the acute phase because the VAMS was recorded only by 42 patients for technical reasons. The VAMS proved not to be a satisfactory method for assessing post-stroke depression.

4.5.4 Discriminatory attributes of the symptoms

The internal consistencies of the BDI and HRSD were good at every time point and gave Cronbach alpha values of 0.82 to 0.86 and 0.70 to 0.84, respectively. The BDI and HRSD correlated significantly during the follow-up (Spearman $r = 0.63$ to 0.71, $p < 0.001$).

When the BDI was divided into cognitive-affective items (1-14) and somatic items (15-21) (Cavanaugh et al. 1983), the internal consistency remained good in the affective subscale (0.85 to 0.91), but not in the somatic subscale (0.37 to 0.56). Somatic symptoms were more common among patients older than 55 years than in younger patients at the acute phase (4.9 versus 3.0, $p < 0.01$) and at two months (4.2 versus 2.9, $p < 0.01$). The scores in the cognitive-affective and somatic subscales tended to be slightly higher among those patients with lower than those with higher SSS values, though none of these differences were significant. The scores for these subscales were

Table 9. The accuracy of the various assessment methods in detecting patients with major depression diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition – revised (DSM-III-R): the percentages of correct classifications, sensitivity and specificity with different cutoff points, and areas under the curve in receiver operating characteristic curves (AUC/ROC).

Acute phase	Classification %	Sensitivity %	Specificity %	AUC/ROC
BDI ≥ 7	49	100	46	
BDI ≥ 10	76	80	76	0.88**
BDI ≥ 14	88	80	88	
HRSD ≥ 7	73	80	73	
HRSD ≥ 10	92	80	93	0.93**
HRSD ≥ 12	94	60	96	
CGI mean mild	79	80	79	0.93**
CGI nurse mild	56	80	54	0.77*
2 months				
BDI ≥ 7	63	100	60	
BDI ≥ 10	78	100	76	0.86**
BDI ≥ 14	86	43	89	
HRSD ≥ 7	84	100	82	
HRSD ≥ 10	95	100	94	0.99***
HRSD ≥ 12	97	71	99	
VAMS ≥ 50	80	20	84	ns
CGI mean mild	85	100	84	0.98***
6 months				
BDI ≥ 7	69	100	66	
BDI ≥ 10	82	71	83	0.88**
BDI ≥ 14	87	29	93	
HRSD ≥ 7	81	63	83	
HRSD ≥ 10	90	50	94	0.89***
HRSD ≥ 12	92	25	99	
VAMS ≥ 50	83	40	89	ns
CGI mean mild	85	100	82	0.98***
Caregiver				
≥ 10	54	42	55	ns
≥ 14	60	29	63	

	Classification %	Sensitivity %	Specificity %	AUC/ROC
12 months				
BDI ≥ 7	71	100	68	
BDI ≥ 10	87	100	86	0.93***
BDI ≥ 14	88	63	91	
HRSD ≥ 7	85	88	85	
HRSD ≥ 10	90	63	92	0.94***
HRSD ≥ 12	92	38	97	
VAMS ≥ 50	79	0	93	ns
CGI mean mild	88	100	86	0.98***
18 months				
BDI ≥ 7	69	100	64	
BDI ≥ 10	83	83	84	0.89***
BDI ≥ 14	88	50	93	
HRSD ≥ 7	88	85	89	
HRSD ≥ 10	88	54	94	0.95***
HRSD ≥ 12	89	54	96	
VAMS ≥ 50	83	60	87	0.85***
CGI mean mild	87	93	86	0.96***
Caregiver				
≥ 10	57	78	55	ns
≥ 14	67	44	70	

BDI = Beck Depression Inventory, HRSD = Hamilton Rating Scale for Depression, VAMS = Visual Analogue Mood Scale, CGI = Clinical Global Impression,'mean mild' indicating study personnels' mean CGI rating mild or greater than mild, and 'nurse mild' indicating nurse's rating mild or greater than mild. Caregiver indicates caregivers' BDI rating of the patient's depression. ns = nonsignificant * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

also similar in patients of the three infarct location groups (left hemisphere, right hemisphere, brain stem). At 18 months, men had higher scores than women both for the cognitive-affective and somatic subscales.

The discriminatory capacity of discrete depression symptoms of the BDI was assessed using discriminant models for major depression (DSM-III-R), BDI (cutoff point of 10), CGI (mild or more severe), nurse CGI, caregiver BDI, and VAMS (cutoff point of 50 mm) as the classification criteria. The significant results of analyses for

Table 10. Structure matrix of the items of the Beck Depression Inventory (BDI) in discriminant analyses at the acute phase, 6 months, and 18 months after stroke. Discriminant loadings with major depression, BDI score 10 or more, Clinical Global Impression (CGI) of study personnel and CGI of nurse (mild depression or more severe) as discriminant criteria. Loadings over 0.30 in bold.

	Major depression			BDI ≥ 10			CGI mild			nurse
	0	6	18	0	6	18	0	6	18	0
1. Sadness	0.27	**0.47**	**0.46**	0.24	**0.33**	**0.55**	**0.53**	**0.38**	**0.74**	0.19
2. Discouraged about the future	**0.36**	0.27	**0.49**	**0.41**	0.27	**0.42**	**0.47**	0.29	**0.37**	0.21
3. Feeling like a failure	**0.46**	**0.34**	**0.35**	**0.35**	0.26	0.29	**0.37**	**0.37**	**0.32**	0.03
4. Dissatisfaction	0.18	**0.48**	**0.42**	**0.40**	**0.54**	**0.49**	**0.44**	**0.58**	**0.58**	0.05
5. Feeling guilty	**0.33**	0.21	0.21	**0.35**	0.15	0.16	**0.38**	0.25	0.16	0.02
6. Feeling punished	0.11	**0.33**	0.14	**0.33**	0.18	0.19	**0.35**	0.17	0.19	0.18
7. Feeling disappointed in myself	0.22	0.05	**0.35**	0.26	0.08	**0.40**	**0.39**	0.25	**0.40**	0.05
8. Feeling critical of myself	0.12	**0.40**	0.28	0.29	0.24	0.26	0.20	0.22	0.23	0.17
9. Suicidal ideation	**0.34**	**0.44**	**0.47**	0.20	0.11	0.23	**0.41**	0.11	**0.41**	0.21
10. Crying	0.25	0.02	0.25	0.14	0.21	0.22	**0.56**	**0.44**	0.25	0.27
11. Irritability	0.07	**0.32**	**0.38**	0.15	0.29	0.23	0.16	0.23	**0.56**	0.05
12. Loss of interest in people	0.16	**0.46**	**0.40**	0.23	0.19	**0.36**	**0.50**	0.21	**0.35**	**0.37**
13. Difficulty with decisions	0.28	**0.39**	**0.42**	0.23	0.29	**0.41**	0.20	0.29	**0.45**	0.17
14. Looking unattractive	**0.34**	0.29	**0.43**	**0.39**	0.25	**0.33**	**0.37**	0.28	0.23	0.25
15. Work inhibition	0.18	**0.41**	0.16	**0.32**	0.21	**0.32**	**0.32**	**0.34**	**0.30**	0.19
16. Sleep disturbance	0.19	-0.14	**0.47**	**0.37**	0.24	0.19	0.20	0.09	**0.38**	-0.02
17. Fatigue	0.25	0.10	**0.38**	0.28	0.19	0.26	0.22	**0.45**	**0.40**	0.29
18. Poor apetite	**0.48**	**0.30**	0.08	0.12	0.15	0.23	0.14	0.17	0.25	**0.33**
19. Weight loss	0.06	-0.03	-0.07	0.04	0.09	0.11	0.03	-0.04	0.06	0.07
20. Worried about health	0.03	0.15	**0.34**	0.24	0.20	0.17	0.00	**0.30**	0.17	0.00
21. Decreased interest in sex	0.17	0.20	**0.37**	**0.30**	0.13	0.17	0.22	0.13	0.25	0.19
	***	***	**	***	***	***	**	***	**	**

*** = $p < 0.001$, ** = $p < 0.01$.

DSM, BDI, CGI and nurse CGI are presented in Table 10. The models were not significant for the VAMS and caregiver BDI. At acute phase, the most important common discriminators for depression according to DSM-III-R (major depression), BDI and CGI criteria were being discouraged about the future, feeling like a failure, feeling guilty, and looking unattractive. In addition to these, almost all cognitive-affective items were important discriminators for depression according to the CGI scale with the highest correlation coefficient for crying, which was not associated with major depression or with the BDI criteria. At 18 months, the most accurate common discriminators for depression according to the same three criteria were sadness, being discouraged about the future, dissatisfaction, feeling disappointed, loss of interest in people, and difficulty with making decisions. In addition to these, suicidal ideation, sleep disturbance and fatigue had good discriminatory capacity for major depression and CGI, but not for the BDI.

4.5.5 Caregiver ratings

The caregivers rated their respective patients' depressive symptoms using the BDI at approximately 4 points higher than did the patients themselves [11.2 (sd 8.5) versus 6.6 (sd 5.5.) at six months; 10.8 (sd 8.0) versus 6.9 (sd 6.6) at 18 months; $p < 0.001$]. In addition, there was a significant correlation between the caregivers' ratings of their patients and caregivers' own BDI scores (0.60 to 0.61, $p < 0.001$). That correlation was even higher than the correlation between the caregivers' ratings of their patients and patients' own BDI ratings (0.37, $p < 0.005$ to 0.43, $p < 0.001$). Stroke severity, location of lesion, patients' or caregivers' gender or spousal relationship did not account for the disagreement.

We then analysed if the caregiver BDI scores also accounted for the discrepancies between caregivers' and researchers' ratings of patient depression. Patients who scored 10 or more in caregivers' BDI but were not depressed according to researchers' CGI, were compared with those patients who were rated as depressed by researchers but not by the caregivers. The caregivers' own BDI scores were higher in the first group ($n = 28$) than in the latter group ($n = 10$) at 6 months (12.1. versus 3.1, $t = 5.3$, $p < 0.001$) and at 18 months (10.1 versus 3.4, $t = 3.7$, $p < 0.05$). Patients' own BDI or stroke severity did not account for the discrepancy.

4.5.6 Visual analogue mood scale

The VAMS did not correlate significantly with the BDI until at 18 months follow-up (Spearman $r = 0.52$, $p < 0.001$). The correlations remained low and nonsignificant up to 18 months in both the subgroups of patients with aphasia and without aphasia, and thereafter the correlation reached significance only among patients without aphasia ($r = 0.61$, $p < 0.001$). In the subgroup of patients with an Albert test score < 40 indicating neglect or other inattention disorder, the correlations were negative and nonsignificant during the first year after stroke and did not reach significance at 18 months. On the other hand, significant correlations were attained at the acute phase ($r = 0.45$, $p < 0.01$), at 6 months ($r = 0.35$, $p < 0.05$), and at 18 months ($r = 0.49$, $p < 0.001$) among patients with normal test results. Nonetheless, we have to treat these results with caution, because only a maximum of 20 patients with aphasia were compared with 53 patients without aphasia and a maximum of 12 patients with an Albert test score < 40 were compared with 59 patients with normal test results.

4.6 Depression among caregivers of stroke survivors (Study IV)

4.6.1. Prevalence of depression among caregivers

During the follow-up, from 30 to 33 per cent of caregivers were defined as depressed (BDI $\geq$ 10). The rates for all caregivers, spouses, and other non-spousal caregivers separately are presented in Table 11. Only 2 per cent of the caregivers scored 20 points or more (at least moderate depression) at the acute phase, 6 per cent at 6 months, and 9 per cent at 18 months. The mean BDI scores for spouses were significantly higher than those of other caregivers (7.6 versus 5.2 at the acute stage, 7.9 versus 4.3 at 6 months, and 7.6 versus 4.6 at 18 months, for spouses and non-spouses respectively; $p < 0.05$ at all stages).

Table 11. Prevalence of depression in percentages (the Beck Depression Inventory score ≥ 10) among spouses and other caregivers

	All caregivers	Spouses	Other
Acute	33	38	19
6 month	30	34	21
18 months	30	33	23

4.6.2 Acute-stage predictors of caregiver depression

The correlations between caregiver BDI at different time points after stroke and patient age, sex, acute-phase stroke-related variables and acute-phase caregiver BDI are presented in Table 12. Stroke severity (SSS), functional disability (BI), and poor right-hand tapping correlated significantly with caregiver BDI scores at acute phase. Caregivers of male patients had more depressive symptoms than those of female patients. Thereafter at 6 months and at 18 months depression in caregivers had a strong association with the their depression (BDI scores) at acute phase. The acute phase BI and male sex of the patient continued to be associated with later depression in caregivers. At 18 months patients' advanced age and poor acute-phase left-hand tapping gave also significant correlations with caregiver BDI scores. Neuropsychological test scores in the acute phase did not correlate with caregiver BDI, nor was depression of caregivers found to be associated with lesion location (left hemisphere, right hemisphere, or brain stem) by ANOVA.

Table 12. Correlations between acute-phase factors and caregiver depression, measured by the Beck Depression Inventory (BDI) score, at different time points

	Caregiver BDI		
	Acute	6 months	18 months
Patient age	ns	ns	0.23 *
Patient sex	male *	male *	male **
SSS	-0.28 **	ns	ns
BI	-0.30 **	-0.29 **	-0.26 *
Tapping, right	-0.21 *	ns	ns
Tapping, left	ns	ns	-0.23 *
Patient BDI	ns	ns	ns
Caregiver BDI		0.65 ***	0.63 ***

SSS = Scandinavian Stroke Scale, BI = Barthel Index. Only variables with significant correlations are included. ns = nonsignificant, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

A series of linear regression analyses was computed to identify the independent contribution of correlating variables to the overall caregiver BDI score. First, the caregiver BDI at the acute phase was the dependent variable, and patient age, sex, stroke severity (SSS), and patient BDI were the independent variables. The BI was not included because of its strong correlation with stroke severity. Stroke severity and the age of the patient were the significant associated factors for depression in caregivers ($F = 5.7$, $p < 0.001$, adjusted $R^2 = 18\%$; Table 13).

Regression analyses were then performed to determine whether the acute phase variables (patient age, sex, SSS, and caregiver BDI) could predict later caregiver depression. The model was highly significant ($p < 0.001$), accounting for 41 per cent of the variance at six months and 41 per cent at 18 months. The only independent predictor was caregiver BDI scores at acute phase ($\beta = 0.61$, $p < 0.001$; $\beta = 0.60$, $p < 0.001$, respectively; Table 13).

Both the univariate analyses and the series of linear regression analyses were then repeated with only spouses included. The correlation results are presented in Table 14. At acute phase we chose a linear regression model with three predictors: patient age, patient sex and stroke severity. At acute phase, the model ($p < 0.001$) accounted for 21 per cent of the variance. Stroke severity and patient age were significant independent associated factors for spouses' depression.

Table 13. Acute-stage predictors of caregiver depression, measured by the Beck Depression Inventory (BDI) score, as determined by linear regression analyses.

	Acute		6 months		18 months	
	β	p	β	p	β	p
Patient age	0.22	*	ns		ns	
Male patient	ns		ns		ns	
SSS	-0.32	**	ns		ns	
Patient BDI	ns					
Caregiver BDI			0.61	***	0.60	***
Model						
P	< 0.001		< 0.001		< 0.001	
Adjusted R^2	0.18		0.41		0.41	

SSS = Scandinavian Stroke Scale.
ns = nonsignificant, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

Table 14. Correlations between acute-stage factors and depression, measured by the Beck Depression Inventory (BDI) in spouses at different time points.

	Spouses' BDI		
	Acute	6 months	18 months
Patient age	0.30 *	0.32 **	0.39 **
Patient sex	ns	male *	male *
SSS	-0.36 **	ns	ns
BI	-0.33 **	-0.34 **	-0.32 *
WAIS Similarities	-0.24 *	ns	ns
WAB Reading	-0.28 *	ns	ns
Tapping, right	-0.24 *	ns	ns
Tapping, left	ns	-0.34 **	-0.32 *
Patient BDI	ns	ns	ns
Caregiver depression		0.61 ***	0.61 ***

SSS = Scandinavian Stroke Scale, BI = Barthel Index, WAIS = Wechsler Adult Intelligence Scale, WAB = Western Aphasia Battery. Only variables with significant correlations are included.
ns = nonsignificant, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

Regression analyses were then performed to determine whether the acute phase variables (patient age, sex, SSS, and spouse BDI) could predict spouses' depression later on in follow-up. The model was highly significant ($p < 0.001$), and accounted for 37 percent of the variance at six months. The only significant predictor was spouse BDI at the acute phase ($\beta = 0.53$, $p < 0.001$). At 18 months, the model accounted for 39 per cent of the variance ($p < 0.001$), with spouse BDI ($\beta = 0.56$, $p < 0.001$) and patient age ($\beta = 0.24$, $p < 0.05$) being the independent predictors (Table 15).

Table 15. Acute stage predictors of spouse depression, measured by Beck Depression Inventory (BDI) score, as determined by linear regression analyses.

	Acute		6 months		18 months	
	β	p	β	p	β	p
Patient age	0.30	**	ns		0.24	*
Male patient	ns		ns		ns	
SSS	-0.37	**	ns		ns	
Spouse BDI			0.53	***	0.56	***
Model						
p	< 0.001		< 0.001		< 0.001	
adjusted R^2	0.21		0.37		0.39	

SSS = Scandinavian Stroke Scale. ns = nonsignificant, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

4.6.3 Correlations at different time points

Patient's age and sex continued to be an associated factor with depression of the caregiver after acute phase (Tables 12 and 14). Nonetheless, most associations between stroke related factors and depression in caregivers found in acute phase, were no longer significant at later follow-ups. At six months, depression in caregivers correlated significantly with left-hand tapping ($r = -0.25$, $p < 0.05$). At 18 months, it correlated with WAIS Digit symbol ($r = -0.23$, $p < 0.05$) and patient BDI ($r = 0.27$, $p < 0.05$). The regression models could predict only 9 per cent to 14 per cent of the variance, and none of the variables appeared to be independent associated factors of caregiver depression.

4.6.4 Exhaustion

A total of 38 per cent of the spouses were exhausted at six months and 29 per cent at 18 months. The rates were lower (21% at six months and 5% at 18 months) when caregivers other than the spouses were assessed. The difference was significant at 18 months ($p < 0.05$).

At six months, spouses of patients who were not independent in their ADL functions were more often exhausted than spouses of independent patients ($\chi^2 = 9.9$, $p < 0.01$). A total of 47 per cent of the wives of male patients were exhausted. In contrast, only 8 per cent of the husbands of female patients were exhausted ($\chi^2 = 6.6$, $p < 0.01$). These differences were no longer significant at 18 months. Exhaustion in caregivers did not differ significantly when patients with different lesion locations were compared and when older patients were compared with younger patients. Spouses who were exhausted were also significantly more often depressed than those who were not at 6 months and 18 months ($\chi^2 = 33.8$ and 20.9, respectively, $p < 0.001$).

A series of logistic regression analyses was computed using exhaustion (present or not) as the dependent variable and patient's age, sex and dependence in ADL as the independent variables. When all caregivers were included, 72 per cent were correctly classified, with dependence in ADL as the only significant ($p < 0.01$) predictor. When spouses only were included, 75 per cent were correctly classified, with dependence in ADL ($p < 0.01$) and with the female sex of the caregiver ($p < 0.05$) as the independent predictors. At 18 months, this model did not predict exhaustion.

Inclusion of depression of the caregiver as an independent factor increased the explanatory power of the model. At six months, 85 per cent were correctly classified, with caregiver's depression ($p < 0.001$) and patient's dependence in ADL ($p < 0.05$) as significant independent predictors. At 18 months, 84 per cent were correctly classified, with only caregiver's depression as an independent predictor ($p < 0.001$). When spouses only were included at six months, 88 per cent were correctly classified, with spouse's depression ($p < 0.001$) and patient's dependence in ADL ($p < 0.05$) as significant independent predictors. At 18 months, 70 per cent were correctly classified, when spouse depression was an independent predictor ($p < 0.001$).

5 Discussion

5.1 Main findings

Depressive symptoms were frequent among patients with ischaemic stroke, and in most cases, it had an early onset. Mild depressive symptoms were often persistent with little change during the 18-month follow-up, whereas there was an increase in the prevalence of major depression over the same time period.

Stroke severity was associated with depression especially from 6 to 12 months post-stroke. However no specific neuropsychological profile was independently associated with depression. At the acute phase, older patients were at higher risk for depressive symptoms, and men were more depressed than women at 18 months after having the stroke. No significant association between the hemispheric side of the lesion and depression were found. However, at the acute phase, there was an association between stroke severity and depression among patients with lesions in the left hemisphere or in the brainstem. Even so, no such association was found among those with right hemisphere lesions. Depressive symptoms declined during the first two months only among patients with the brain stem or cerebellar lesions.

The various depression assessment methods did not differ much from each other in their feasibility, but the prevalence rates differed widely. According to the DSM-III-R criteria – similar to those of the DSM-IV-TR – 6 to 16 per cent of patients had major depression, whereas the caregivers rated about half of the patients as depressed. The sensitivity and specificity against DSM-III-R criteria for the CGI, BDI, and HRSD were acceptable. The BDI had higher sensitivity than the more specific the HRSD. Both cognitive-affective and somatic symptoms were associated with depression, but symptoms that discriminated depressed from non-depressed patients changed during the follow-up period. The VAMS was not a sensitive assessment method and did not correlate with the BDI during the first year after stroke. The caregivers rated the patients more depressed with the BDI than the patients themselves and this difference also correlated with the caregivers' ratings of their own depression.

Depressive symptoms of caregivers were even more frequent than those of stroke patients themselves. Almost one-third of the caregivers were depressed. Among spouses

the prevalence of depressive symptoms was higher than among non-spousal caregivers. At the acute phase, caregiver's depression was associated with stroke severity and the more advanced age of the patient. The caregiver depression at acute phase was the best predictor of caregiver depression at later stages.

5.2 Course of post-stroke depression

In this study the rates for depression were similar to or somewhat lower than those found in many other studies (Table 1). The patients in this study had experienced their first stroke, were younger, with a mean age only 55 years, than stroke patients in general, and had no other severe concomitant disorders. In addition to this, the long-follow-up study offered several visits to researchers according to the study protocol and the opportunity to contact the study nurse when needed, which may have reduced prevalence of depressive symptoms (Joubert et al. 2008). However, the present study did not have an especially large number of patients and was not intended to be a prevalence study per se.

The prevalence of depressive symptoms measured by the BDI showed little or no change during the 18-month follow-up. The results are in line with those by Pohjasvaara et al. (2001) and Kotila et al. (1998), who used the BDI scores with a cutoff point 10 and followed their patients up to either 12 or 15 months. In a study by House et al. (1991), 32 per cent of patients scored 10 points or more at one month and at six months: thereafter the prevalence rate decreased to 16 per cent at 12 months. The differing course in prevalence rates may be caused by different types of patient samples and using different methods for assessing depression. Our study included hospital-admitted patients, whereas House et al. (1991) studied a community based sample in which patients with milder strokes were included. In our study, over 80 per cent of the patients were not independent in ADL (BI < 20) immediately after the stroke, whereas the rate was 45 per cent in the study by House et al. (1991). The present study revealed the strongest association between stroke severity and depression from six to 12 months after stroke. Therefore, it can be supposed, that depression of patients with milder strokes decreases during such a period. Descending prevalence rates of depression were also reported by Verdelho et al. (2004). Results of this present study are based on the BDI or DSM-III-R and thus are not directly comparable with their results, because they

assessed depression by the observer-rated MADRS. The MADRS gives a higher prevalence rate than other mood assessment methods (Hackett et al. 2005) and seems therefore to be more sensitive to the mildest depressive symptoms, which possibly have different kinds of courses than more severe forms of depression.

The result of increasing prevalence of major depression during the first 18 months after stroke seen in this study is in line with the results of Kauhanen et al. (1999) and Brodaty et al. (2007) whose respective studies had follow-ups from 3 to12 and 15 months among hospitalized patients with ischaemic strokes. Results of studies in which patients with non-ischaemic strokes also were included are controversial. Results of Robinson et al. (1983, 1984b, 1987) support the trend towards increasing depression over time, whereas the results of House et al. (1991) and Åström et al. (1993) show decrease in major depression from 1 or 3 months to 12 months, respectively. Åström et al. (1993) followed their patients for up to three years and found that major depression had increased after 12 months. These three studies had fairly small patient groups with heterogeneous diagnoses of stroke. Among patients with ischaemic strokes case-fatality is lower, but the long-term quality of life is poorer than among patients with intracerebral haemorrhages (Feigin et al. 2003, Haacke et al. 2006). Åström et al. (1993) even included patients with transient ischaemic attacks, which have better prognosis than patients with ischaemic and haemorrhagic strokes. This heterogeneity may be an important cause of conflicting results in studies dealing with the course of post-stroke depression.

Symptoms of depression appeared within the first two months in most cases. Of those patients who were found to be depressed (BDI $\geq$ 10) at least once during the follow-up, only 12 per cent scored above the cutoff point first time in late follow-up at 12 or 18 months. The result of early onset of post-stroke depression is supported by the findings of other studies (Andersen et al. 1994, Aben et al. 2003, Paolucci et al. 2005). Depressive symptoms were often persistent after stroke. Almost half of the patients who were depressed in the acute phase and/or at two months were also depressed at 12 and/or 18 months. The finding of persistent symptoms of depression is in line with other studies (Wade et al. 1987, Burvill et al. 1995, Herrmann et al. 1998). Robinson et al. (1987) suggested that the persistence of depressive symptoms may be particularly strong in patients with mild depression, which was also case in the present study.

5.3 The associated factors of post-stroke depression

5.3.1 Lesion location

Depressive symptoms were not significantly associated with the hemispheric side for the location of the lesion. No consensus can be found in the literature about this association, which remains very controversial, but the results of this study are in line with the meta-analysis carried out by Carson et al. (2000). Of all studies, in those with hospital inpatients at the acute phase left hemisphere lesion location has most often associated with post-stroke depression (Bhogal et al. 2004). They also have the most heterogeneous results (Bhogal et al. 2004). Moreover, the very few longitudinal studies, in which the effect of the lesion location is studied with a follow-up for the first year after stroke, are highly variable. In the studies by Åström et al. (1993) and by Shimoda and Robinson (1999) patients with left hemisphere lesion suffered depression more often only at the acute phase. In contrast, Wade et al. (1987) found higher prevalence of depression at the acute phase among patients with right hemisphere lesions. House et al. (1990a) did not find a difference related to the side of lesions at any phase of the follow-up: a finding which agrees with that of our study.

Several methodological differences may account for the inconsistencies between some of these studies and ours. First, there is the apparent diversity of assessment methods used in the acute phase (see also Table 1). This study and that by House et al. (1990a) are based on the BDI scores and neither study found significant differences between hemispheric groups. Åström et al. (1993) and Shimoda and Robinson (1999) used diagnostic assessment method and obtained results suggesting that depression was more likely to occur in patients with left hemisphere lesions. Further, the results by Wade et al. (1987), suggesting that depression followed more often lesions in the right than left hemisphere, were based on the Wakefield self-assessment depression inventory (Snaith et al. 1971). It includes several questions about anxiousness, irritability, and panicky feelings, which are not strictly included in the diagnosis of major depression. Moreover, instead questions about suicidality, weight, and worthlessness are missing from this method. The result by Wade et al. (1987) may reflect anxiousness more than actual depression in patients with right hemisphere lesion in the acute phase. Second, time after stroke seems to be important (Shimoda and Robinson 1999, Bhogal et al.

2004). Because patients in this present study were first studied about two weeks after the stroke had occurred, we cannot exclude the possibility that depressive symptoms are associated with lesion location within the first days but not weeks after a stroke. Third, varying patient inclusion criteria produces samples of patients with differing stroke severities and prior stroke histories, which may be reflected in the results. At the acute phase an interaction trend for stroke severity and lesion site was found: among patients with more severe strokes only those with left hemisphere lesions had higher scores for depression than those with right hemisphere lesions. However, this trend needs to be dealt with cautiously because of small number of patients included in the comparisons. This interaction was no longer present in later follow-up and might suggest that a psychological reaction immediately after a stroke is modulated by the awareness of consequent functional impairments after stroke. In addition to this, our patients had first-ever strokes, whereas in samples of Åström et al. (1993) and Robinson et al. (1983), 20 and 24 per cent of patients had a history of prior stroke. The studies by Åström et al. and Robinson et al. suggest that depression was associated with lesions in the left hemisphere. After numerous study efforts from lesion location perspective, some researchers have recently suggested a change of focus from the side of single stroke to cumulative vascular pathology as a determinant of post-stroke depression (Brodaty et al. 2007, Santos et al. 2009).

Depressive symptoms measured by the HRSD at 2 months declined from the acute phase only among those patients with lesions in the brain stem/cerebellum, which are areas supplied by vertebral-basilar arteries. This could not be confirmed with significant differences using the BDI in our study. However, an early study by Starkstein et al. (1988) is in line with our result. They found, that patients with brain stem or cerebellar infarcts had a significantly shorter duration of depression than patients with lesions in the MCA. Lower rates for depression were also reported by Nys et al. (2005), Desmond et al. (2003) and recently by Provincialli et al. (2008) for patients with lesions in areas of posterior circulation than in those patients with lesions affecting the areas of anterior circulation, although the differences were not typically significant. In addition to this present study, there are no other studies with long follow-ups, in which the change in depressive symptoms in this patient group is studied separately from patients with lesions affecting anterior circulation. Because stroke symptoms and disabilities are of

different type in this subgroup of patients (Ng et al. 2007), it may result in different types of prevalences and courses of depression.

5.3.2 Stroke severity and neuropsychological impairments

The present study adds to the earlier data (see Hackett et al. 2005) in stating that stroke severity is associated with depression after stroke. According to our follow-up study the association between stroke severity and depression is at its highest at 6 to12 months post-stroke and declines thereafter. Significant correlations between cognitive impairments and depression emerged in later follow-up, a finding that has been supported later by Brodaty et al. (2007). However, even if depressed stroke patients had more cognitive impairments as indicated by detailed neuropsychological tests than non-depressed patients, this association would not be independent of overall stroke severity. In other studies where both cognitive impairment and overall disability or stroke severity have been included in multivariate analysis, cognitive abilities alone have not been statistically significant (Sharpe et al. 1994, Townend et al. 2007c), even when univariate associations were significant. These analyses were not performed by Nys et al. (2005) and Kauhanen et al. (2005). In our study, patients with aphasia were no more depressed than non-aphasic patients. Unfortunately, when the present study is compared with those by Nys et al. (2005) and Kauhanen et al. (1999), it can be seen they are all based on different kinds of neuropsychological test batteries and also different depression criteria, which makes it difficult to compare the results meaningfully. On the basis of the present study and the literature with many heterogeneous assessment methods and mixed results, the independent association between aphasia and other specific cognitive impairments and post-stroke depression remains open.

Our study does not implicate the direction of causation between cognitive and functional impairments and depression. We did not have enough patients with major depression to find out possible cognitive changes following changes in depression. Such associations have been noticed in endogenous depression (Austin et al. 2001). The literature offers contradictory conclusions on causality between cognitive impairment and post-stroke depression (Andersen et al. 1996, Murata et al. 2000, Narushima et al. 2003, Brodaty et al. 2007). After becoming suddenly seriously ill, some kind of psychological reactions with depressive symptoms are to be expected. However, at the

very acute phase stroke patients may not be aware of the impairments. Therefore, depression as a reaction to impairments would be expected to follow only after the development of this awareness. Unawareness of cognitive deficits typically follows right hemisphere lesions. In this study, an interaction between lesion location and stroke severity was only found at the acute phase. Patients with more severe strokes were more depressed when the lesion was in the left hemisphere or the brain stem, but not when it was in the right hemisphere. This finding is in line with the results by Bolla-Wilson et al. (1989) who used a neuropsychological test battery and with the results by House et al. (1990b) and Spalletta et al. (2002) who used the MMSE. In addition to this interaction, the finding that an association between stroke severity and depression is most apparent at 6 to 12 months post-stroke supports the possibility that depression is a psychological reaction to the novel impairments. Depressive symptoms increase among bereaved individuals up to six months post-loss and then decrease thereafter (Majciejewski 2007). However, post-stroke depression is often persistent and a minority of patients develop a delayed-onset depression, even for the major form of depression, during late follow-up. These observations suggest, that we cannot consider post-stroke depression only as a depressive reaction or an acute adjustment disorder after loss (ICD-10, WHO 1993). Neurophysiological mechanisms in combination with personal vulnerability for depression have also to be considered as possible mechanisms.

5.3.3 Demographic risk factors for post-stroke depression

Advanced age was associated with depressive symptoms during the first two months, but it did not remain as an independent predictor in multivariate analyses. This is contradictory to several studies, in which younger patients were found to be more depressed (Robinson et al.1983, Eriksson et al. 2004, Verdelho et al. 2004) or yet other studies in which no association was found (Åström et al. 1993, Andersen et al. 1995, Herrmann et al. 1998, Pohjasvaara et al. 1998, Aben et al. 2002a, Desmond et al. 2003, Appelros et al. 2004, Caeiro et al. 2006). There are also some studies which found that older patients were more vulnerable to depression (Sharpe et al. 1994, Kotila et al. 1998, Kauhanen et al. 1999). The patients in this present study were not older than 70 years, and therefore were younger than stroke patients in general. If age does not have a linear association with the prevalence of depression throughout the whole age spectrum,

then different kinds of associations may emerge in younger age groups. A study of the general population found, that old age was associated with a low prevalence of major depressive disorder (Pirkola et al. 2005). On the other hand, an earlier Mini Finland Health Survey reported that, the prevalence of depression increased with age up to 64 years, and especially perceived mental symptoms became commoner with advancing age (Lehtinen et al. 1990, Lehtinen and Joukamaa 1994). Between the different assessment methods an increasing number of discrepancies have been found in populations over 60 to 65 years old (Lehtinen et al. 1990). In this study somatic, but not cognitive-affective symptoms, were found to be more common among older patients during the 2 first months post-stroke. The various assessment methods stress somatic and cognitive-affective symptoms in different ways, which may be one cause for such variable results. Further, it has been suggested that healthy, normally functioning older adults have no greater risk for depression than younger adults, though depression in older adults can be attributable to problems with declining physical health (Roberts et al. 1997). The aspect of physical health is most apparent during the first months after stroke.

The sex of the stroke patient was not associated with depression in this study during the first year after stroke. Even so, men were more depressed than women at 18 months after the stroke, which was unexpected. Further, the follow-up showed a worse outcome for men than for women. More than half of the men but fewer than one-third of the women who were depressed in the acute phase and/or at two months were still depressed at 12 and/or 18 months. Depression without stroke is more common among females than males (Pirkola et al. 2005, Grigoriadis and Robinson 2007). Nonetheless, studies of stroke patients have given controversial results (Hackett et al. 2005a). The depression rates found in our study are almost identical to those of Burvill et al. (1995) who found, that although there were no prevalence differences between men and women at 4 months after stroke, men had much poorer outcome at 12 months. In their study, about half of the men who were depressed in early follow-up, remained depressed at 12 months. Post-stroke depression may be of a different nature in men and in women, and may also be affected by cultural differences. Inability to work has been found to be associated with depression in young adults (Neau et al. 1998). Physical ability may be of greater importance for men of working age, or men may have poorer

abilities than women to cope with health problems in general. Because the question of working ability is not yet actual during the first months, possible reactions to diminished working ability are to be expected after a longer follow-up. The author does not know if there might also be some genetic factors (Ramasubbu et al. 2008) interacting with the different kinds of changes that a stroke induces.

5.4 Assessment of depression

5.4.1 The BDI and HRSD rating scales

The feasibility rates of the two rating scales, the BDI and the HRSD, were fairly similar throughout the follow-up. Both scales had internal consistencies high enough for adequate internal reliability among stroke patients. These findings agree with those of studies by Aben et al. (2002) and by Quaranta et al. (2008). Retest or inter-rater reliability of these scales among stroke patients has not been reported. However, criticism for the poor retest and inter-rater reliability of the HRSD has been increasing in the psychiatric literature (Bagby et al. 2004). Skill and expertise of the interviewer and scoring guidelines may affect the reliability even more among stroke patients, than among psychiatric patients.

The BDI and HRSD differed from each other in their sensitivity and specificity measuring validity of the assessment methods. Both rating scales had well acceptable sensitivities of 0.80-1.00 from the acute phase to 2 months, but after that only the BDI was found to remain sensitive. The HRSD had a higher specificity than the BDI throughout the follow-up. There are very few studies to which our results could be directly compared. Aben et al. (2002b) did not find any substantial differences in the accuracy of depression screening between the BDI and the HRSD one month post-stroke. For the BDI scale, sensitivity was similar in both studies, but specificity was found to be higher in our study at the acute phase (0.76 vs. 0.61). The HRSD with a cutoff point of 12 was less sensitive (0.60 vs. 0.78) but more specific (0.96 vs. 0.75) in our study than in the study by Aben et al. (2002b). The differing results may partly be caused by the different percentages of patients with major depression. Only 6 per cent of patients suffered from major depression at acute phase in this present study, compared with 16 per cent in the study of Aben et al. (2002b). The only follow-up study

that reports the sensitivity and specificity of the BDI among stroke patients (House et al. 1989) had results comparable those of this present study. In both studies sensitivities and specificities changed during the follow-up. Specificity increased after some time had elapsed, whereas there was a temporary fall in sensitivity during the recovery. The BDI may indicate other emotional problems, such as anxiety instead of depression, which may lower specificity of diagnosis. Follow-ups with the HRSD are missing however. Two validity studies of the HRSD among stroke patients reported differing sensitivities and specificities and also found very differing cutoff points as optimal, 6 (Naarding et al. 2002) and 18 (Quaranta et al. 2008). In addition to the differences in patient samples, this may also reflect problems with inter-rater reliability.

The author suggests that the BDI is an acceptable screening method, a suggestion that is in line with previous investigators (House et al. 1989, Aben et al. 2002, Lincoln et al. 2003). Nevertheless the BDI is not specific enough to be used as a diagnostic tool. High sensitivity is more important than high specificity for a screening instrument, in order to avoid missing true cases. In addition to this, the BDI has the benefit not needing psychiatric professionals or specially trained personnel for its use. In contrast to that recommended by Andersen et al. (1994), but in agreement with House et al. (1989) the author does not recommend higher cutoff points for the BDI with stroke patients. Further, it has to be remembered that there is no optimal cutoff point independent of the purpose for which the scale is being used.

Both affective and somatic BDI items were associated with depression in this study, a finding that agrees with those of Paradiso et al. (1997). However, when the BDI was divided into cognitive-affective and somatic subscales, the somatic subscale could not retain good internal consistency possibly because somatic symptoms may have various causes. The frequency of depressive symptoms was described by Verdelho et al. 2004, whereas this study investigated which symptoms in the BDI are the strongest indicators of post-stroke depression at various time points after stroke. ‘Discouraged about the future’ was among the best indicators of depression both at the acute phase and at 18 months, and when DSM-III-R, BDI or CGI were used as the criteria. Other symptoms that discriminated depressed and non-depressed patients best at acute phase had changed by 18-month follow-up. Such a change was also found by Paradiso et al. (1997), although the symptoms they found best characterizing depression were not

identical with those of this study. Other important discriminators at the acute phase for all three criteria were ‘feeling like a failure’, ‘feeling guilty’, and ‘looking unattractive’; and at 18 months ‘sadness’, ‘dissatisfaction’, ‘feeling disappointed’, ‘loss of interest in people’, and ‘difficulty with decisions’. Crying, which is frequent at the very acute phase (Caeiro et al. 2006), was not among the items best discriminating depression when major depression and the BDI were used as criteria, even though it was important in the acute phase for CGI. Of somatic symptoms, poor appetite was the best discriminator for major depression at the acute phase in this study. DeCoster et al. (2005) also found poor appetite sensitive for depression, but their results are not directly comparable with those of this study, because they analysed scores at different time points when the first diagnosis was achieved. Fatigue and sleep disturbances that are common somatic symptoms were not discriminatory at the acute phase, but did become so during the later follow-up. DeCoster et al. (2005) did not study the effect of time on the indicators, but also found these same symptoms sensitive for depression. Weight loss was not associated with depression, which is in line with the result of Paradiso et al. (1997). No differences in the somatic or affective subscales between the three lesion location groups were found in this study. This is in line with that found by Stein et al. (1996) and Andersen et al. (1994) neither group found any differences in symptoms between patients with left or right hemisphere lesions.

5.4.2 The VAMS

If a patient’s mood cannot be assessed with the BDI or DSM ratings, then it likewise cannot be assessed with the VAMS either, as was also found by House et al. (1989). The VAMS had insufficient sensitivity and/or specificity during the first 18 months after stroke. In addition, the VAMS scores appeared not to be satisfactorily comparable with other measures throughout the first year after stroke: a finding which was also reported by House et al. (1989) and Tang et al. (2004). In this study the correlation between the VAMS and other measures of depression only appeared for the first time at 18 months when all patients were analysed together. However, there was still no significant correlation at 18 months between the VAMS and other assessment methods among patients with aphasia or inattention disorder. The more positive conclusions about the VAMS by Stern et al. (1997) were based on healthy volunteers whereas those

of Arruda et al. (1999) were based on a very small sample of patients without severe aphasia. In addition, Bennett et al. (2006) claimed to find an appropriate cutoff point for VAMS ('sad' item), but unfortunately this was not done against any diagnostic criteria, but against the Hospital Anxiety and Depression Scale. Price et al. (1999) also concluded that many patients after a stroke are unable to successfully complete Visual Analogue Scales regardless of any format. Based on this study's data, the VAMS seems not to be a reliable and valid method to assess depression after stroke among patients with aphasia or with other cognitive impairments.

5.4.3 Caregiver ratings

In this study caregiver ratings using the BDI were neither sensitive nor specific against those of the DSM criteria. These data differ from those of House et al. (1989), who found that caregivers reported all cases with major depression. They used a special carer's depression rating scale. However, only 49 per cent of identified caregivers completed the rating scale. In this present study, caregivers rated patients as more depressed than did the patients themselves, although there was some correlation between the caregiver ratings and patient ratings. This result partly agrees with the studies on the quality of life among stroke patients (Williams et al. 2006, Hilari et al. 2007), in which proxies tended to score the patients as being more severely affected than the patients scored themselves. In the current study, the caregivers' tendency to score higher depression than did the patients themselves was more prominent if caregivers' self BDI scores were high and patients' self BDI scores low. In the study by Williams et al. (2006), caregiver depression was associated with their ratings of patients' health-related quality of life (HRQL) at one to two months after stroke. In the present study it was also found that there was disagreement between the caregiver ratings (BDI) and study personnel ratings (CGI) on patient depression, and these discrepancies were associated with caregiver depression. The caregiver's own mood seems to be important when he/she assesses the mood of a patient with whom he/she has a close relationship. Laska et al. (2007) found that the assistance of relatives and staff increases feasibility and decreases validity of assessing depression. The use of informants, however, is the most common adaptive method used in assessing those

patients with aphasia (Townend et al. 2007a). It is concluded that caregivers may be a valuable source of information, but their assessment should be used with caution.

5.4.4 Clinical Global Impression

The CGI was the assessment method that achieved highest feasibility of all methods assessed in this study. This was also found by Laska et al. (2007). When used by the study personnel, who had a good contact with the patients and special interest in depression, the sensitivity and specificity were good enough for screening. Under these conditions the inter-rater correlation was good.

Nurses identified most patients with depression using the CGI assessment method (sensitivity 80%), but without specific training their assessment was poor in specificity. About half of the patients rated as depressed by them were false-positive. The inter-rater reliability of the nurses' CGI scoring was not investigated in this study, therefore these results can only be regarded as preliminary. More specific observational screening method by nurses was not found to be efficient enough by House et al. (1989) and by Lightbody et al. (2007). If nurses' observational ratings of any kind are used in depression screening, special training on depression diagnostic questions including eliciting and rating symptoms would be needed.

5.5 Depression among caregivers of stroke survivors

Caregiver depression had a prevalence of 30 to 33 per cent and was even more common than patient depression as determined by the BDI (23-29%). The rates are comparable to the average level of the variable rates reported in the literature (Anderson et al. 1995, Dennis et al. 1998, Kotila et al. 1998, Smith et al. 2004). For spouses only, the rates were 33 to 38 per cent, and a recent study by Visser-Meily et al. (2009) reported even higher percentages (50-68%). However, the study by Kotila et al. (1998) was based on the same BDI criteria as used in this study, and the small difference in prevalence rates (40-42% vs. 30-33%) is probably due to the generally better health and younger average age of patients in this study.

This research is one of the few follow-up studies on depression in stroke caregivers. The rates of depression were highest at the acute phase among all caregivers and also

among spouses only, and there was only a weak trend in decreasing symptoms after the acute phase. Consequently the prevalence of depression remained similar up to 18 months. This finding has recently been confirmed by Visser-Meily et al. (2009) in a follow-up for 3 years after the stroke. There are also studies that suggest decreasing depression from 3 to 12 months after a patient's stroke (McCullagh et al. 2005) whereas others report increasing depression from 1 to 3 years after stroke (Carnwath and Johnson 1987). The criteria for depression used by different studies may be a reason for these variable results. Carnwath and Johnson (1987) used diagnostic criteria for caregivers' depression. In the present study, more severe depression (BDI $\geq$ 20) increased from 2 per cent to 9 percent during the 18-month follow-up, suggesting that the course of major depression may differ from that of milder depression.

The spouses had more depressive symptoms than other next of kin. This finding is most prominent in the acute phase, and agrees with an earlier study (Schulz et al. 1988). The association between stroke severity and caregiver depression was strongest at the acute stage but was no longer significant at 18 months. The length of time elapsed since stroke may also be a critical factor behind the differences found in earlier studies. A number of studies (Dennis et al. 1989, Kotila et al. 1998 and Van Puymbroeck et al. 2005) found an association between stroke severity and caregiver depression. However, other studies did not find such an association (Anderson et al. 1995, Smith et al. 2004 and Visser-Meily et al. 2005). In those studies that found an association caregivers were examined one to six months after stroke. In contrast, caregivers were examined only once about one year post-stroke in those studies that found no association. The current study, together with earlier longitudinal investigations (Wade et al. 1986, Schulz et al. 1988), support the idea that caregiver depression is associated with stroke severity and/or functional disability during the first months after stroke, but not at later follow-ups. The author found no cognitive impairments that were independent predictive factors; the overall stroke severity covered these impairments. From the caregivers' points of view, the overall stroke severity seems to describe the status and condition of the patient better than do specific cognitive deficits. However, the possibility that some other and more specific measures would have revealed interactions between and caregiver depression and specific cognitive or behavioural defects in a larger sample can not be excluded. Interestingly, the association between stroke severity and depression

appears earlier after stroke among caregivers than among patients themselves. The association between stroke severity and patient depression first became significant at 2 months post-stroke. The author suggests this is because caregivers can recognize the problems earlier than patients who may initially be unaware of their impairments at the acute stage.

The correlation between advanced age of the patients and depression in spouses became stronger throughout the follow-up, which was also found by Smith et al. (2004) and Jönsson et al. (2005). The continuous caring needs of stroke patients may become truly overwhelming for the caregiver when the patient and his/her spouse are older. Poorer physical health is often associated with advanced age, and caregivers with poorer health are known to have more depressive symptoms and to be under greater strain (Carnwath and Johnson 1987, Bugge et al. 1999). Not all studies have found this association (Dennis et al. 1998, van den Heuvel et al. 2001, Grant et al. 2004). The heterogeneity of both patients and caregivers probably affect results, and it is also difficult to compare the results of spouse-caregivers with those of all categories of non-professional caregiver including spouses, children and other next-of-kin. The correlation between patient depression and caregiver depression at 18 months suggests some interaction between these variables during the long follow-up. This point is also highlighted by Suh et al. (2005).

During the late follow-up caregiver depression was best predicted by the caregiver's acute-phase depression. A similar finding was also reported by Visser-Meily et al. (2005). It is possible, that caregivers' acute phase BDI responses may reflect their personal reactions to a stressful event as much as it does to developing diagnosable depression per se. This study focused on patient- and stroke-related factors, but the importance of coping strategies and other caregiver-related factors cannot be ignored (Grant et al. 2000, Grant et al. 2001, Chumbler et al. 2004, Visser-Meily et al. 2009).

The factors associated with exhaustion were not identical to those associated with depression. When advanced age was significantly associated with spouses' depression, the female sex of the caregiver was an important factor in exhaustion. When gender differences are reported in the literature, female caregivers have a higher prevalence of being exhausted (van den Heuvel et al. 2001). In this present study stroke severity and/or dependency in ADL were associated with caregiver depression and exhaustion

during the first six months, a finding that agrees with Bugge et al. (1999), but thereafter other factors became more important. Bugge et al. (1999) found that caregiver stress appeared to increase in the early post-stroke period, whereas this study showed a slightly descending rate of exhaustion from six to 18 months. In their follow-up for 3 years, Visser-Meily et al. (2009) found a decreasing burden when time elapsed. Exhaustion and depression were associated with each other at 18 months after a patient's stroke in this study, a result in line previous findings (Chumbler et al. 2004). It is probable that exhaustion is one cause of depression.

5.6 Evaluation of the study

The present study on post-stroke depression is a carefully examined prospective 18-month follow-up with detailed neuropsychological assessment. It provided longitudinal data on several depression assessment methods for stroke patients to an extent not reported earlier. These include diagnostic criteria, observational and self-rating scales, proxy assessment and a visual analogue scale. The study design made it possible to study the course of depression in its milder forms, as reported using the BDI, and when it was severe enough to meet the criteria for major depression. In addition to this, this study followed also caregivers of the patients and measured depression by the same assessment method in both groups.

This study had a homogenous sample of consecutive hospital-admitted patients who had had their first ischaemic stroke. The study did not include patients older than 70 years and patients with severe health problems that might have a risk of interfering with the medication of the drug trial. Thus the study patients were younger and healthier than stroke patient in general: a factor which has to be considered when comparing the results with those of earlier studies. Apart from the advantages of the very good follow-up rate and broad examination of the patients, the inclusion of only those patients without other severe health problems, made it possible to study the impact of stroke without a very large sample size.

The randomised use of an antidepressant study drug can be seen as a limitation of this study. It might have affected the severity, the symptoms and the course of post-stroke depression from the period from acute phase to 12 months post-stroke. However, no significant differences were found in the BDI or HRSD scores or in the prevalence of

major depression between the treatments groups at any follow-up point, either in the present study or in the study by Palomäki et al. (1999) on the same patients. In addition to this, the impact of medication was controlled for in the present study with several analyses, but no significant effect of medication was revealed at any time point. Of the separate symptoms of depression, those related to sleep might be expected to be affected by mianserin because of its sedative effect. In the study by Palomäki et al. (2003) using the same patients as in the present study, symptoms of insomnia did decrease more rapidly in patients treated with mianserin than in those on placebo. However, there was no significant decrease in symptoms of depression as measured by the BDI. On the other hand, in some other studies, in which randomisation was not used, 19 to 36 per cent of depressed and 8 to 10 per cent of nondepressed patients used antidepressive medication (Kauhanen et al. 1999, Herrmann et al. 1998). The impact of medication could be controlled somewhat better in this study than in the above-mentioned studies. Taken together, the medication used, mianserin, was found not to have any major effects on the results. If mianserin had reduced the symptoms of especially severe depression, then the conclusions which could have been drawn about the data would have been more limited.

The study design did not have control patients. Nonetheless as the aim was to investigate the course and associated factors of depression instead of the actual prevalence of depression after a stroke, a control group would not have provided any crucial information. Brodaty et al. (2007) found that the prevalence of major depression increased during the follow-up, a finding in line with this study's results. However, in their study depression remained relatively stable in the normal volunteer control sample (Brodaty et al. 2007). Aben et al. (2003) followed patients with first ever stroke and patients with first ever myocardial infarction, and found depression to occur equally in both patient groups when sex, age and the severity of handicap were taken in account. They concluded that post-stroke depression would not reflect a specific pathogenic mechanism, but instead be associated with generalised vascular damage common to both stroke and myocardial patients that might affect mood regulatory process.

This study did not investigate patients' pre-stroke histories of mood disorders, which are known to be a risk for post-stroke depression (Pohjasvaara et al. 1988). Anosognosia is often associated with neglect among patients with right hemisphere lesions (Spalletta

et al. 2007) and so may contribute to the development of depression. It might have been useful to include these variables in the study design. Factors of emotionalism and exhaustion of the patients, in addition to the health of the caregivers or their coping abilities were not taken into account. However, an increase in the number of patient or caregiver variables would also have required a larger patient sample in order to give statistically robust data.

6 Conclusions

Because depressive symptoms have an early onset in most cases, and a chronic course of possibly more than 12 months' duration, it is important to assess depression early during the first months after stroke.

At acute phase older patients are more vulnerable to depressive symptoms. Stroke severity is associated with depression especially from six to 12 months after the stroke. More attention should be focused on depressive symptoms of male patients, the long-term prognosis of whom may be poorer than that of females. The best predictor of later depression was found to be acute phase depression.

None of the assessment methods clearly stand apart from the others in screening or diagnosing ability to be recommended as the primary method of choice. Self-rating methods such as the BDI with a satisfactory sensitivity, are useful in screening depression in patients with stroke. The VAMS cannot be recommended in screening depression among stroke patients with aphasia or other cognitive impairments. This research found that the VAMS has poor sensitivity, poor specificity and no better feasibility compared to any other method studied. Proxies often rate patients' depression more severe than the patients themselves, and the proxies' ratings seem to be influenced by their own depression. We found that CGI assessments had promising sensitivity characters. More research is needed on observational assessments and symptoms characterising depression during the acute and chronic post-stroke period in order to develop better depression assessment methods for stroke patients. Only a minority of depressed stroke patients receive treatment for depression (Paul et al. 2006, Eriksson et al. 2004), a finding that probably reflects inadequate detection and treatment of post-stroke depression. Thus the assessment of post-stroke depression must be highlighted with any of the acceptable methods in clinical work.

Depressive symptoms in caregivers of stroke patients are even more frequent than those in patients. At the acute phase caregivers of older patients with more severe stroke are the most vulnerable to depressive symptoms. The prevalence of depression remains fairly stable during the first 18 months after stroke. The best predictor of caregiver depression at later stages is its presence in the acute phase after a patient's stroke. Identifying those caregivers at high risk for poor emotional outcome requires not only

assessment of patient-related factors but also interview of the caregiver during the early post-stroke period. This suggests that the assessment of caregivers' medical, social, and emotional needs should be included as part of the general rehabilitation plan of the stroke patient.

7 References

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