Cognitive impairment and depressive symptoms in stroke rehabilitation patients:
Frequency, risk factors, and relation to outcome

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“Du er ikke ferdig med livet
så lenge ikke livet er ferdig med deg”

Johannes Møllehave, f. 1937, dansk prest
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Finally, warm thanks to my family Oda, Marie, Tone and Findus.

Oslo in November 2010.
List of papers


Abstract

Background: In Norway 14500 people are struck by a stroke each year, and most of them are elderly over 65 years of age. Cognitive impairment and symptoms of depression are frequent after a stroke, but often go unnoticed and untreated in Norwegian stroke units today, and are scarcely studied in research.

Aims: The aim of the project was to describe the frequency and course of cognitive impairment and symptoms of depression in a stroke rehabilitation population, to examine risk factors of cognitive impairment and symptoms of depression, and to study how cognitive functioning and symptoms of depression in a subacute phase were related to long-term prognosis. Specifically, we wanted to: 1) study whether genetic vulnerability through the presence of the ApolipoproteinE ε4-allele (ApoE ε4) was a risk factor for cognitive impairment after a stroke, 2) examine whether cognitive performance as measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in a subacute phase after a stroke could predict the patients’ functional long-term prognosis, 3) examine the frequency and course of clinical significant symptoms of depression over a 13 months period as measured by the Montgomery Aasberg Depression Rating Scale (MADRS), examine the risk factors for changes in symptoms of depression, and to explore whether symptoms of depression in a subacute phase could predict mortality and nursing home placement at 13 months post-stroke.

Methods: One hundred ninety four stroke patients with mean age 76.9 years, of whom 49 % were females, admitted to the Stroke Rehabilitation Unit at the Ulleval University Hospital (today Oslo University Hospital, Ulleval) were included. The patients were examined with structured tests and questionnaires on average 2-3 weeks after the hospital admittance, and 13 months later on measures of cognitive, emotional, neurological and Activities of Daily Living (ADL) functioning. Information of the patients’ pre-stroke cognitive and ADL-functioning were collected through semi-structured interviews with next-of-kin. Data of personal characteristics, vascular risk factors, medicines, and other clinical information were collected from the patients’ medical records at the hospital or directly from the patient or next of kin. ApoE-genotyping was made on the basis of blood samples collected from the patients during their stay at the Stroke Rehabilitation Unit. The patients’ place of residence and number of deaths were registered at 13 months follow-up examination.

Results: The frequency of cognitive impairment, defined by a RBANS Total Index Score ≤ 77.5, on average 2-3 weeks after the stroke was 61 % while the corresponding figure at 13 months follow-up was 50 %. Cognitive impairment at 2-3 weeks after the stroke was a strong predictor of cognitive impairment at 13 months. Among the patients, 18 % had shown a marked decline in cognitive functioning in the years ahead of the present stroke according to information collected from next of kin.

Independent, significant risk factors of cognitive impairment at two-three weeks post-stroke were pre-stroke cognitive reduction (The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) score), level of stroke-related neurological impairment (The National Institute of Health Stroke Scale (NIHSS)), topographical stroke location (total or partial anterior stroke syndromes), and genetic vulnerability through the presence of one or two copies of the ApoE ε4-allele. At 13 months follow-up the corresponding factors were previous stroke (according to medical records), pre-stroke cognitive reduction (IQCODE), level of
stroke-related neurological impairment (NIHSS), and genetic vulnerability through the presence of the ApoE ε4-allele.

The hypothesis that the ApoE ε4-allele is an independent, significant risk factor of post-stroke cognitive impairment was thereby confirmed. The ApoE ε4-allele was not only a risk factor of cognitive impairment at both times of examination, but carriers of the ApoE ε4-allele also showed a reduction in cognitive performance during the follow-up period, especially within the domain of episodic verbal learning and memory. Patients without the ε4-allele showed an improvement in cognitive performance during the same period. There was no significant difference in level of pre-stroke cognitive reduction between the ApoE ε4-carriers and non-carriers (based on next of kin’s reporting on the IQCODE).

Cognitive performance as measured by the RBANS Total Index Score at two-three weeks post-stroke was a significant predictor of both functional outcome (measured by the modified Rankin Scale (mRS)) and nursing home placement at 13 months even when other well-established sociodemographical, medical and functional risk factors were controlled for. Among the twelve RBANS subtests, Coding and Figure Copy were the two tests which best predicted functional long-term outcome. There was no association between early RBANS-performance and mortality at 13 months post-stroke.

The frequency of clinical significant symptoms of depression (defined as a MADRS total score > 6) was 56 % at two-three weeks after the stroke, and 48 % at 13 months post-stroke. For the majority of the patients, the symptoms were of a mild character. Neither at baseline nor follow-up examination did any patient report major symptoms of depression. Among patients with depressive symptoms at baseline, 55 % also reported depressive symptoms at 13 months (persistent depression), while 35 % free from depressive symptoms at baseline reported clinical significant depressive symptoms at 13 months (incident depression).

The only baseline-variable predicting significant depressive symptoms at 13 months post-stroke was a low score on instrumental ADL-functioning ahead of the stroke (Frenchay Social Activity Index). Baseline-predictors of persistent depression were low instrumental ADL-functioning ahead of the stroke (Frenchay Social Activity Index), high level of neurological stroke-related impairment (NIHSS Total Score), high level of global handicap (mRS), and, additionally, high personal ADL-functioning (Barthel Index), and high cognitive performance (as measured by the MMSE). The only predictors of incident depression were reduced episodic memory performance at baseline (RBANS Delayed Memory Index) and receiving municipal home help ahead of the stroke.

After 13 months 35 of 163 patients (21%) were living in nursing homes, and 37 of 163 patients (23 %) were dead. Depressive symptoms at baseline predicted nursing home placement after 13 months, but not mortality.

**Conclusions:** Stroke rehabilitation patients are at high risk of cognitive impairment both in the subacute phase and at thirteen months post-stroke. Besides well-established risk factors, like pre-stroke reduced cognitive performance and stroke characteristics (lesion size and localisation), a genetic factor through the presence of the ApoE ε4-allele probably contribute to explain the development of post-stroke cognitive impairment, and also why some patients show progression of cognitive decline over time after a stroke, particularly within the domain of episodic verbal learning and memory.
Cognitive performance as measured by RBANS at two-three weeks post-stroke was a strong predictor of functional outcome and nursing home placement at 13 months, but was not associated with mortality. The results confirm previous studies which report that the test has good predictive validity in a stroke rehabilitation population. Among the RBANS’ subtests, Coding and Figure Copy were the strongest predictors of functional performance at 13 months. Both tests are quick and easy to administer, and may be considered as attractive screening tools in clinical settings.

Depressive symptoms were frequent among the stroke rehabilitation patients both at two-three weeks and at 13 months post-stroke, but were primarily of a mild character. Still, it is recommended that the symptoms are taken seriously by health personnel, not only because of the distress they cause the patient and that they may reduce motivation for rehabilitation, but also because early depressive symptoms are a negative prognostic factor for nursing home placement. There was no association between depressive symptoms and mortality, which is contrary to several previous studies, but may be explained by the high frequency of patients with mild depressive symptoms in our material.

The study confirms that post-stroke depression follow different courses and to some extent can be predicted by different factors, including pre-stroke social activity level and the severity level of the stroke. Standard screening of depressive symptoms is uncommon in Norwegian stroke rehabilitation units today, but should be considered. Depression is treatable, but few patients are offered anti-depressive treatment. Future studies should examine the benefit of cognitive behavioural therapy possibly in combination with anti-depressive medication in the patient group.
Sammendrag

Bakgrunn: Årlig får 14 500 mennesker hjerneslag i Norge, og det er særlig eldre over 65 år som rammes. Kognitiv svikt og depressive symptomer opptrer hyppig etter hjerneslag, men blir mangelfullt utredet og behandlet i norske slagenheter i dag, og er i forsknings sammenheng lite studert.

Formål: Formålet med prosjektet var å beskrive forekomst og forløp av kognitiv svikt og depressive symptomer i en slagrehabiliteringspopulasjon, undersøke risikofaktorer for kognitiv svikt og depressive symptomer, og studere hvordan kognitivt funksjonsnivå og depressive symptomer i en subakutt fase etter hjerneslaget var relaterte til langtidsprognose. Spesielt ville vi: 1) studere om genetisk sårbarhet gjennom tilstedeværelse av ApolipoproteinE ε4-allelet (ApoE ε4) var en risikofaktor for kognitiv svikt etter hjerneslag, 2) undersøke om kognitivt funksjonsnivå målt med the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) i sub-akutt fase etter hjerneslag kunne predikere pasientenes funksjonelle langtidsprognose, 3) undersøke forekomst av depressive symptomer over en 13-måneders periode målt med the Montgomery Aasberg Depression Rating Scale (MADRS), hvilke risikofaktorer som lå til grunn for endring i depressive symptomer, og hvorvidt depressive symptomer i subakutt fase kunne predikere mortalitet og risiko for sykehjemssinnleggelse etter 13 måneder.


Resultater: Forekomsten av kognitiv svikt, definert som en RBANS Total Indeks Skåre ≤ 77,5, i gjennomsnitt to til tre uker etter hjerneslaget var 61 %, mens tilsvarende forekomst etter 13 måneder var 50 %. Kognitiv svikt to til tre uker etter slaget var en sterk prediktor for kognitiv svikt etter 13 måneder. Av pasientene ble 18 % rapportert av pårørende til å ha utviklet en markert reduksjon i kognitiv fungering i årene forut for slaget. Uavhengige, signifikante risikofaktorer for kognitiv svikt, forutsatt av slaget var kognitiv reduksjon forut for slaget (The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) skåre), nevrologisk alvorlighetsgrad av aktuelt slag (The National Institute of Health Stroke Scale (NIHSS)), topografisk slaglokalisasjon (total eller partial anterior stroke syndromes), og genetisk sårbarhet ved tilstedeværelse av et eller to kopier av ApoE ε4-allelet. Tilsvarande risikofaktorer for kognitiv svikt ved 13 måneder var tidligere hjerneslag (i henhold til journal), kognitiv reduksjon forut for hjerneslaget (IQCODE skåre), nevrologisk alvorlighetsgrad av aktuelt hjerneslag (NIHSS), og genetisk sårbarhet gjennom tilstedeværelse av ApoE ε4-allelet.
Hypotesen om at ApoE ε4-allelet er en uavhengig, signifikant risikofaktor for kognitiv svikt etter hjerneslag ble dermed bekreftet. ApoE ε4-allelet var ikke bare en risikofaktor for kognitiv svikt ved begge undersøkelsetidspunkter, men bærere av ε4-allelet hadde også reduksjon i kognitiv fungering gjennom oppfølgingsperioden, spesielt når det gjaldt episodisk verbal innlæring og utsatt hukommelse. Pasienter uten ε4-allelet fikk en bedre utvikling i kognitiv fungering gjennom samme periode. Det var ingen signifikant forskjell i kognitiv reduksjon forut for slaget mellom ApoE ε4-bærere og ikke-bærere (basert på pårørendes rapportering på IQCODE).

Kognitiv fungering målt med RBANS Total Indeks Skåre to til tre uker etter hjerneslaget var en signifikant prediktor både for grad av funksjonssvikt (målt med modified Rankin Scale (mRS)) og for å bo på sykehjem etter 13 måneder selv når sosio-demografiske, medisinske og funksjonelle risikofaktorer ble kontrollert for. Blant de tolv RBANS deltestene var det Koding og Figurkopiering som best predikerte funksjonelt langtidsutfall. Det var ingen sammenheng mellom RBANS-prestasjoner i tidlig fase og død etter 13 måneder.

Forekomsten av klinisk signifikante depressive symptomer, definert som MADRS-skåre > 6, var 56 % to til tre uker etter hjerneslaget, og 48 % etter 13 måneder. For majoriteten av pasientene var symptomene av en mild karakter. Ingen pasienter rapporterte symptomer av alvorlig karakter verken ved baseline- eller oppfølgingsundersøkelse. Av pasienter med depressive symptom i tidlig fase rapporterte 55 % også depressive symptomer etter 13 måneder (persistent depresjon), mens 35 % uten depressive symptomer to til tre uker etter slaget, rapporterte klinisk signifikante depressive symptomer etter 13 måneder (insident depresjon).

Den eneste baseline variabelen som predikerte signifikante depressive symptomer etter 13 måneder var lav skåre på instrumentell ADL-fungering før slaget (Frenchay Social Activity Indeks). Baseline-prediktorer for persistent depresjon var lav instrumentell ADL-fungering før slaget (Frenchay Social Activity Indeks), høy grad av nevrologisk slagrelatert svekkelse (NIHSS total skåre), høy grad av funksjonssvikt (mRS), og i tillegg god personlig ADL-fungering (Barthel Indeks) og høy kognitiv fungering (målt med Mini Mental Status Examination (MMSE)). De eneste prediktorene for insident depresjon var svækket episodisk hukommelse i tidlig fase (lav skåre på RBANS utsatt hukommelse indeks) samt å motta hjemmehjelp før slaget.

Etter 13 måneder var 35 av 163 pasienter (21 %) innlagte på sykehjem og 37 av 163 pasienter (23 %) døde. Depressive symptomer ved baseline predikerte sykehusinnleggelse etter 13 måneder, men ikke mortalitet.

**Konklusjon:** Slagrehabiliteringspasienter har stor risiko for å utvise kognitiv svikt både i subakutt fase og tretten måneder etter hjerneslaget. Foruten veletablerte risikofaktorer, som premorbid kognitiv fungering og slagkarakteristika (lesjons-størrelse, lokalisasjon), fant vi at en genetisk faktor gjennom tilstedevarsel av ApoE ε4-allelet bidro til å forklare utviklingen av kognitiv svikt etter et hjerneslag, og også hvorfor en del pasienters kognitive svikt progredierte etter slaget, spesielt når det gjaldt episodisk verbal læring og utsatt hukommelse.

Kognitivt funksjonsnivå målt med RBANS to til tre uker etter et hjerneslag var en sterk prediktor for funksjonssvikt og sykehjemsinnleggelse etter 13 måneder, men var ikke assosiert med mortalitet. Resultatet støtter opp om tidligere studier som rapporterer at testen har god prediktiv validitet i en slagrehabiliteringspopulasjon. Av RBANS deltester fremsto...
Koding og Figurkopiering som de beste prediktorer i forhold til pasientenes funksjonssnivå ved 13 måneder. Begge deltester er enkle og raske å administrere, og vil med fordel kunne anvendes som screening tester i klinisk sammenheng.

Depressive symptomer var hyppige blant slagrehabiliteringspasientene både etter 2-3 uker og etter 13 måneder, men var primært av mild karakter. Likevel anbefales det at symptomene tas på alvor av helsepersonalet, ikke bare på grunn av ubehaget det påfører pasientene og at de kan bidra til redusert motivasjon for rehabilitering, men også fordi depressive symptomer er en negativ prognostisk faktor i forhold til sykehjemsinnleggelse. Det var ingen sammenheng mellom depressive symptomer og mortalitet, hvilket er kontrært til flere tidligere studier, men kan skyldes den høye forekomsten av milde depressive symptomer i vårt materiale.

Studien bekrefter at depresjon etter et hjerneslag har ulike forløp og delvis kan predikeres av ulike faktorer, inklusive premorbid sosial aktivitetsnivå og slagets alvorlighetsgrad. Standard screening for depressive symptomer er uvanlig i norske slagrehabiliteringsenheter i dag, men bør vurderes. Depresjon kan behandles, men få pasienter tilbys antidepressiv behandling. Fremtidige studier bør undersøke nytten av kognitiv atferdsterapi eventuelt i kombinasjon med antidepressiv medikasjon i pasientgruppen.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
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<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
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<tr>
<td>ApoE</td>
<td>Apolipoprotein E</td>
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<td>BI</td>
<td>Barthel Index</td>
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<td>BDI</td>
<td>Beck Depression Inventory</td>
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<td>CAMCOG</td>
<td>Cambridge Cognitive Examination</td>
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<td>CVA</td>
<td>Cerebrovascular accidents</td>
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<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of mental disorders 4th edition</td>
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<td>EEG</td>
<td>Electroencephalography</td>
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<td>FAI</td>
<td>Frenchay Social Activities Index</td>
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<tr>
<td>FIM</td>
<td>Functional Independence Measure</td>
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<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<td>GDS</td>
<td>Geriatric Depression Scale</td>
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<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<tr>
<td>HDRS</td>
<td>Hamilton Depression Rating Scale</td>
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<tr>
<td>ICD-10</td>
<td>International Classification of Diseases 10th edition</td>
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<td>IQCODE</td>
<td>Informant Questionnaire on Cognitive Decline in the Elderly</td>
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<td>LACS</td>
<td>Lacunar Circulation Syndrome</td>
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<td>MADRS</td>
<td>Montgomery and Åsberg Depression Rating Scale</td>
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<tr>
<td>MCI</td>
<td>Mild Cognitive Impairment</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>MMSE</td>
<td>Mini Mental Status Examination</td>
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<td>mRS</td>
<td>modified Rankin Scale</td>
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<td>NIHSS</td>
<td>National Institute of Health Stroke Scale</td>
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<td>NINDS</td>
<td>National Institute of Neurological Disorders and Stroke</td>
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<td>NINDS-AIREN</td>
<td>National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences</td>
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<tr>
<td>OCSP</td>
<td>Oxfordshire Community Stroke Project</td>
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<tr>
<td>PACS</td>
<td>Partial Anterior Circulation Syndrome</td>
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<tr>
<td>PET</td>
<td>Positron emission tomography</td>
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<tr>
<td>POCs</td>
<td>Posterior Circulation Syndrome</td>
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<tr>
<td>PSD</td>
<td>Post-stroke depression</td>
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<tr>
<td>RBANS</td>
<td>Repeatable Battery of Neuropsychological Status</td>
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<tr>
<td>SSS</td>
<td>Scandinavian Stroke Scale</td>
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<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
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<tr>
<td>TACS</td>
<td>Total Anterior Circulation Syndrome</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1. Introduction

Stroke is a frequent disease and has often dramatic consequences. More than every 6th person will experience a stroke in their lives (Seshadri et al. 2006). It is the most common cause of chronic disability, and, after coronary heart decease and cancer, the third most common cause of death in the western world (Sarti et al. 2000).

Although stroke was described by Hippocrates, the father of medicine, more than 2400 years ago, systematic research in the field were scarce until the establishment of the first specialized stroke rehabilitation units 20-25 years ago. Since then, the impact of stroke on physical disability and death has been extensively documented.

Stroke is a disease which attacks the brain, the seat of our thoughts and emotions. It may therefore appear strange that cognitive and emotional symptoms to a far less degree have been studied in stroke compared to physical ones. There may be several reasons for this, but, in the author’s view, one important factor is that stroke primarily has been understood as a physical disease. Cognition and emotions are domains of psychology, but psychologists are seldom represented in the multidisciplinary rehabilitation teams of specialized stroke units, in which physicians, nurses, physiotherapists, occupational therapists, and speech therapists presently dominate. According to the proposed national guidelines for treatment and rehabilitation of stroke in Norway (Helsedirektoratet 2009a), these latter health professions are recommended in stroke units.

A greater focus on cognitive and emotional symptoms in stroke patients may be considered beneficial for several reasons. Firstly, it is documented that cognitive and emotional symptoms occur frequently in stroke patients (Chemerinski and Robinson 2000; Fure et al. 2006a; Hochstenbach et al. 1998; Rasquin et al. 2004). Secondly, they easily go undetected in the rehabilitation setting unless formal testing is provided (Edwards et al. 2006; Fure 2007). Thirdly, both cognitive impairment and emotional symptoms are major sources of confusion and burden for patient and relatives, and concise information may ease this burden (Thommessen et al. 2001; Thommessen et al. 2002; van den Heuvel et al. 2001). Fourthly, emerging evidence indicates that these symptoms could be at least as important in prognostic terms as physical symptoms (Galski et al. 1993; Sundet et al. 1988; Tatemichi et al. 1994). Fifthly, in some cases, both cognitive and emotional symptoms may be available for treatment (Kimura et al. 2000; Murata et al. 2000; Robinson 2003). Finally, stroke is a disease which
primarily attacks the elderly. With an increasing proportion of elderly in the population, it has been suggested that stroke, cognitive impairment and vascular dementia may be the silent epidemic of the 21st century, and that greater attention to these patients is warranted (Roman 2003).

Systematic research of cognitive and emotional symptoms in stroke patients is a young, complex and exciting field with many unresolved issues. Still, there is no consensus on how best to define and measure cognitive and emotional symptoms, how frequent and stable the symptoms are, what their risk factors are, how treatable they are, and how well cognitive impairment and emotional symptoms in the early post-stroke phase predict long-term stroke outcome measures, like death, institutionalization, and function in daily activities.

This thesis is an attempt to contribute to further understanding of some of these issues. By following a sample of stroke rehabilitation patients over a one-year period, the primary focus has been given to study cognition in stroke and the association to risk factors and long-term prognosis.

A striking phenomenon that can be observed in a stroke rehabilitation unit is that some patients improve, other remain stable, while some patients decline in their cognitive functioning over time. This may happen even though essential patient characteristics, like age, sex, stroke severity, and motivation for training and rehabilitation are the same. One may wonder why the patients show different developmental pathways after the stroke. The answer to this question is probably complex, but one hypothesis could be that genetic factors may play a role and make some patients particularly vulnerable of developing decline in cognition.

Several socio-demographic, vascular and stroke-related risk factors are already well-established factors that can explain cognitive decline after stroke, but the knowledge of how genetic factors may make a patient susceptible to cognitive reduction after a stroke is limited. The presence of the Apolipoprotein E ε4 allele (ApoE ε4) is well documented as a risk factor of late onset Alzheimer’s disease, the most frequent type of dementia. As both Alzheimer’s disease and stroke primarily affect the elderly, share many of the same risk factors, and both affect cognitive functioning, common genetic vulnerability factors might be expected. The hypothesis that the ApoE ε4 may be a risk factor of post stroke cognitive impairment is therefore explored in this thesis.
Furthermore, the association between early post stroke cognitive performance and long term functional outcome is analyzed. Today, cognitive evaluations of stroke patients are routinely undertaken by the health personnel in most rehabilitation settings, both to identify type and extent of impairments, to plan for the rehabilitation, and to guide patients and relatives with regard to the prognosis. However, the methods used are often crude, and based on clinical judgements or broad cognitive tests (e.g. the Mini Mental Status Examination (MMSE), which have been shown to be insensitive to the type of cognitive impairments frequently appearing after a stroke. Thus, there is a need to validate new cognitive tests, which measure central cognitive functions, have prognostic utilities and is not too time-consuming to administer. The Repeatable Battery of Neuropsychological Status (RBANS) may be such an alternative. RBANS is a cognitive test battery developed especially for the elderly, and has been validated both in patients with dementia and stroke, but only in American populations (Randolph et al. 1998). A Norwegian translation of the RBANS exists, and has been preliminary validated in psychiatric patients (Løberg EM et al. 2006), but never in stroke rehabilitation patients. As a first step of the validation process, the prognostic utility of early post-stroke performance of RBANS in relation to long-term functional outcome is examined.

Emotional symptoms occur frequently after a stroke, particularly among patients who are cognitively impaired (O'Brien et al. 2003). These symptoms include depression, anxiety, emotional lability, apathy, indifference to one’s medical state and life circumstances, and euphoria/mania. Post-stroke depression has been considered the most frequent of the emotional symptoms, since at least one third of stroke survivors experience depression both early and late after a stroke. Formal screening for post-stroke depression is uncommon, and the condition goes unnoticed and untreated in many stroke rehabilitation patients today. This is unfortunate, especially as there are indications that post-stroke depression can have an adverse impact on cognitive function, functional recovery and survival, but this needs to be better documented. In this thesis, the relation between post-stroke depressive symptoms and outcome is further explored.

1.1 Definition of a stroke
According to the definition of The World Health Organisation (WHO) a stroke can be defined as “rapidly developing clinical signs of focal (at times global) disturbance of cerebral
function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin” (Hatano 1976).

The diagnosis of stroke is set on the basis of clinical symptoms and signs, although brain imaging techniques like Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) have become important aids. The most common acute neurological symptoms include one or more of the following: Sudden numbness or weakness of face, arm, or leg, especially in one side of the body; sudden confusion, trouble speaking or understanding speech; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; and sudden severe headache with no known cause (“Stroke Risk Factors and Symptoms”, National Institute of Neurological Disorders and Stroke (NINDS), June 2008).

1.2 Incidence and prevalence of stroke
Stroke is a widespread disease. In Norway, 14500 persons suffer a stroke every year, and of these, 3500 persons have had a stroke before. About 55000 of the Norwegian population have experienced a stroke and must live with its consequences (Ellekjaer and Selmer 2007).

The reported incidence and prevalence rates may be markedly higher if silent strokes, i.e. small strokes which go unrecognized, are included. Silent stroke is said to be the most common type of stroke, and estimated to occur five times as often as obvious strokes (Hachinski 2008). The term ‘silent’ may be misleading though, as persons with ‘silent strokes’ reveal subtle neuropsychological and neurological deficits when examined (Vermeer et al. 2007; Yakushiji et al. 2008)

1.3 Risk factors of stroke
The risk of suffering a stroke increases dramatically by age. The incidence is only 3/10000 in the age group 30-40 years, and rises to 300/10000 in the age group 80-90 years, i.e. a 100-fold increase in incidence (Bonita 1992). According to Swedish figures, the mean age of the stroke patient is 75 years, and more than 80% are above 65 years of age. Males are at a slightly higher risk than females, and also experience their first stroke on average 4.5 years earlier (mean age 74 years for males and 78 years for females) (Socialstyrelsen 2004).

Numerous vascular and life-style related factors contribute to a person’s stroke risk. Among the most important are hypertension, cardiovascular disease (coronary heart disease, cardiac
failure, or symptomatic peripheral arterial disease), hypercholesterolemia, atrial fibrillation, diabetes mellitus, transient ischemic attack (TIA), cigarette smoking, heavy alcohol consumption, and obesity (Galimanis et al. 2009; Goldstein et al. 2006; Mathiesen et al. 2007). These are all modifiable factors. Risk intervention should be targeted towards reduced hypertension, blood glucose and blood lipids according to recommended international standards in addition to life-style changes.

In summary, several factors dispose a person for a stroke. Therefore, a stroke seldom hits blindly. The typical stroke patient will be elderly and have one or more vascular risk factors and/or co-morbid diseases. These factors not only predispose the person of a stroke, but also influence on the prognosis after stroke. Stroke research, in general, has to a large extent ignored this fact, as the bulk of studies have focused on younger patients with first-ever stroke, often with an average age under 65 years (Ballard et al. 2002). Of course, these younger patients reflect an important subgroup of the stroke population, but are hardly representative of the typical stroke patient one meets in a stroke rehabilitation unit.

1.4 Stroke types and how to define them

Stroke is a heterogeneous disease group, which can be classified in two main groups according to the cause, ischemic and haemorrhagic. The distinction is critical as the medical and surgical therapies differ between them. An ischemic stroke is caused by a physical blockage of blood flow to an area of the brain, usually due to a local thrombosis or an embolus. A haemorrhagic stroke is caused by a rupture of a blood vessel in the brain, allowing blood to leak out and accumulate inside or around the brain tissue. In most cases the bleeding takes place within the brain (intracerebral haemorrhage), but may also occur between two of the three membranes which cover the brain (subarachnoid haemorrhage). Although subarachnoid haemorrhage is included in the WHO’s definition of stroke, it is often studied separately in stroke research, due to its different pathophysiology and epidemiology. Ischemic stroke is the most frequent type and occurs in 85-90% of all stroke patients, followed by intracerebral haemorrhagic strokes (10-12%), and subarachnoidal haemorrhage (3-5%) (Ellekjaer and Selmer 2007).

The symptoms a stroke patient presents can vary depending on the topographical location and size of the lesion. Size and localisation have important implications for both rehabilitation planning and prognosis. The Oxfordshire Community Stroke Project Classification (OCSP-
classification), Table 1, which is widely used in both clinical settings and research, categorizes ischemic strokes into four subtypes based on clinical symptoms and signs, and has later also been applied to categorize haemorrhagic strokes (Bamford et al. 1991; Dewey et al. 2001; Mead et al. 2000).

**Table 1:** The Oxfordshire Community Stroke Project Classification (OCSP-classification) (Bamford et al. 1991)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Symptoms</th>
<th>Anatomical basis</th>
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<tbody>
<tr>
<td>Lacunar Circulation Syndrome (LACS)</td>
<td>A pure motor stroke, pure sensory stroke, sensori-motor stroke, or ataxic hemiparesis</td>
<td>Lesion in the basal ganglia or the pons.</td>
</tr>
<tr>
<td>Total Anterior Circulation Syndrome (TACS)</td>
<td>The combination of new higher cerebral dysfunction (e.g. dysphasia, dyscalculia, visuospatial disorder), homonymous visual field defect, and ipsilateral motor and/or sensory deficit of at least two areas of the face, arm, and leg.</td>
<td>Large lesion affecting both the deep and superficial territories of the middle cerebral artery (MCA)</td>
</tr>
<tr>
<td>Partial Anterior Circulation Syndrome (PACS)</td>
<td>Two of the three components of the TACI syndrome, with higher cerebral dysfunction alone, or with a motor/sensory deficit more restricted than those classified as LACS (e.g. confined to one limb, or to face and hand but not to the whole arm)</td>
<td>More restricted cortical lesion, either of the upper or the lower division of the MCA, or anterior cerebral artery (ACA) territory</td>
</tr>
<tr>
<td>Posterior Circulation Syndrome (POCS)</td>
<td>Any of the following: Ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit, bilateral motor and/or sensory deficit, disorder of conjugate eye movement, cerebellar dysfunction without ipsilateral long-tract deficit (i.e. ataxic hemiparesis), or isolated homonymous visual field defect</td>
<td>Brainstem, cerebellum or occipital lobes</td>
</tr>
</tbody>
</table>

Type and extent of neurological symptoms and signs are also frequently measured and quantified with validated scales like the National Institute of Health Stroke Scale (NIHSS) (Goldstein et al. 1989) and the Scandinavian Stroke Scale (SSS) (Scandinavian Stroke Study Group 1985; Scandinavian Stroke Study Group 1987). The scales are not only used for diagnostic purposes but also in order to predict stroke outcome.

The NIHSS is the most comprehensive of the two, and measures thirteen different aspects of neurological function, including level of consciousness (alertness, response to questions and commands), eye movements, visual fields, facial symmetry, motor strengths (arm/leg),
sensation, limb ataxia, language, dysarthria and extinction/inattention. Sometimes an extra item is added, motor strength of hand. Total NIHSS-score ranges from 0-42 points, with a higher score indicating more severe impairment.

The SSS comprises nine items, including consciousness, eye movement, arm (motor power), hand (motor power), leg (motor power), orientation, speech, facial palsy and gait. The maximum total score is 58 points, indicating no neurological impairments.

1.5 The prognosis of stroke and how to measure it
Stroke outcomes are usually classified according to survival (death), impairment (sign and symptoms of the underlying pathology), disability (limitations in functional activities), handicap (limitations in role functions), and quality of life (patient’s general well-being resulting from physical, psychological, and social aspects of life) (Barker-Collo and Feigin 2006).

Mortality after stroke is high, especially in the acute phase, but also in the following years. At 30 days post-stroke the mortality rate is approximately 19-25%, at 12 months 35-40%, and after 5 years 55-60% (Donnan et al. 2008; Ellekjaer et al. 1997; Hankey et al. 1998; Hankey et al. 2000; Hankey 2003). The mortality rate during the first 12 months is equivalent to a 10-fold risk compared to the general population of same age and sex. The major causes of death during the first year are stroke related (brain oedema and secondary complications such as infections and venous thrombosis), while a cardiovascular disease is the major cause one to five years post-stroke (Hankey et al. 2000).

However, for most patients, a stroke is not lethal, but lead to functional impairments affecting their daily lives. According to figures from the Swedish Stroke Registry (Socialstyrelsen 2004), as many as 80% of stroke survivors lived in their own house two years after the stroke. However, a large proportion was dependent in primary (personal) and secondary (instrumental) activities of daily living (ADL). With respect to primary ADL, 36% were dependent in outdoor mobility, 24% in grooming and dressing, 18% in toilet use, 15% in indoor mobility, and 7% were dependent in situations related to eating and drinking. The proportion dependent in secondary ADL was even higher. More than 60% needed help in preparing meals, local shopping, and housework activities.
A similar picture is reported in two population-based studies from Auckland, New Zealand. Almost 75% of the stroke survivors were living at home six months after the stroke (Bonita 1992). At three years post-stroke more than 50% of the survivors reported incomplete recovery (i.e. dependent in at least one secondary ADL-activity), and, of these, 20% were dependent in at least one primary ADL-activity (Bonita et al. 1997).

Considering the serious impact on functional outcome, it may not come as a surprise that both an association between stroke and reduced quality of life in the patient (Carod-Artal and Egido 2009), and an increased psychosocial burden on the caregiver is well-documented (Thommessen et al. 2001; Thommessen et al. 2002; Wyller et al. 2003).

Different impairments in functional abilities may be measured by validated scales like Barthel Index (BI) (Mahoney and Barthel 1965), the Frenchay Social Activities Index (FAI) (Schuling et al. 1993), the Functional Independence Measure (FIM) (Hamilton et al. 1994; Kidd et al. 1995), and the modified Rankin Scale (mRS) (van Swieten et al. 1988).

BI measures impairments in personal ADL and comprises ten different aspects of self-care, including incontinence (bowels and bladder), grooming, toilet use, feeding, transfers bed to chair and back, mobility on level surfaces, dressing, stairs, and bathing. Total score can vary from 0 (maximum impairment) to 20 (functional independence).

FAI is a measure of instrumental ADL and consists of 15 items, including preparing main meals, washing up, washing clothes, light and heavy housework, local shopping, social outings, walking outside, actively pursuing hobby, driving car/bus travel, outings/car rides, gardening, household/car maintenance, reading books and gainful work. Minimum score is 15 (inactive) and maximum is 60 points (very active).

FIM consists of 18 items and addresses two basic domains, physical (13 items) and cognitive (5 items). The physical items resemble those found in the BI and include measures of self-care, sphincter control, mobility and locomotion, while the cognitive items measures aspects of social interaction, problem-solving and memory. Total FIM-score can vary from 18 (complete dependence/total assistance) to 126 points (complete independence). Subscale scores of the physical and cognitive domains can be calculated separately, and may yield more useful information rather than relying solely on the total FIM score.
In contrast to the BI, FAI and FIM which focus on ability to perform specific tasks, the mRS is a global disability scale. It is quick and easy to administer, and consists of seven categories: 0 (no symptoms), 1 (no significant disability despite symptoms; able to carry out all usual duties and activities), 2 (slight disability; unable to carry out all previous activities but able to look after own affairs without assistance), 3 (moderate disability; requiring some help, but able to walk without assistance), 4 (moderate severe disability; unable to walk without assistance, and unable to attend to own bodily needs without assistance), 5 (severe disability; bedridden, incontinent, and requiring constant nursing and attention), and 6 (dead). Scoring is done on the basis of the administrator’s subjective judgement. A limitation is the lack of clear cut criteria to assign grades, which may reduce the reliability of the scale. A structured interview with specific questions to grade each category has been developed and may enhance reliability.

The type of stroke, its size and topographical location have an impact on the prognosis. The prognosis for patients with hemorrhagic strokes is more severe than for ischemic strokes with a 30 days mortality rate of 38-50% (Ellekjaer et al. 1997). Stroke severity and topographical location according to the OCSP-classification have been shown to predict mortality in ischemic strokes. TACS have the worst prognosis with a 12-months mortality rate of 60%, followed by PACS and POCS with 15-20%, while LACS have the best prognosis with a rate of 11% (Bamford et al. 1991).

For the stroke survivors, size and topographical location of the lesion seem more important than stroke type (ischemic or hemorrhagic) in relation to functional prognosis. Less than one in ten patients suffering a TACS reaches independence within one year (defined as mRS-score=0-2), in contrast to approximately six in ten of those with PACS, POCS or LACS (Bamford et al. 1991; Fure et al. 2006b).

Improvement in functional impairments may be expected in the majority of patients with first-ever stroke, but mainly takes place within the first 6 months after a stroke (Jorgensen et al. 1999). In the Copenhagen Stroke Study, neurological (measured with the SSS) and functional recovery (measured with the BI) was assessed weekly from stroke onset to end of rehabilitation, and again six months later. The time course of functional recovery was strongly correlated with the initial neurological stroke severity, but for 95% of the patients the
functional recovery was completed within 13 weeks from stroke onset. Patients with mild strokes reached their best function within 9 weeks, moderate strokes within 13 weeks, severe strokes within 17 weeks, and very severe strokes within 20 weeks after stroke onset. Both compensational and intrinsic neuronal mechanisms probably contribute to the functional recovery seen after a stroke. Compensation involves teaching patients with persistent functional deficits new approaches to perform important tasks of daily living, either by using the affected or non-affected limb. In the Copenhagen Stroke Study, compensation was associated with younger age, less severe strokes, and more intact higher cortical functions. Neurological recovery involves at least three processes: Restoration of cerebral blood flow by spontaneous reperfusion, resolution of oedema or hemorrhage, and transfer of lost neural function to intact parts of the brain.

An understanding of factors affecting the prognosis is important. There are strong indications that cognitive abilities may be at least as important as sensori-motor functioning in predicting outcome.

1.6 Cognition in stroke

1.6.1 Definition of cognition

The concept of cognition derives from the Latin word cognoscere, which is made up of "co-" + "gnoscere" = to come to know. According to the Webster’s New World Medical Dictionary 3rd edition, cognition can be defined as the process of knowing and, more precisely, the process of being aware, knowing, thinking, learning and judging (WebMD 2008).

Cognition is a core concept in neuropsychology, a scientific discipline which studies the relationship between brain and behaviour. In neuropsychology, cognition is formally assessed through the administration of neuropsychological tests. Neuropsychological assessment may serve several purposes, but central is to examine the effects of brain injury or neuropathological processes that a person may have experienced. Cognitive functions which typically are assessed include attention, learning, memory, language, visuospatial/constructional functions, executive functions, and sensori-motor functions. These
are functions which can be temporarily or permanently impaired when a person suffers a stroke. In addition, a measure of overall cognitive performance level is often given.

The size and location of a brain damage are two major factors which determine type and severity of cognitive impairment. It would be far beyond the scope of this thesis to give a detailed presentation of all the cognitive impairments which may appear after a stroke. Table 2 gives an overview of the most important cognitive functions and how they are related to brain structure and blood supply (Weinstein and Swenson 2000).

**Table 2:** Neuropsychological impairment in stroke as related to brain structure and blood supply (Weinstein and Swenson 2000).

<table>
<thead>
<tr>
<th>Function</th>
<th>Impairment</th>
<th>Brain structure</th>
<th>Blood supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensorimotor</td>
<td>Paralysis of contralateral face, arm, and leg</td>
<td>Primary motor area, precentral gyrus</td>
<td>Middle cerebral artery, anterior cerebral artery</td>
</tr>
<tr>
<td></td>
<td>Sensory impairment over face, arm, and leg</td>
<td>Primary sensory area, postcentral gyrus</td>
<td>Middle cerebral artery, anterior cerebral artery</td>
</tr>
<tr>
<td>Language</td>
<td>Broca’s aphasia</td>
<td>Inferior frontal gyrus in dominant hemisphere</td>
<td>Middle cerebral artery</td>
</tr>
<tr>
<td></td>
<td>Wernicke’s aphasia</td>
<td>Superior temporal gyrus in dominant hemisphere</td>
<td>Middle cerebral artery</td>
</tr>
<tr>
<td>Visual perception</td>
<td>Homonymous hemianopia</td>
<td>Optic radiation deep in temporal convolution</td>
<td>Middle cerebral artery, posterior cerebral artery</td>
</tr>
<tr>
<td></td>
<td>Visual integration, spatial neglect, visual agnosia</td>
<td>Parietal-occipital lobe</td>
<td>Middle cerebral artery, posterior cerebral artery</td>
</tr>
<tr>
<td></td>
<td>Constructional apraxia, dressing apraxia</td>
<td>Parietal lobe, non-dominant hemisphere</td>
<td>Middle cerebral artery</td>
</tr>
<tr>
<td></td>
<td>Gerstmann’s syndrome (agraphia, acaclulia, alexia, finger agnosia, right-left confusion)</td>
<td>Angular gyrus of the dominant hemisphere</td>
<td>Middle cerebral artery</td>
</tr>
<tr>
<td>Movement</td>
<td>Ideomotor and ideational apraxia</td>
<td>Left temporal, parietal, occipital area</td>
<td>Middle cerebral artery, posterior cerebral artery</td>
</tr>
<tr>
<td>Memory</td>
<td>Short-term and long-term memory impairment</td>
<td>Hippocampus, medial temporal lobes, frontal lobes, basal forebrain,</td>
<td>Medial cerebral, posterior cerebral, anterior choroidal, and posterior communicating arteries</td>
</tr>
<tr>
<td></td>
<td>Working memory impairment</td>
<td>medial thalamus</td>
<td>Anterior cerebral artery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dorsolateral frontal lobes</td>
<td></td>
</tr>
<tr>
<td>Frontal executive</td>
<td>Impairment in set maintenance, problem solving, planning, self-evaluation, ability to modify behaviour</td>
<td>Dorsolateral frontal</td>
<td>Middle cerebral artery</td>
</tr>
<tr>
<td></td>
<td>Impairment in inhibition, emotional regulation Akinesia, bradykinesia, dyskinesia</td>
<td>Orbital frontal</td>
<td>Anterior cerebral artery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Basal ganglia, putamen, globus pallidus, caudate nucleus, amygdaloid</td>
<td>Anterior choroidal artery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Middle cerebral artery</td>
</tr>
</tbody>
</table>
As the brain’s vascular territories are only partially congruent with its subdivision into functional neural networks and circuitries, the cognitive symptoms seen in stroke are seldom pure, but will involve several cognitive functions.

1.6.2 The problem of terminology and methodology

Although there is no disagreement that cognitive impairments are frequent after stroke, the published data on prevalence rates are highly inconsistent and vary from as low as 7% (Kokmen et al. 1996) up to 82% (Rasquin et al. 2004). Differences in terminology, the characteristics of the study samples, the choice of cognitive tests, the applied cut-off score to define cognitive impairment, and the time period between stroke onset and cognitive testing all contribute to this confusing picture and make comparisons between the studies difficult (de Haan et al. 2006; Pendlebury 2009).

Post-stroke dementia has been extensively studied, which refers to a very serious chronic condition characterized by a loss of cognitive and intellectual abilities severe enough to interfere with the ability to cope with activities of daily living. However, by focusing entirely on dementia, one is likely to underestimate the true prevalence of post-stroke cognitive impairment. Generally, the current diagnostic criteria for dementia are heavily weighted toward memory impairment, which is a core symptom in Alzheimer’s disease (AD), but less common in stroke. (O’Brien et al. 2003; Rockwood 2002; Stephens et al. 2004). The consequence is that stroke patients could have serious cognitive impairments, e.g. in attention or executive functions, affecting rehabilitation, quality of life and mortality, but not fulfil the diagnostic criteria of dementia. Also many stroke patients have mild cognitive impairment which do not fulfil the criteria of dementia, but still negatively affect their lives and put them at substantial risk of developing subsequent dementia. In fact, about 40-50% of the patients with mild cognitive impairments after a stroke go on to develop dementia over the next five years (Ingles et al. 2002; Serrano et al. 2007; Wentzel et al. 2001). The term post-stroke cognitive impairment no dementia (post-stroke CIND) is frequently applied to refer to this latter condition.

Presently, there is no consensus as to how post-stroke cognitive impairment should be measured. Time-consuming, sensitive neuropsychological test batteries, e.g. the Halstead-Reitan Battery, Wechsler Adult Intelligence Scale or Wechsler Memory Scale are costly to administer and not well tolerated in this patient group, due to serious capacity restraints in
many of the patients (e.g. fluctuating consciousness level, dementia, aphasia, fatigue, lack of initiative/motivation) On the other hand short cognitive screening tests, like the MMSE and Clock Drawing Test have been shown to be insensitive to different cognitive symptoms frequently appearing after stroke (Blake et al. 2002; Nokleby et al. 2008; Nys et al. 2005a). “Intermediate” cognitive test batteries which can be tolerated by most stroke patients exist, e.g. Cambridge Cognitive Examination (CAMCOG), RBANS, The Neurobehavioral Cognitive Status Examination, and the Montreal Cognitive Assessment, and may be interesting alternatives.

The choice of cognitive tests, norms and the applied cut-off score to define cognitive impairment will influence on the reported prevalence rates. Cut-off scores between 2nd and 10th percentile are used to define impairment on a cognitive test. A cut-off score of 10th percentile is in accordance with the Mayo clinic's recommendation for mild cognitive impairment (MCI) (Petersen et al. 1999), while a cut-off of 2nd percentile is usually considered indicative of a severe cognitive disorder (Lezak 2004).

Generally, population studies report lower prevalence rates than hospital studies, probably as a consequence of a higher proportion of patients with the mildest strokes (Pendlebury and Rothwell 2009).

In this author’s view, the heterogeneity in methodology and design is unfortunate, not only because it affects the reported prevalence rates, but more importantly, because it can obscure knowledge of risk factors, treatment/rehabilitation, and prognosis. International harmonisation standards are warranted in this field to ensure valid clinical and research data in the future. Attempts to harmonise standards have been made by the National Institute for Neurological Disorders and Stroke (NINDS) and Canadian Stroke Network (Hachinski et al. 2006; Moorhouse and Rockwood 2008; Rockwood et al. 2003).

1.6.3 The prevalence of post-stroke cognitive impairment and dementia
Hospital-based studies which have applied neuropsychological testing within the first three months post-stroke report prevalence rates of cognitive impairment varying from 33% to 82% in patients with first-ever stroke and free from pre-stroke dementia (Hoffmann 2001; Lesniak et al. 2008; Nys et al. 2005b; Nys et al. 2007; Pohjasvaara et al. 1997; Rasquin et al. 2005a; Rasquin et al. 2004; Stephens et al. 2004; Tatemichi et al. 1994).
A higher frequency of cognitive impairment in stroke patients compared with aging control subjects is confirmed. In Tatemichi et al.’s (1994) study, cognitive performance of 227 ischaemic stroke patients free from pre-stroke dementia (mean age 70.8, SD 7.9) were examined three months post-stroke and compared with 240 stroke free controls. A total of seventeen tests were used to assess memory, orientation, verbal skills, visuospatial ability, abstract reasoning, and attention. Cognitive impairment, defined as a failure on four tests or more (with cut-off score of 5th percentile on each test), occurred in 35.2% of the stroke patients compared to 3.8% of the controls. Reduced performance on at least one test was present in 78% of the stroke patients. Compared to the controls, the most frequently affected cognitive domains in the stroke patients were memory, orientation, language and attention. Cognitive impairments in the stroke patients were more frequent in cases of major cortical syndromes and in patients with infarctions in the left anterior and posterior cerebral artery territories.

A stroke is said to be characterized by its focal effects. This may be true for neurological symptoms, but in relation to cognition, deficits in more than one domain frequently occur. Pohjasvaara et al. (1997) examined 486 consecutively admitted ischemic stroke patients between 55 and 85 years of age (mean 71.2 years), and found that cognitive impairment of any kind was present in 61.7% of the subjects 3 months post-stroke. However, about 27% of the subjects were impaired in three or more cognitive domains. The functions most frequently affected were constructional and visuospatial abilities (37%), memory functions (23%-34%), executive functions (25%), orientation (23%), attention (22%), and aphasia (14%).

Cognitive changes as assessed by neuropsychological tests are also confirmed by 50% or more of the patients and their next of kin in interviews 3-9 months post-stroke. (Hochstenbach et al. 2005; Visser-Keizer et al. 2002). In the study of Hochstenbach et al. (2005) the most frequent cognitive complaints were forgetfulness (60%), mental slowness (56%), poor concentration (55%), and inability to do two things simultaneously (53%). Interestingly, the degree of agreement between patients and their next of kin tended to be low in both studies. Visser-Keitzer et al. (2002) found that while left hemisphere stroke patients agreed with their partners on the number and severity of most changes, partners of right hemisphere patients reported more frequent and more severe changes than the patients themselves. The level of observed altered behaviour, distress of the partner, distress of left-
sided stroke patients and hemispatial neglect of right-sided stroke patients emerged as factors related to disagreement between the stroke patients and their partners.

Is there a specific cognitive profile of stroke patients? Albeit debated, some researchers have suggested that independent of the lesion site and size, deficits in executive functions, attention, and psychomotor speed may be the most frequent and most severely affected after a stroke, while memory functions are relatively preserved (in contrast to the early stages of Alzheimer’s Disease) (Desmond 2004; Lesniak et al. 2008; Nys et al. 2007; O'Brien et al. 2003; Sachdev et al. 2004; Stephens et al. 2004). The reason could be that both executive function and attention involve widely distributed networks of cortical, subcortical, and infratentorial areas of the brain, making these functions vulnerable to the effect of a stroke independent of site (Baker et al. 1996; Egner et al. 2008; Fassbender et al. 2004; Liu et al. 2003; Posner and Petersen 1990; Vataja et al. 2003). Such symptoms are less obvious and may therefore be overlooked or misattributed by health personnel unless formal testing is provided. They can also constitute a source of burden and confusion for the patients and their relatives. Misattributions include lack of motivation, cooperation or symptoms of depression.

With respect to frequency of post-stroke dementia, a recent systematic meta-analysis, based on twenty two hospital-based and eight population-based studies with a total of 7511 patients, concluded that 10% of the patients had dementia before their first stroke, 10% developed new dementia soon after their first stroke, and more than a third had dementia after recurrent stroke (Pendlebury and Rothwell 2009). The meta-analysis illustrates well how differences in study setting (hospital based vs population based) and patient characteristics (whether persons with pre-stroke dementia and/or previous or recurrent strokes are included or not) heavily influence the reported prevalence figures of post-stroke dementia. These factors explained more than 90% of the variance between the studies. In fact, the prevalence of post-stroke dementia varied from 7% in a population-based study which excluded persons with pre-stroke dementia to 40% or more in a hospital-based study which included pre-stroke dementia and recurrent strokes. Previously, it has been reported that choice of criteria to define post-stroke dementia (e.g. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN)) affects the reported prevalence figure (Pohjasvaara et al. 1997). However, this was not
confirmed in the meta-analysis, in which diagnostic criteria only explained 2% of the variance between the studies.

A higher frequency of dementia in stroke patients compared with aging control subjects is confirmed in epidemiological studies. In a cohort of 251 hospitalized ischemic stroke patients aged 60 years or older examined 3 months after the stroke, dementia (according to DSM-III R-criteria) was diagnosed in 26.3% of the patients, while the corresponding figure in a control sample of 249 subjects free from stroke, recruited from the community, and matched by age was 3.2% (Tatemichi et al. 1992). The researchers reported an almost 10-fold increased risk of dementia (odds ratio = 9.4) in the stroke patients compared to the controls.

1.6.4 Risk factors of post-stroke cognitive impairment and dementia

Several risk factors have been associated with post-stroke cognitive impairment and dementia, which support the view that post-stroke cognitive performance is determined by multiple factors. These may be divided into socio-demographic variables, stroke characteristics, pre-stroke functioning, and vascular risk factors.

Of the socio-demographic variables, older age has, with a few exceptions (Tatemichi et al. 1994), consistently been reported to increase the risk of post-stroke cognitive impairment (Pohjasvaara et al. 1997; Sachdev et al. 2006). For example, The Helsinki Stroke Aging Memory Study (Pohjasvaara et al. 1997) examined 486 consecutively admitted stroke patients between 55 and 85 years of age (mean age 71 years) three months post-stroke, of which 93% were testable. Cognitive decline of any kind was present in 62% of the patients, but the prevalence rates varied significantly depending on age. In the age groups 55-64 years, 65-74 years and 75-85 years, the prevalence rates of cognitive impairment were 46%, 54% and 74% respectively, and for dementia (according to DSM-IV criteria) the prevalence rates were 10%, 19%, and 24% in the different age-groups. Lower cognitive capacity, co-morbidity, and polypharmacy among the elderly probably contribute to the increased risk. Fewer years of education is associated with post-stroke cognitive impairment in many studies, possibly as an effect of lowered constitutional capacity in combination with less efficient post-stroke coping strategies. Increased risk of post-stroke cognitive impairment in females has been reported in a few studies, but could have resulted from age-confounding (Pendlebury and Rothwell 2009).
Stroke characteristics (location and size of lesion) are understood as crucial factors explaining severity of cognitive impairment and dementia (de Haan et al. 2006; Kalaria and Ballard 2001; Pendlebury 2009). Lesions in cortical structures (TACS/PACS), especially bilaterally or in the dominant hemisphere, rather than subcortical (LACS), in the brainstem or cerebellum (POCS) are generally considered to produce more severe cognitive impairments (Censori et al. 1996; Tatemichi et al. 1993), although recent studies provide evidence that cognitive impairments is frequent in lacunar (Fure et al. 2006b; Gold et al. 2005) and cerebellar strokes (Hokkanen et al. 2006; Kalashnikova et al. 2005). With respect to lesion volume, earlier studies suggested that volumes larger than 50 mL of infarcted tissue might be associated with dementia and larger than 1100 mL were always associated with dementia (Mielke et al. 1992; Tomlinson et al. 1970). Later studies have demonstrated that dementia also occur in patients with infarcted volumes of less than 20 mL (and some less than 10 mL) (Leys et al. 1999). Stroke complications, like hypoxic ischaemic episodes, incontinence, acute confusion, early seizures, and abnormal electroencephalography (EEG) are also significantly related to post-stroke dementia, but could merely reflect stroke severity (Pendlebury 2009). Other brain imaging factors significantly associated with post-stroke dementia have been leukoaraiosis, general brain atrophy, and medial temporal lobe atrophy (Pendlebury 2009).

Some stroke patients diagnosed with post-stroke cognitive impairment or dementia may have had pre-existing mild cognitive impairments or dementia. In the meta-analysis of Pendlebury and Rotwell (2009) pre-stroke dementia was common with a pooled prevalence rate of 14.4% in hospital-based studies and 9.1% in population based studies. Dementia of mild degree may easily go unnoticed and affects prognosis (Henon et al. 1997), and is associated with medial temporal atrophy suggestive of Alzheimer-pathology in many of these patients (Henon et al. 1998; Henon et al. 2006).

Among vascular risk factors, previous strokes, atrial fibrillation and diabetes are frequently reported to be significantly associated with both post-stroke cognitive impairment and dementia. The role of ischaemic heart disease, previous TIA, hypertension, homocysteinemia, smoking, and moderate alcohol consumption is uncertain (Kalaria and Ballard 2001; Pendlebury and Rothwell 2009).
1.6.5. The long-term course of post-stroke cognitive impairment

Longitudinal studies following the course of post-stroke cognitive performance are relatively scarce (Ballard et al. 2003; del Ser et al. 2005; Firbank et al. 2007; Hochstenbach et al. 2003; Lesniak et al. 2008; Rasquin et al. 2004; Tham et al. 2002). Although the results of the few studies conducted are not conclusive, the general impression is that the majority of stroke patients follow a fairly stable course in overall cognitive performance over the first 1-3 years, but that some patients improve and others decline over time. In the study of del Ser et al. (2005), 193 consecutive patients were tested with an extensive neuropsychological battery three months after the stroke and followed for two years. At follow up, cognitive status according to change in Clinical Dementia Rating Score had improved in 8%, was stable in 78%, and had declined in 14%. It has been argued that the degree of early recovery is often underestimated, as most studies have waited until three months post-stroke for their baseline examination. The implication is that spontaneous cognitive recovery through self-repair mechanisms of the brain (perilesional changes, contralateral reorganisation, striatal neurogenesis) taking place in the early post-stroke phase is overlooked (de Haan et al. 2006).

Variables associated with improvement in cognitive performance over time are right-sided lesions, higher baseline MMSE-score (indicating relatively preserved cognitive functioning), and female sex (Ballard et al. 2003; del Ser et al. 2005; Hochstenbach et al. 2003; Rasquin et al. 2005b; Serrano et al. 2007). Reported risk factors for progression include older age, pre-stroke cognitive decline, medial temporal atrophy on CT-scan, polypharmacy, hypotension during admission (del Ser et al. 2005), expressive aphasia (Ballard et al. 2003), impaired cognitive performance at baseline (Sachdev et al. 2009; Serrano et al. 2007), and recurrent stroke (Srikanth et al. 2006). It has been suggested that medial temporal atrophy of the brain may be of greater importance than white matter hyperintensities for subsequent post-stroke cognitive decline and increasing brain atrophy (Firbank et al. 2007), implying a link between Alzheimer-pathology and progressive cognitive decline in stroke patients. As a genetic component through the presence of the ApoE ε4-allele is well-documented as a strong risk factor for late onset Alzheimer’s disease (AD), i.e. AD occurring after the age of 65 years (Bales 2010), one interesting question arises: Is the ApoE ε4-allele also a risk factor of post-stroke cognitive impairment?
The ApoE ε4 allele - a genetic risk factor of cognitive impairment

1.7.1 Characteristics of the ApoE gene

The possible contribution of genetic factors as predictors of post-stroke cognitive impairment has so far received relatively little research interest, and the results have varied.

The Apolipoprotein E (ApoE) gene stands out as a particular interesting candidate. The gene is located on chromosome 19 and codes for the plasma protein Apolipoprotein E (APOE), which is a multifunctional circulating plasma protein synthesized in several organs of the body, including liver, spleen, kidney and brain. It is an important mediator of cholesterol and lipid transport, and is also involved in neural repair processes of the brain (Mahley 1988; Mahley and Rall, Jr. 2000).

The gene is polymorphic with three common variants or alleles, denoted as ApoE ε2, ApoE ε3, and ApoE ε4. (In addition, there exist some rare variants, ApoE ε1, ApoE ε5, and several forms of ApoE ε2, but these constitute less than 1% of the polymorphisms (Zannis and Breslow 1981)). The frequency of the different alleles varies in different populations of the world. Independent of populations, however, the ε3-allele is the most common. In Western samples the frequency of the ε3-allele is approximately 70-80%, the ε4 is 10-15% and ε2 is 5-10%. The ApoE ε4-allele is more common in populations of the northern Europe compared to southern Europe.

As every person inherits one allele from each parent, six common combinations of the APOE-genotype exist, ε2ε2, ε2ε3, ε2ε4, ε3ε3, ε3ε4 and ε4ε4. The distribution of APOE genotypes in a meta-analysis of 45 studies from 17 countries (n=14799) is presented in table 3, showing that the most common genotypes are ε3ε3, ε3ε4 and ε2ε3 (in that order) (Dallongeville et al. 1992).
### Table 3: The distribution of APOE genotypes in a meta-analysis of 45 studies from 17 countries (n=14799) (Dallongeville et al. 1992)

<table>
<thead>
<tr>
<th>Allele</th>
<th>ε2</th>
<th>ε3</th>
<th>ε4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ε2</td>
<td>0.6%</td>
<td>10.7%</td>
<td>1.6%</td>
</tr>
<tr>
<td>ε3</td>
<td></td>
<td>62.4%</td>
<td>22.3%</td>
</tr>
<tr>
<td>ε4</td>
<td></td>
<td></td>
<td>2.3%</td>
</tr>
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Few studies have examined the distribution of APOE-genotypes in elderly persons with normal cognition in Scandinavia. However, in a recent study of 561 Norwegians with a mean age of 75.1 years (SD 7.3), a genotypic distribution is reported which compares quite well with the figures of Dallongeville et al (1992), ε2ε2 (0.7%), ε2ε3 (17.1%), ε2ε4 (4.1%), ε3ε3 (55.8%), ε3ε4 (20.0%) and ε4ε4 (2.3%) (Sando et al. 2008). There were no difference in genotypic distribution between men and women. These studies confirm that possession of one or two copies of the ApoE ε4-allele is common, and can be expected to occur approximately in 20-25% of the persons in Norway.

#### 1.7.2 ApoE ε4 and Alzheimer’s disease

Possession of the ApoE ε4-allele has been established as a major risk factor for late onset AD, i.e. AD which occurs after the age of 65 years, and is also associated with increased risk of early onset AD (Alberts et al. 1995; Corder et al. 1993; Saunders et al. 1993; Strittmatter et al. 1993; Tanzi and Bertram 2005). In the Norwegian study of Sando et al. of 376 AD patients (mean age 79.5 years, SD 8.2) and 561 controls (mean age 75.1, SD 7.3), one or two copies of the ApoE ε4-allele was present in 56% of the AD patients compared to 22% of the controls. There appears to be a dose-dependent effect of the ApoE ε4-allele both with respect to disease risk and debut age of late onset AD. Depending on whether the person possesses zero, one, or two copies of the ε4-allele, the risk of developing the disease rises from 20%, to 50% and up to 90%, while the mean age at onset declines from 84.3, to 75.5, and down to 68.4 years respectively (Corder et al. 1993).

AD is the most common of the neurodegenerative diseases causing dementia and constitutes approximately 60-80% of all dementia cases. The disease is characterized by an irreversible, progressive cognitive decline, and especially in the domains of episodic learning/memory and
attention in the early stages of the disease. As the disease progresses the cognitive deterioration is accompanied with loss of body functions and personality changes, and inevitably leads to helplessness and death. A loss of neurons and synapses in the cerebral cortex and certain subcortical regions leads to atrophy of the AD-brain. Both MRI- and positron emission tomography (PET)-studies confirm that these changes are most prominent in the medial part of the temporal lobe, including hippocampus, at the initial stages, but spread to other parts as the disease progresses, including the parietal lobe, and parts of the frontal cortex and cingulate gyrus. Although the cause and progression of AD is not well understood, degeneration of the cholinergic neuronal network in the brain, and aggregation of amyloid plaques outside the neurons and formation of neurofibrillary tangles inside the neurons are hypothesized to be central in the disease (Wenk 2003). Plaques are dense, mostly insoluble deposits of amyloid-beta peptide and cellular material outside and around neurons. The neurofibrillary tangles are aggregates of the microtubule-associated protein tau which has become hyperphosphorylated and accumulate inside the cells themselves (Mahley and Huang 2009). Carriers of one or two copies of the ApoE ε4-allele are especially vulnerable to these processes.

There is an interesting relation between AD and post-stroke cognitive impairment. Both diseases affect cognition and share common risk factors (e.g. higher age, less years of education, and vascular factors including hypertension, atrial fibrillation, diabetes mellitus, previous smoking). Although cases of dementia most frequently are diagnosed as pure AD, autopsy studies clearly suggest that cerebrovascular pathology is common in AD-patients, with 60-90% of the patients exhibiting variable cerebrovascular pathology (e.g. white matter hyperintensities, lacunar infarctions or microhemorrhages), and nearly 30% cerebral infarcts (Kalaria 2002; Viswanathan et al. 2009). The contribution of cerebrovascular disease may be important in determining the presence and severity of symptoms in AD. In a study of 102 elderly nuns (aged 76-100 years), cognitive performance and prevalence of dementia were determined while they were alive. At autopsy, lacunar and larger brain infarcts were identified, and senile plaques and neurofibrillary tangles in the neocortex quantified. Half of the nuns met neuropathologic criteria for AD, and, of these, those with brain infarcts had poorer cognitive function and a higher prevalence of dementia than those without infarcts. Less degree of AD-pathology in the neocortex were necessary to trigger dementia when infarcts co-occurred, especially in cases of lacunar infarcts in the basal ganglia, thalamus, or
deep white matter (Snowdon et al. 1997). These results suggest that cerebrovascular disease may interact additively or synergistically with AD to produce a mixed pathology.

1.7.3 ApoE ε4 and Mild Cognitive Impairment

In normal aging, some types of cognitive reduction are expected (e.g. slower information processing speed and episodic learning ability). This natural process is denoted age-associated cognitive decline in the literature. For some persons, however, the cognitive decline is more than expected considering their age and education level, but still do not interfere significantly with their daily activities, necessary to fulfill the criteria of a dementia diagnosis. This transitional stage between age-associated cognitive decline and dementia is termed Mild Cognitive Impairment (MCI), and affects about 20% of the population above 70 years of age. According to the Mayo Clinic, commonly used criteria for the diagnosis are deficient memory (which should be confirmed by another person), essentially normal judgment, perception and reasoning skills, largely normal activities of daily living, and reduced performance on cognitive tests of learning and memory adjusted for age and education. MCI is associated with a substantial increased risk of converting to AD with an annual progression rate of 10-15% (Celsis 2000; Petersen et al. 2001). In a large community-based study, individuals with MCI were about 3 times more likely to develop AD over a 4.5 year period than those without cognitive impairment, and also had 1.7 increased risk of dying (Bennett et al. 2002). The ApoE ε4-allele is not only a risk factor of MCI, but is also associated with a higher risk of progression from MCI to AD (DeCarli et al. 2001; Petersen et al. 1995; Traykov et al. 1999). As in AD, a significant dose-effect of the ε4-allele is reported in MCI-patients who convert to AD (Smith et al. 1998).

1.7.4 ApoE ε4 and normal aging

A negative effect of the ApoE ε4-allele on cognition, particularly on memory tasks, in normal middle-aged (>50 years) and elderly persons (> 65 years) is reported in several studies (Dik et al. 2000a; Driscoll et al. 2005; Greenwood et al. 2005; Nilsson et al. 2006), but not confirmed in others (Bennett et al. 2005; Small et al. 2000; Smith et al. 1998). Differences in the sensitivity of the cognitive tests, small sample sizes, and unequal samples could potentially contribute to the conflicting results. In a meta-analysis of 38 studies, in which cognitive performance was collapsed into 8 domains, carriers of the ApoE ε4-allele scored significantly worse than non-carriers on measures of global cognitive functioning, episodic memory, and executive functioning, while there were no differences in primary memory, attention, visuospatial skills,
verbal ability, or perceptual speed (Small et al. 2004). Notably, the authors conclude that the ApoE ε4 genotype does affect cognitive performance in healthy aging, but stress that the influence is relatively small and specific to certain domains of cognitive performance. An important question is whether the cognitive deficits merely reflect accelerated normal aging or are early symptoms of yet undiagnosed AD in the ApoE ε4-carriers. The literature is ambiguous in this respect (Bondi et al. 1999; Nilsson et al. 2006; Savitz et al. 2006; Small et al. 2000). Bondi et al. (1999) reports disappearance of the ApoE ε4-effect on memory function when subjects who went on to develop AD were excluded from the analysis. On the other hand, Nilsson et al. (2006) reports that the ApoE ε4-effect on episodic memory specific tasks remained significant even when all subjects diagnosed with dementia within ten years after examination were excluded.

The association between reduced memory performance and the ApoE ε4-allele in non-demented elderly has been linked to smaller hippocampal volume in the ApoE ε4-carriers. Hippocampus, which is part of the medial temporal lobe, is a key structure for declarative memory functioning, and, hence, such an association could be expected. However, cross-sectional structural brain imaging studies have produced mixed results, with some studies in support of a smaller hippocampal volume (Lemaitre et al. 2005; Lind et al. 2006; Tohgi et al. 1997), while other studies could not confirm this finding (Jack, Jr. et al. 1998; Killiany et al. 2002). In a longitudinal MRI-study (Jak et al. 2007), cross-sectional comparisons showed no differences in hippocampal volume between ApoE ε4 carriers and non-carriers, but the percentage of volume loss over the 17-months follow-up period was significantly higher in the ε4-carriers. Interestingly, all brain functional imaging studies done during rest in middle-aged and elderly non-demented persons have reported decreased cerebral metabolism in ε4-carriers, and usually in the areas normally affected in AD, including posterior cingulate, parietal, temporal, and prefrontal cortex. (Scarmeas and Stern 2006). Even in younger persons (aged 20-29) a lower rate of glucose metabolism in the same brain areas have been reported in ε4-carriers, despite no differences in neuropsychological test scores between ε4-carriers and non-carriers (Reiman et al. 2004). A recent Finnish autopsy study supported these findings (Kok et al. 2009). Of 603 consecutive cases examined after sudden or unexpected out-of-hospital deaths, less than 5% had a history of AD, dementia or memory disorders. In the brains of these persons senile plaques were common in the ε4-carriers even at younger ages. In the age group 50-59 years, 65% of all cases with senile plaques were ε4-carriers, while in the age group 60-69 years the corresponding figure was 62%. In sum, the results suggest that
beta amyloid deposits co-occur with decreased cerebral metabolism early in life in the *ApoE ε4* carriers, and may make their brains especially vulnerable to the effects of traumas, structural brain changes of any kind, and neurological diseases.

**1.7.5 *ApoE ε4* and traumatic brain injury**

Accumulating evidence suggest that the *ApoE ε4*-allele may negatively influence the outcome of acute neurological insults, including traumatic brain injury, hemorrhagic stroke, subarachnoid hemorrhage, and uncomplicated endarterectomy (Heyer et al. 2005; Waters and Nicoll 2005). With respect to traumatic brain injury, several studies have shown that *ApoE ε4*-carriers have a worse outcome (death or vegetative state) after severe head injury (Horsburgh et al. 2000). Athletes in contact and collision sports, like boxing, football, rugby and hockey, are at particular risk of repetitive closed injury (mostly concussions and mild head injuries), which is not only an established risk factor of AD but also of chronic traumatic encephalopathy, earlier denoted dementia pugilistica. In a recent review (McKee et al. 2009), the *ApoE ε4*-allele was listed as a risk factor for chronic traumatic encephalopathy. Boxers carrying the *ApoE ε4*-allele and who had repeatedly been exposed to head injuries, showed a higher frequency of progressive neurological symptoms, cognitive impairment and dementia (Jordan 2000). Similar findings is reported in a study of elderly football players, which found that *ApoE ε4*-carriers with repeated exposure to head trauma performed worse on measures of general cognitive functioning, information-processing speed and accuracy, attention, and memory (Kutner et al. 2000).

The mechanisms underlying the negative effects of ε4 in neurodegenerative disease and brain injury have not been definitely clarified, but several, possibly overlapping mechanisms have been suggested (Horsburgh et al. 2000; Mahley and Rall, Jr. 2000). Among these are reduced efficiency of lipid transport, increased and more widespread accumulation of beta amyloid, decreased protection against oxidative injury, poor brain perfusion after injury, a cytoskeleton more vulnerable to damage, diminished growth and branching of neuritis resulting in poorer repair, increased disposition for cerebral oedema and brain inflammation, pre-existing atherosclerotic vascular disease, more widespread pre-existing amyloid deposits, slower recovery to anaerobic metabolism, and worse N-methyl-D-aspartate excitotoxicity (Blackman et al. 2005).
1.7.6 ApoE ε4 and stroke

Few studies have examined the relation between the *ApoE* ε4-allele and post-stroke cognitive impairment, and the results have been inconclusive. Two studies have reported a positive association (Ballard et al. 2004; Kalmijn et al. 1996), and seven studies no association (Baum et al. 2007; Bour et al. 2010; Dik et al. 2000b; Klages et al. 2005; Qiu et al. 2006; Reitz et al. 2006; Rowan et al. 2005).

Ballard et al. (2004), methodologically probably the soundest of these studies, examined longitudinally the effect of the *ApoE* ε4-allele on cognitive decline among stroke patients > 75 years with vascular cognitive impairment but no dementia (vascular CIND) three and fifteen months after the stroke. At baseline (3 months after stroke), the *ApoE* ε4-carriers were 2.5 times more likely to have CIND, and the *ApoE* ε4-carriers with CIND also showed a greater progression of cognitive decline over the study period, with memory functions showing the greatest decline. A limitation of the study, however, was the lack of control for the effect of possible pre-stroke cognitive impairment.

A closer examination reveals methodological limitations in all seven studies reporting negative findings. In two of the studies, (Baum et al. 2007; Qiu et al. 2006), the MMSE was chosen as the cognitive test to measure cognition, despite being shown to be a broad screening measure and insensitive to the cognitive deficits often seen in a stroke population. In three community studies, (Dik et al. 2000b; Klages et al. 2005; Reitz et al. 2006), the number of *ApoE*-carriers in the study samples was low (n= 53, 21, 73 respectively) possibly leading to type II-error, i.e. acceptance of the null-hypothesis when false. In the cross-sectional study of Rowan et al. (2005), the authors commented that the exclusion criteria in the study (subjects with dementia, aphasia or serious illnesses and disabilities) could have reduced the chance of detecting an association. In the longitudinal study of Bour et al. (2010) the number of ApoE-carriers were low (n=92), the participants were of younger age than the typical stroke patient (mean age abt 67 years), and patients with severe cognitive impairment (MMSE<16 points) were excluded.

In conclusion, the relationship between the *ApoE* ε4-allele and post-stroke cognitive performance has not yet been clarified. Considering the well-documented association between the *ApoE* ε4-allele and cognitive impairment in neurological disease and injury, such an association might be expected. In our project, we wished to analyze this association closer by
utilizing appropriate cognitive testing in a typical stroke population and controlling for the effects of possible pre-stroke cognitive impairment.

1.8 Early post-stroke performance as predictor of long-term functional outcome

1.8.1. Predictors of long-term functional outcome

Identification of early factors predicting long-term stroke outcome is important both in order to set realistic targets for rehabilitation and to guide patients and their relatives of the prognosis.

An underlying assumption in stroke outcome research is that the acute stroke-related neurological symptoms may lead to permanent impairments, disabilities, handicaps and compromised quality of life (Kelly-Hayes et al. 1998). However, it is important to underline that neurological impairment alone does not define stroke outcome. Some patients adapt rather well to severe neurological impairments, while others with only minimal impairments can be severely disabled. Although significant associations between impairments, disability, and handicap have been documented (de Haan et al. 1993; del Ser et al. 2005; Schuling et al. 1993; Wolfe et al. 1991), the current stroke scales measuring neurological impairments (e.g. NIHSS or SSS) do not fully explain the variance in levels of disability and handicaps. With respect to quality of life the explained variance is rather low (de Haan et al. 1993). In sum, these studies clearly suggest that stroke outcome is complex and multidimensional, and that variables that measure other functions than neurological impairment may influence levels of disability, handicap, and quality of life in stroke victims.

Disabilities, i.e. limitations in functional activities, have attracted particular interest as a stroke outcome variable, possibly because physical impairments and disabilities are the most eye-catching aspects of stroke and also are heavily emphasized in the rehabilitation of stroke patients (Hochstenbach 2000). More than 150 different factors are analyzed for their predictive utility in relation to long-term functional outcome, including both socio-demographic variables, vascular risk factors, clinical examination findings, laboratory tests, and imaging studies (Demchuk and Buchan 2000). Due to differences in samples, methodology and design, the studies are difficult to compare. However, it is well established that early mobilisation and training in multidisciplinary specialised stroke unit care will
improve both survival and functional outcome. Other predictors are initial severity of the stroke, age, previous stroke, urinary continence, level of consciousness at onset, disorientation for time and place, severity of paralysis, sitting balance, and ADL score at admission. In addition, diabetes, hypertension, atrial fibrillation, physical inactivity, cardiac diseases, depression, cognitive impairment, visuospatial deficits, and perceived level of social support have frequently been reported to affect the long term functional prognosis (Counsell and Dennis 2001; Demchuk and Buchan 2000; Eriksson et al. 2008; Jongbloed 1986; Kwakkel et al. 1996).

1.8.2 Cognitive performance in the early phase after stroke as predictor of long-term functional outcome

A limitation of many studies examining early predictors of long-term functional outcome, however, is that the findings are based on simple bivariate associations between the predictor variables and outcome measures. The major question in terms of prediction, however, is whether the examined variable remains an independent predictor of outcome when other known predictors are taken into account (Counsell and Dennis 2001). This criticism also holds true for early post-stroke cognitive performance as a predictor of stroke outcome. While simple bivariate associations between early post-stroke cognitive performance and both long-term cognitive performance, functional outcome, survival, and risk of institutionalisation have been documented in several studies, only a few have examined the independent predictive effect of early post-stroke cognitive performance (Nys et al. 2005b). Thus, in order to justify the use of cognitive tests as a prognostic tool in a stroke rehabilitation setting, their independent prognostic validity needs to be better documented. In this respect, it is worth noticing that cognitive tests were initially not developed to predict how brain-injured patients were likely to function in real-world settings, but rather to identify type and extent of cognitive impairments in order to guide in the detection and localisation of neuropathology (Sbordone 2001). Still, their predictive ability is more or less taken for granted in clinical stroke rehabilitation settings.

Recent studies have indicated that cognitive test results in the early post-stroke phase may represent an independent factor in predicting post-stroke development (de Haan et al. 2006; Nys et al. 2005b). In the study of Nys et al. (2005) 168 stroke rehabilitation patients with first-ever stroke (mean age 60.1 years, sd 14.2) were examined within three weeks after hospital admission and subsequently re-examined after 6-10 months. The prognostic value of demographic, clinical, neuropsychological and neuroimaging variables were examined in
relation to long-term cognitive and functional outcome (dependence in ADL). Three prognostic models were compared using regression analyses: a medical model (including medical factors at hospital admission, pre-stroke vascular risk factor, neuroimaging, and socio-demographic data), a cognitive model (covering seven different cognitive domains), and a mixed model (consisting of medical and cognitive predictors). The researchers found that a combined model predicted long-term ADL outcome better than the cognitive or medical models separately, with lateralized visual inattention and visuoperceptual/memory performance as the most important predictors. Notably, the predictive validity of lateralized visual inattention and visuoperceptual/memory impairments in relation to long-term functional outcome has also been reported in previous studies. With respect to long-term cognitive performance, early abstract reasoning and executive functioning were the only two predictors that remained significant in the combined model.

1.8.3 RBANS as predictor of long-term functional outcome
The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) has become increasingly popular as a neuropsychological screening battery in stroke patients. Its predictive validity has previously been examined in this type of patients and the results are promising (Larson et al. 2005; Larson et al. 2003; Terryberry-Spohr et al. 2000).

Terryberry-Spohr et al. (2000) examined the relationship between impairment as measured by RBANS and rehabilitation outcome assessed with the FIM in 118 acute rehabilitation in-patients (60 patients diagnosed with cerebrovascular accidents (CVA), 118 with traumatic brain injury, and 27 with other diagnosis). A two-factor model of FIM has earlier been proposed: a motor disability factor and a cognitive disability factor (Linacre et al. 1994). By utilizing this model, the researchers found a significant correlation between RBANS Visual-Construction Index and FIM Motor disability score across all three diagnostic groups, and significant correlations between all the other RBANS Indexes (Immediate Memory, Language, Attention, Delayed Memory and Total Score) and FIM cognitive disability score (all p<0.001). Multiple regression analysis revealed that RBANS Indexes explained 21% of the variance in FIM Motor scores and 51% of the FIM Cognitive score in the CVA-patients. The authors conclude that, across diagnostic groups, RBANS predict functional outcome as well as lengthier neuropsychological test batteries (like the Halstead Reitan Neuropsychological Test Battery).
Larson et al. (2003) tested 34 stroke patients (mean age 65 years, range 31-85) with the RBANS during in-hospital rehabilitation, and interviewed them by telephone again 6 months later on measures of motor and cognitive functioning (FIM), instrumental ADL (The Frenchay Activity Index), limitations in role functions (The Craig Hospital Assessment and Reporting Technique) and quality of life (The Fugl-Meyer Life Satisfaction Questionnaire). RBANS most strongly predicted cognitive functioning (FIM Cognitive score) at six months with explained variance of 46% in the multiple regression analysis, and with the Visuospatial/Constructional and Delayed Memory Indexes making the significant contributions. With respect to the other outcome measures, the explained variance of RBANS was 22% (FIM Motor Score), 14% (Frenchay Activity Index), 21% (The Craig Hospital Assessment and Reporting Technique), and 17% (Fugl-Meyer Life Satisfaction Questionnaire) respectively, suggesting a predictive ability of RBANS also in relation to these outcome measures, but at a modest level. Interestingly, with the exception of quality of life, in-hospital performance on the Visuospatial/Constructional Index was the only RBANS Index making significant contributions in the multiple regression analyses.

A similar longitudinal study was carried out by the same research group (Larson et al. 2005) in which 36 stroke patients (mean age 63.2 years, s.d. 16.2) were tested with RBANS during in-hospital rehabilitation, and telephone interviewed 12 months later with respect to cognitive and motor functional disability, instrumental activities of daily living, and participation restrictions using the same questionnaires as in the 6-months follow-up study. Again strong, significant associations (p<0.001) between RBANS in-hospital performance and FIM Cognitive Functional Disability were reported (for Language, Immediate Memory, Delayed Memory, Visuospatial/Constructional, and Total Score Indexes), while none of the RBANS Indexes were significantly associated with FIM Motor Functional Disability. Furthermore, there was a strong, significant relation between Visuospatial/Constructional Index and Instrumental Activities of Daily Living. With respect to inpatient RBANS indexes and participation restrictions at follow-up, there were no significant associations, although a positive trend (p<0.05) was reported for Language, Immediate Memory, Delayed Memory, Visuospatial/Constructional and Total Score Indexes.

Taken together, these studies suggest that RBANS-performance in an early phase after a stroke is useful in predicting long-term functional outcome. The conclusiveness of these studies are limited by a low number of subjects, restriction of age (60-65 years, which is...
hardly representative of the stroke population in general), and a limited number of variables entered into the prediction analyses. The independent predictive validity of early RBANS performance in a representative in-hospital stroke rehabilitation sample in relation to long-term functional outcome remains therefore to be proven.

1.9 Post-stroke symptoms of depression: Frequency, course and relation to long-term stroke outcome

Emotional symptoms are commonly observed after stroke, and include depression, anxiety, catastrophic reactions, fatigue, and emotionalism. The reported prevalence rates of the different emotional symptoms vary considerably, but are estimated to be as follows: depression >30%, anxiety <30%, catastrophic reactions 20%, and emotionalism 20-25% (Murray and Martensson 2004). Frequently, these symptoms occur together. Formal screening of emotional symptoms is uncommon in Norwegian stroke rehabilitation units today, despite that validated assessment instruments are available (Fure 2007). In one study, it was estimated that a diagnosis of depression may be missed by nonpsychiatric physicians in up to 80% of the cases (Schubert et al. 1992), implicating that few stroke patients receive effective management for their depressive symptoms (Hackett et al. 2005; Pohjasvaara et al. 1998).

1.9.1 Symptoms of a depression

Depression is the most frequently occurring emotional condition occurring after a stroke. The World Health Organisation (WHO) has ranked depression as fourth on the list of the world’s ten most serious disorders in terms of reduced quality of life and life expectancy. The term depression is derived from the Latin verb *deprimere*, "to press down". According to the criteria of the WHO’s ICD-10 Classification of Mental and Behavioural Disorders (1992), a depressive episode is characterized by the following symptoms: (1) depressed mood (2) loss of interest and enjoyment, (3) reduced energy leading to increased fatigability and diminished activity, (4) reduced concentration and attention, (5) reduced self-esteem and self-confidence, (6) ideas of guilt and unworthiness, (7) bleak and pessimistic views of the future, (8) ideas or acts of self-harm or suicide; (9) disturbed sleep, (10) diminished appetite.

In ICD-10, a depressive episode is diagnosed as mild, moderate or severe. Differentiation rests upon clinical judgement that involves the number, type, and severity of symptoms
present. In order to fulfil the criteria of a mild depressive episode, at least two of the three cardinal symptoms (1 to 3) should be present, in addition to at least two of the other listed symptoms (4 to 10). A moderate episode is characterized by at least two of the three cardinal symptoms (1 to 3) and at least three (up to four) of the other symptoms (4 to 10). For a severe episode, all the three cardinal symptoms should be present (1 to 3), plus at least four of the other symptoms (4 to 10). The symptoms should be present most of the day for at least two weeks.

It has been hypothesised that the phenomenology of post-stroke depression (PSD) differs from a primary depressive disorder. This hypothesis has not been confirmed in several recent studies (Narushima and Robinson 2002; Robinson 2003).

1.9.2 Depression in the general population

Independent of stroke, every fifth person will, on average, experience a depressive episode during their lives, and depression is more than twice as common in females than in males. Depression is most common between 30 and 40 years of age, and with a later peak in the age 50 to 60 years. For 35-60% of those affected, depression is a recurrent event (Judd et al. 1998; Kennedy et al. 2003; Kessing et al. 2004; Kiloh et al. 1988; Lee and Murray 1988), and it is estimated that a depressed person must expect to experience four episodes during the lifetime (Judd 1997). According to a biopsychosocial model, biological, psychological, and social factors all play a role to varying degree in causing depression. It usually is provoked by a severe psychosocial event, like death of a loved one, a divorce or a serious physical illness. The role of psychosocial stressors may be more predominant in the onset of the first and second depressive episodes, but probably play a less role in subsequent episodes. The prognosis of depression is in general good. Even for persons with a major depression, it will end in complete remission in about 2/3 of the cases. However, for the remaining 1/3, the remission will only be partial or the condition may become chronic. It is estimated that approximately ¾ of depressed persons do not receive any treatment. For those receiving treatment, clearly the most frequent alternative is anti-depressive medication prescribed by the family doctor. However, according to the new National Guidelines for the Treatment of Depression (Helsedirektoratet 2009b), the recommended choice of treatment of a mild-moderate depressive episode is psychological intervention and counselling. This recommendation also holds for elderly people. Anti-depressive medication should first be considered when the person is not responding to the psychological intervention, or in cases
were the person has had previous depressive episodes of modest or major character. For major depressive episodes, structured psychotherapy (typically 16-20 sessions over a 6-9 months period) in combination with anti-depressive medication is recommended.

1.9.3 Depression in the elderly

Although the majority of elderly people report that they are satisfied with their lives, depression still afflicts many of them. Based on a review of 55 studies between 1990 and 2001, the average prevalence rate of depression among people 60 years and above has been estimated to be 19% in the general population and 31% in hospital-based populations (Rosenvinge and Rosenvinge 2003). Depression in the elderly may by overlooked as the symptoms can be different and less obvious, and because elderly may be less inclined to experience or acknowledge feelings of sadness or grief (Gallo and Rabins 1999). Elderly are more prone to chronic diseases (e.g. heart disease, stroke) which may cause depressive symptoms or depression-like symptoms, and are more likely to take medications with depressive symptoms as a potential side effect.

The term ‘vascular depression’ (also described as arteriosclerotic depression or subcortical ischemic depression) was introduced to describe a form of depression particularly affecting the elderly caused by long-term or silent vascular disease preventing the normal blood flow to the brain. Vascular depression is fairly consistently associated with white matter hyperintensities affecting frontal-subcortical circuits, and is shown to have a poor response to treatment and a tendency to become chronic (Dieguez et al. 2004). Accompanying cognitive symptoms are impairments of attention and executive function, with slowing of motor performance and information processing (O'Brien et al. 2003). Vascular depression is not only a risk factor for cardiovascular disease and stroke, but may also develop as a consequence of these diseases (Krishnan et al. 2004).

Similar to younger individuals, about 80% of older adults with depression improve when they receive treatment with an antidepressant, psychotherapy, or a combination of both (Little et al. 1998). Anti-depressive medication alone and combination treatment are both effective in reducing the rate of depressive recurrences in older adults (Whyte et al. 2006). Psychotherapy alone can also be effective in prolonging periods free of depression, especially in older adults with minor depression, and it is particularly useful for those who are unable or unwilling to take antidepressant medication (Dombrovski et al. 2007; Lebowitz et al. 1997; Reynolds, III et
al. 2006). As already mentioned vascular depression is more resistant to any kind of treatment (Kales et al. 2005).

1.9.4 The prevalence of post-stroke depression (PSD)

The reported prevalence of PSD varies across studies, ranging from 5% to 64% (Aben et al. 2001; Robinson 2003; Townend et al. 2007). Methodological issues like the selection of the study population, the choice of assessment instrument, operational criteria, and the time interval between stroke onset and assessment may contribute to this variability (Hackett and Anderson 2005; Kouwenhoven et al. 2010; Robinson 2003). Hospital-based studies generally report a higher prevalence of PSD than community-based studies, which probably could be explained by the more severe strokes suffered by hospital patients. However, in a review of 51 studies (comprising a total of 25207 subjects) carried out between 1977-2002, the pooled frequency of PSD was estimated to be 33% (29-36% with 95% confidence interval) (Hackett et al. 2005), with no significant differences between population-, hospital- or rehabilitation patients. The authors comment that the figure is likely to be a conservative estimate due to potential underreporting and the inherent difficulties in assessing mood in neurological impaired patients, particularly in cases of aphasia and dementia. One might expect that such difficulties are greater in hospital and rehabilitation populations compared to community populations, due to a higher frequency of severe strokes seen in these settings. The high frequency of PSD is confirmed in another review (Robinson 2003), which report a mean frequency of 19.3% for major depression and 18.5% for minor depression in stroke patients in acute and rehabilitation hospitals. The corresponding figures in community-based studies were 14.1% and 9.1% respectively. Stroke patients have more than six times increased risk of developing clinically significant depressive symptoms even two or more years post-stroke compared to age-matched controls (Whyte et al. 2004). A interesting question is whether there are differences in prevalence of PSD between patients with ischemic and haemorrhagic strokes. According to one review (Gaete and Bogousslavsky 2008), studies of PSD have predominantly included ischemic strokes only. However, in the recent review of Kouwenhoven et al. (2010) of depression in acute stroke, there were no difference in prevalence rates between studies including both ischemic and haemorrhagic strokes compared to ischemic strokes only.
1.9.5 Screening instruments for symptoms of depression

Screening instruments for symptoms of depression have been developed, and include the Montgomery Aasberg Depression Rating Scale (MADRS) (Davidson et al. 1986; Montgomery and Asberg 1979), Beck Depression Inventory (BDI), the Geriatric Depression Scale (GDS) (Lesher and Berryhill 1994), the Hamilton Depression Rating Scale (HDRS) (Hamilton 1960), and the Hospital Anxiety and Depression Scale (HADS) (Johnston et al. 2000). The GDS and BDI comprise items related to depressive symptoms only, MADRS also includes one item (out of ten) concerning anxiety, HDRS two items (out of seventeen) on anxiety, and the HADS contains items on both symptoms of depression and anxiety. None of these instruments have been developed specifically for stroke patients, but preliminary validation support the use of these screening measures in a stroke population (Aben et al. 2002a; Berg et al. 2009; Healey et al. 2008; Laska et al. 2007; Sagen et al. 2009).

In general, examining for depressive symptoms in stroke patients can be a challenge, as typical symptoms of depression can be present in stroke patients without being the expression of a depression. For example, insomnia may be the consequence of a noisy hospital environment, loss of appetite may be the effect of dysphagia, lack of concentration and apathy may be cognitively related. Also, in some cases evaluation of depressive symptoms may be seriously hampered due to serious aphasia, dementia or reduced consciousness (Pfeil et al. 2009). However, the presence of dementia or aphasia does certainly not rule out the diagnosis of a treatable depressive episode. Communication difficulties are likely to make it necessary to rely upon objectively observed somatic symptoms (e.g. psychomotor retardation, loss of appetite and weight, sleep disturbance) or to collect information from a next of kin.

1.9.6 The course of post-stroke depression

The time of onset and course of PSD has been a debated topic, and remains still unclear. In general, PSD may develop both in the acute phase or have a delayed onset. About 1/3 of the patients who are not depressed in the acute phase develop depression between three months and two years after the stroke. The general view is that the frequency of PSD reaches a peak after 3 to 6 months, gradually declines during the first year, and thereafter reaches a second peak after 2 to 3 years (Gabaldon et al. 2007). However, this pattern has not been confirmed in all studies. In the review of Hackett et al. (2005) a fairly stable frequency of PSD over time is reported with pooled frequencies of 32% in the acute phase (within one month post-stroke), 34% in the medium term (between one and six months post-stroke), and 34% in the long-term
(six months or more post-stroke). However, one important issue remains open in this review: The time of onset and course of depression may vary between different stroke patients, implying that a patient depressed at one period of time may not necessarily be depressed in other post-stroke phases.

Time of onset probably affects the course of PSD. Early onset is associated with shorter duration and possibly with greater likelihood of spontaneous remission compared to later onset PSD. In one study, 60% of the subjects with early PSD (0-3 months post stroke) were free of depression at 12 months, while non-recovered subjects were at high risk of developing a chronic condition (Astrom et al. 1993). Similar results were reported in another study (Andersen et al. 1995), in which subjects with onset of PSD seven weeks or later after the stroke showed a lower rate of spontaneous recovery. The differences in onset and course of PSD have lead to the hypothesis that there may be different biologic and psychosocial factors causing early onset PSD with spontaneous remission than in depression occurring later after stroke (Robinson et al. 1987; Robinson 2003). Some evidence supports that early onset PSD is associated with larger lesions, while late onset PSD is associated with poorer social functioning (Robinson 2003). It is likely that PSD emerging immediately after a stroke is more associated with neurological deficiencies than PSD developing later on.

1.9.7 Theories of post-stroke depression
The cause of PSD is at all probability multifactorial, and may involve biological as well as psychosocial mechanisms. Within the biological realm, five mechanisms have been found to be central in the development of PSD: location of brain lesion, loss of neurotransmitters, inflammatory processes, gene polymorphism and long-term or silent cerebrovascular disease (Fang and Cheng 2009; Gaete and Bogousslavsky 2008; Whyte and Mulsant 2002). Concerning lesion location, an association between lesion location (in the left frontal lobe and the basal ganglia) and PSD has been reported in earlier studies, but not been confirmed in more recent studies. According to the neurotransmitter hypothesis, lesions may affect neurotransmitters in the brain causing a deficiency particularly in levels of serotonin and norepinephrine. These are then held to be responsible for the depressive symptoms seen in the patient. In support of this hypothesis, most antidepressant medications work through increasing the levels of serotonin and/or norepinephrine in the brain. The inflammatory hypothesis states that inflammatory hormones, known as cytokines, are stimulated by an activated immune system and sometimes become active following a stroke. Several pro-
inflammatory and anti-inflammatory cytokines may be responsible for altering levels of key neurotransmitters and their metabolites in the blood and brain after a stroke, and cause depression. For gene polymorphism, a significant association between serotonin transporter gene-linked promoter region short variant genotype and post-stroke major depression has been reported (Kohen et al. 2008).

Psychosocial mechanisms may comprise both psychological, personality and social factors, but compared to the biological ones, these mechanisms are far less studied and the results are not conclusive (Gaete and Bogousslavsky 2008; Hackett and Anderson 2005; Hadidi et al. 2009). However, the literature strongly suggests that some patients have a psychiatric vulnerability to develop PSD. A previous history of depression, a previous psychiatric history, and a family history of affective or anxiety disorder have generally been found to be strong predictors of PSD (Caeiro et al. 2006; Leentjens et al. 2006; Morris et al. 1992; Ouimet et al. 2001; Paolucci et al. 2006). A previous depressive episode may increase the risk of PSD with 30%, and rising to nearly 90% when two other recognized risk factors, previous stroke and severe functional disability, are included in the model (Paolucci et al. 2005). Some patients may have a personality which makes them susceptible for developing PSD. Neuroticism, i.e. the tendency to experience negative mood states across situations over the life-span, has been found to increase the risk of PSD (Aben et al. 2002b; Morris and Robinson 1995; Storor and Byrne 2006). Aben et al. (2002b) applied the NEO-Five Factor Inventory (based on the Five Factor Model of personality) in a sample of 190 stroke patients, and found that patients with high neuroticism scores had a 4.6-times-higher risk of developing PSD than patients with low neuroticism scores.

An interesting association between level of social support and PSD are reported in several studies (Astrom et al. 1993; Friedland and McColl 1987; Morris et al. 1991; Ouimet et al. 2001; Robinson et al. 1985; Robinson et al. 1999). In Morris et al. (1991), the perceived adequacy of social support, particularly from a spouse caregiver, was associated significantly with both the presence and severity of a depressive disorder. Also, the depressed patients who perceived their support to be inadequate had a longer duration of depressive illness than depressed patients who perceived their support in a more favourable light. The authors conclude that perception of social support from key relationships may mediate the emotional response to a stroke. Community social support (from neighbours, friends, work colleagues, or service people) may also protect from PSD, at least in patients who have experienced a
high number of stressful life experiences in the past (Friedland and McColl 1987). In sum, these studies are important because they indicate that PSD could be prevented or attenuated through psychosocial interventions.

Notably, there are few mentions of psychological factors in the reviews of risk factors for PSD. In general, however, it is accepted that stroke survivors may react psychologically to the stress and handicaps following a stroke. A (low-grade) association between degree of functional impairment and severity of PSD may well be consistent with a psychological interpretation of PSD (Gainotti and Marra 2002), (but could also be linked to large lesions involving mood processing regions of the brain). The importance of psychological factors as risk factors for PSD is strongly supported in an epidemiological study (Burvill et al. 1997) which reports significant associations between PSD at four months and major functional impairment, living in a nursing home, being divorced and having a high pre-stroke alcohol intake (males only). The researchers conclude that depression among the stroke patients is no more common, and of no more specific aetiology, than it is among elderly patients with other physical illnesses.

Other reported risk factors for PSD include female sex, living alone, severe physical disability, global cognitive impairment, aphasia, previous stroke, high level of education, and life stressors (Gaete and Bogousslavsky 2008; Kales et al. 2005). In a review of 20 studies (Hackett and Anderson 2005), three consistent determinants of PSD were identified: physical disability after a stroke, the severity of the stroke and cognitive impairment.

1.9.8 Consequences of post-stroke depression
An important question is whether depression influences the recovery after stroke and the prognosis. Significant associations between PSD and global handicap, functional impairment and cognitive impairment have fairly consistent been reported in cross-sectional studies, but one debated and unresolved issue is the direction of these relations, i.e. whether PSD impacts global handicap, functional impairments and cognitive decline, or if handicap and impairments leads to PSD.

Longitudinal studies examining the impact of PSD on recovery and prognosis have reported inconsistent findings, which may, at least in part, be due to differences in the methodology, design and patients samples between the studies (Hadidi et al. 2009). However, the trend
seems clear, namely that PSD may have strong negative prognostic implications, both with respect to functional outcome (Gainotti et al. 2001; Kotila et al. 1999; Naess et al. 2010; Nannetti et al. 2005; Paolucci et al. 2001; Parikh et al. 1990; Pohjasvaara et al. 2001; Sinyor et al. 1986; van de Weg et al. 1999), reduced prospects for rehabilitation (Herrmann et al. 1998), increased dependency (Langhorne et al. 2000), increased mortality (Morris et al. 1993a; Morris et al. 1993b; Naess et al. 2010), and strain on the carer (Wyller et al. 2003), but this needs to be better documented (Gainotti and Marra 2002).

With respect to functional outcome, Pohjasvaara et al (2001) examined 390 stroke patients (aged 55-82 years) at 3 months post-stroke and again after 15 months (n=276) with the Beck’s Depression Inventory (BDI). The prevalence of depression (defined as a BDI-score>9) was more than 40% both at 3 months and at 15 months post-stroke. Patients with depression at 3 months more often had a poor functional outcome (defined as a Rankin Scale score >2) and reduced personal ADL (defined as a Barthel Index score <17) at 15 months. Interestingly, the researchers also report that patients with a poor functional outcome at 3 months were at greater risk of depression at 15 months, supporting the view that the impact of PSD and functional abilities is bidirectional. Nannetti et al (2005) examined 117 stroke rehabilitation patients (mean age around 72 years) approximately 2 weeks post-stroke for the presence of depression (according to DSM-IV criteria, and by using the Geriatric Depression Scale and the Cornell Scale; in order to be categorized as depressed, the patients had to fulfil criteria for depression on all three measures). The patients with and without depression were assessed for motor (Fugl-Meyer Assessment Scale) and functional recovery (Barthel Index) at three points of time: At admission, at discharge and at 3 months post-stroke. At two weeks post-stroke, 41.9% of the patients were classified as depressed. Compared to the non-depressed, the depressed patients showed a lower score on both motor and functional measures at all three points of time. Positively, the rate of motor recovery of the depressed patients was comparable to the non-depressed, but their functional recovery followed a different course over time: Functional recovery was comparable while the patients were in hospital, but the depressed showed a significantly lower functional improvement after hospital discharge. The researchers hypothesize that one reason for the latter finding could be that the stroke rehabilitation unit offered a more stimulating setting with more intense training than what met many patients after discharge, and also that anti-depressant medication were terminated in some depressed patients after hospital discharge. Interestingly, the similar pattern was also reported by Sinyor et al 1986.
Considering the likely impact of PSD on post-stroke functional abilities and rate of recovery, one might hypothesize that PSD may be a predictor of long-term nursing home placement. To our knowledge, only one study has explored this hypothesis (Kotila et al. 1999). In their study, data from a stroke register (n=594) of four districts in Finland were examined with respect to depression and functional outcome at 3 and 12 months post-stroke. Depression was defined as a BDI-score >9. The prevalence of post-stroke depression (defined as a BDI-score > 9) was about 47% both at 3 months and at 12 months. Patients depressed at 3 months were more often in institutional care (68.9% vs 57.6%, p=0.05) and were more dependent in ADL (Rankin Scale, Barthel Index) at 12 months.

With respect to mortality, few studies have been carried out, but at least four studies document an independent association between depression within the first 3 months post stroke and an increased mortality rate between 1 year and up to 10 years after the stroke (Morris et al. 1993a; Morris et al. 1993b; Naess et al. 2010; Williams et al. 2004). In another study (Pohjasvaara et al. 2002), an association between post-stroke depression at 3 months and mortality within the first 15 months was reported in the bivariate analysis, but depression fell out in the multivariate logistic regression analysis, in which dependent living at 3 months was the only independent variable remaining in the model. There may be a dose-dependent association between depression and mortality rate. In the study of Morris et al. (1993b), mortality rate at 15 months increased from non-depressed to minor depressed and to major depressed patients diagnosed at 3 months post-stroke according to DSM-III R-criteria (1/48 (2%), 2/21 (10%) and 3/13 (23%). The stroke patients who died also had a higher symptom of depression score than the survivors as measured by the MADRS (mean 17.7, s.d. 6.0 versus mean 9.9, s.d. 7.1). Depressed stroke patients with few social contacts (i.e. living alone, being unmarried and not having a close confidant) may be at particular risk, as expressed by a mortality rate of over 90% after 10 years compared to 53% for the stroke group as a whole in one study (Morris et al. 1993a). Depressive symptoms ahead of the stroke may also increase risk of mortality after a stroke. In a large population-based study in California, subjects reporting five or more depressive symptoms at baseline had an increased risk of stroke mortality over a 29-year period (hazard ratio 1.66, 1.16-2.39 95% C.I.; p<0.006), and the risk remained significant even after controlling for potential confounders like education, alcohol consumption, smoking, body mass index, hypertension, and diabetes mellitus (Everson et al. 1998).
Several explanations why post-stroke depression is unfavourable have been put forward. It is negative, not only for the distress it causes the patients, but also because it reduces the level of energy, concentration, self-efficacy and motivation, and thereby make the patients less likely to actively participate in rehabilitation, adhere to treatment recommendations, and more prone to unhealthy life style habits (e.g. smoking, alcohol consumption) (Hadidi et al. 2009). Depression increases the risk of vascular-related diseases, including arterial hypertension (Bosworth et al. 2003), diabetes related complications (de Groot et al. 2001), and possibly coronary artery disease and myocardial infarction (Barefoot and Schroll 1996; Frasure-Smith and Lesperance 2006; Nemeroff et al. 1998; Pratt et al. 1996; Wulsin 2004), and stroke (Larson et al. 2001). Pathophysiological mechanisms induced by depression which may contribute to increased vulnerability to vascular-related diseases include serotonergic dysfunction/increased platelet aggregation, hypothalamic-pituitary-adrenal axis and autonomic nervous system dysfunction, increased production of inflammatory cytokines, and enhanced carotid atherosclerosis progression (Gaete and Bogousslavsky 2008; Musselman et al. 1998; Sher et al. 2010).

In sum, the negative implications of PSD for long-term stroke outcome are strongly suggested in these studies but need to be better documented. Since stroke mainly affects older people and is associated with vascular disease and ischemic risk factors, studies examining the effect of PSD on long-term outcomes should control for the influence of sociodemographic, somatic and functional variables.
2. THE PRESENT STUDY

2.1 Aims

The overall aim of this study was to follow the development of post-stroke cognitive and depressive symptoms over time across a period of 13 months, and ascertain how such symptoms were associated with risk factors and long-term prognosis.

Specifically, we wanted to examine:

a) Whether the ApoE ε4-allele is a risk factor for cognitive impairment in the early phase after stroke.

b) The relationship between the ApoE ε4- allele and cognitive impairment 13-months after the stroke.

c) If sub-acute post-stroke cognitive functioning was independently related to long-term functional outcome at 13 months.

d) To describe changes in depressive symptoms in elderly stroke patients across a time-span of one year, to examine risk factors for such changes and to explore whether depressive symptoms have any independent impact upon one year mortality and nursing home placement.

2.2 Study design

The study comprises four separate substudies. Substudy 1, ApoE ε4 as a risk factor for cognitive impairment in the early post-stroke phase, is a cross-sectional study. Substudy 2, ApoE ε4 and cognitive impairment 13-months after stroke, substudy 3, sub-acute post-stroke cognitive functioning and long-term functional outcome, and substudy 4, depressive symptoms, are all longitudinal studies.

2.3 The Stroke Rehabilitation Unit - the source for selection of study subjects

The four separate substudies were carried out among 194 stroke rehabilitation patients consecutively admitted to the Stroke Rehabilitation Unit at Oslo University Hospital, Ullevaal, Oslo, during the period between March 2005 and August 2006. The hospital serves a population of approximately 180000 people, and virtually all persons with an acute stroke are admitted. However, only those judged to benefit from rehabilitation are transferred to the Stroke Rehabilitation Unit, when their medical conditions are stabilized. In practice, this
means that patients with minor or very severe strokes are excluded from the cohort. The patients were recruited consecutively except for periods when the examiners (LF and JW) were off duty due to holidays, courses/conferences, and sick leaves.

Only patients diagnosed with an ischaemic or intracerebral haemorrhagic stroke according to the WHO-definition (Hatano 1976) were included. The diagnoses were set on the basis of clinical examination and/or CT-scans. Exclusion criteria were non-fluency in the Norwegian language, severe visual or hearing impairment, severe alcohol or drug abuse, or a history of serious psychiatric illness. All 194 patients were not analysed in the four substudies. Figure 1 gives an overview of the patient samples and study design in the four substudies.

Figure 1: Overview of the patient samples and study design in the four substudies

2.4 Characteristics of the subjects

The 194 patients had a mean age of 76.9 years (SD 10.5). There were 95 (49%) females and 99 males (51%) males. Females had a higher mean age than males with 79.4 years (9.6 SD) and 74.5 years (SD 10.9) respectively. Table 3 shows mean age and gender distribution for the patients included in the four sub studies.
Table 3: Age and gender distribution for the patients included in the four substudies

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2.5 Procedures
The first examination (baseline) was carried out in the Stroke Rehabilitation Unit at a mean of 18.3 days (SD13.4) after hospital admission. The patients were reassessed in a follow-up examination 12-15 months later (mean 408 days, SD 41.2). Patients living at home at follow-up were assessed in the geriatric out-patient clinic at the hospital, while patients living in nursing homes were assessed in their wards. At follow-up examination 91 subjects (47%) lived at home, 35 (18%) in nursing homes, 37 (19%) had died, and 31 (16%) had withdrawn from the study. The subjects who withdrew from the study during the follow-up period were more often women (65%), but otherwise did not differ from those examined on any demographic or baseline clinical measures.

2.6 Methods
All subjects underwent a comprehensive neuropsychological examination at both baseline and follow-up examination, in which information regarding demographics, ApoE-genotype, medical history, cognitive performance (pre/subacute/13 months), personal and instrumental ADL functioning (pre/subacute/13 months), symptoms of depression (pre/subacute/13months), and neurological impairments (subacute/13months) were collected.

Demographics and historical medical data were collected from the medical records, the patients or close informants. Blood samples were collected from the patients, immediately frozen, and later analyzed for ApoE genotype in the laboratory of the Department of Medical Genetics at Oslo University Hospital, Ullevaal according to method described in paper I and II.

Information of the patients’ pre stroke cognitive, ADL- and emotional functioning were collected through structured interviews with close informants. As 39 patients were either lacking or unwilling to involve an informant, only 155 informant interviews were obtained.
We found no significant differences between subjects with and without informants with respect to demographical variables, baseline cognitive (RBANS total index) or neurological functioning (NIHSS total score), or frequency of the \textit{APOE} ε4-allele.

All examinations of post-stroke cognitive, emotional, neurological and ADL functioning were undertaken by two psychologists, Lasse Farner and Jørgen Wagle.

The following structured questionnaires and assessment tools were administered.

\textbf{2.6.1 Pre-stroke cognitive status}

The Norwegian version of The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) was administered to measure potential pre-existing cognitive reduction ahead of the present stroke. The IQCODE is a structured questionnaire consisting of 26 items assessing cognitive change over the last 10 years. It has been widely used for screening of dementia. We used the IQCODE as a measure of possible cognitive reduction over the last 10 years preceding the stroke. A review article (Jorm 2004) showed that the IQCODE has adequate psychometric properties, measures a general factor of cognitive decline, and is relatively unaffected by educational and pre morbid intellectual ability level. Cut-off score for dementia screening in patient samples have generally been in the range between 3.4 and 4.0. We chose a cut-off of 3.44 which is in accordance with recommendations given by Jorm (Jorm 2004).

\textbf{2.6.2 Post-stroke cognitive status}

Cognitive performance in the subacute phase and after 13 months was measured by administering the Norwegian versions of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) – form A (Løberg EM et al. 2006; Randolph et al. 1998) and the Mini Mental Status Examination (MMSE) (Engedal et al. 1988; Folstein et al. 1975).

RBANS is a neuropsychological screening battery originally developed to assess cognitive functioning among the elderly, with a particular emphasize on detecting dementia (Randolph et al. 1998). RBANS consists of twelve subtests and takes about 30 minutes to administer. Besides giving a total score of general, overall cognitive performance, it also measures performance within five different cognitive domains; Immediate Memory, Visuospatial/Constructional function, Language, Attention, and Delayed Memory.
Studies have shown that RBANS is a sensitive test battery for measuring cognitive impairment after stroke both in an acute and rehabilitation setting, and have also been found to predict functional outcome after stroke (Larson et al. 2005; Larson et al. 2003; Wilde 2006). However, doubts about its ability to measure executive functions have been put forward.

RBANS was administered to all subjects, even those with aphasia, apraxia or hemiplegia in dominant side. Subjects with severe aphasia or apraxia were scored with error on tasks they were incapable of performing. Patients with hemiplegia that severely affected dominant arm/hand used non-dominant hand for tests requiring writing/drawing skills (Figure Copy and Recall, Coding).

For subjects aged 65 years and older, RBANS Index Scores were calculated on the basis of age- and education corrected norms for the geriatric population (Duff et al. 2003). Original RBANS norms were applied for subjects under 65 years. These norms correct for age, but not for education.

MMSE is a screening measure of global cognitive functioning, and is widely used in both psychiatric, geriatric and stroke rehabilitation settings, especially as a screening tool for dementia. Considering its widespread use both in clinical settings and research, the MMSE has been poorly evaluated in stroke populations. Although acceptable sensitivity in detecting early post-stroke cognitive impairments was found in a sample of geriatric stroke patients (Agrell and Dehlin 2000), other studies report low sensitivity, and especially within the domains of abstraction, executive functions, and visuoperception (Fure et al. 2006b; Nys et al. 2005a). A standard cut off-point of 24 points among elderly patients (above 75 years) is usually applied to identify subjects with cognitive impairments compatible with mild dementia (Ward et al. 2002). In accordance with recommendations (Fillenbaum et al. 1988) non-responses on any of the MMSE items were scored as errors.

2.6.3 Activities of Daily Living (ADL)
Personal ADL-functioning was assessed by the Barthel Index (BI) (Mahoney and Barthel 1965), which has been shown to be a reliable disability index for stroke patients (D'Olhaberriague et al. 1996). The Index is reported to predict prognosis, including rate of recovery (Wade and Hewer 1987) and return to home (Granger et al. 1979). BI measures ten different aspects of self-care, including incontinence (bowels and bladder), grooming, toilet
use, feeding, transfers bed to chair and back, mobility on level surfaces, dressing, stairs, and bathing. Total score can vary from 0 (min) to 20 (max), and according to (Patel et al. 2002) the scores can be interpreted as follows: 0-9 = severely disabled; 10-14 = moderately disabled; 15-19 = mildly disabled; 20 = functionally independent.

Instrumental ADL-functioning was measured with the Frenchay Activities Index (FAI) (Holbrook and Skilbeck 1983). FAI is specifically developed for stroke patients and has been shown to have acceptable psychometric properties to assess functional status both in pre and post stroke samples (Schuling et al. 1993). It consists of 15 items, including preparing main meals, washing up, washing clothes, light and heavy housework, local shopping, social outings, walking outside, actively pursuing hobby, driving car/bus travel, outings/car rides, gardening, household/car maintenance, reading books and gainful work. Minimum score is 15 and maximum is 60 points and the scores can be interpreted as follows. 15-30 = Inactive; 31-45 = Moderately active; 46-60 = Active/very active.

The modified Rankin Scale (mRS) (van Swieten et al. 1988) was used to measure degree of handicap. MRS is widely used for evaluating stroke patient outcome. In contrast to the BI that focuses on ability to perform specific tasks, the mRS is a global disability scale and is a measure of degree of disability. It consists of seven categories, varying from 0 (no symptoms) to 6 (death).

Pre stroke BI- and FAI-measures were collected retrospectively through interviews with informants. BI-measures at baseline were obtained through interviews with caring nurses in the stroke rehabilitation unit. BI- and FAI-measures at 13 months post-stroke were obtained either through interviews with patients or informants (subjects living at home) or from caring nurses (subjects living in nursing homes). The mRS at both baseline and follow-up was scored by two psychologists (Lasse Farner and Jørgen Wagle) on the basis of clinical evaluation.

2.6.4 Symptoms of depression

Symptoms of depression were examined by administering the Montgomery Aasberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979) to the subjects at baseline and at follow-up. MADRS consists of ten items, including apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude,
inability to feel, pessimistic thought, and suicidal thoughts. Each item is rated on a seven point scale and total score can thus vary from zero to 60 points, with a higher score indicating more severe depressive symptoms. We divided the subjects in two groups based on a recommended cut-off of seven points (no depression vs mild/severe depression) (Snaith et al. 1986).

2.6.5 Neurological impairment

Neurological stroke-related impairments were examined with The National Institute of Health Stroke Scale (NIHSS) (Goldstein et al. 1989). Acceptable intra and inter-rater reliability has been documented and it has also been shown to predict stroke outcome (Lyden et al. 1994; Muir et al. 1994). NIHSS comprises 14 items, including level of consciousness (alertness, questions, commands), eye movements, visual fields, facial symmetry, motor strength (arm/leg), sensation, limb ataxia, language, dysarthria and extinction/inattention. In addition we also included the extra item: motor strength of hand. Each item is assessed on a 3-5 point ordinal scale. The total score can vary from zero to 35 point (37 points including extra item), with a higher score indicating more severe neurological impairment. Both examiners (LF and JW) underwent video training (NIH Stroke Scale Training Tape) and received advice from a neurologist (dr med Brynjar Fure) ahead of the data collection.

2.6.6 Stroke classification

Based on results from CT-scans and evaluation of clinical symptoms, the strokes were classified according to type (infarct and/or hemorrhage) and hemispheric location (left, right, bilateral, brainstem, cerebellar, unknown).

Topographical location and severity of the lesions were categorized according to the Oxfordshire Community Stroke Project (OCSP) classification (Bamford et al. 1991) described in chapter 1. In order to secure reliable categorizations, an experienced neurologist (Brynjar Fure) assisted in the procedure.

2.7 Statistical analyses

For the statistics we used SPSS, version 14.0 (substudy 1 and 2) and version 16.0 (substudy 3 and 4) and performed table analyses, bivariate and multivariate regression analyses. All continuous variables were checked for normality. In the bivariate analyses, parametric tests
(independent-samples t-test) were applied for continuous variables satisfying normality assumptions, for non-normally distributed continuous variables and ordinal variables non-parametric tests (Mann Whitney U Test, Kruskal-Wallis-tests) were used, and for categorical variables Pearson chi-square and Fisher’s exact tests were applied. Only variables in the bivariate analyses with a p-value<0.05 were entered into the multivariate regression analyses. Significant independent variables were checked for multicollinearity before entering the regression analyses. A problem of multicollinearity only existed in sub study 3, in which the NIHSS Total scale and Barthel Index at baseline correlated highly (Pearson’s r>0.7). Table 4 gives an overview of the statistical methods used in the four sub studies.

### Table 4: Statistical methods used in the four sub studies:

<table>
<thead>
<tr>
<th>Sub study</th>
<th>Statistical methods</th>
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<tbody>
<tr>
<td>I. <em>APOE ε4</em> and cognition&lt;br&gt;Cross-sectional, subacute phase,</td>
<td>Table analyses, bivariate analyses, multivariate logistic regression analyses</td>
</tr>
<tr>
<td>II. <em>APOE ε4</em> and cognition&lt;br&gt;13 months longitudinal</td>
<td>Table analyses, bivariate analyses, multivariate logistic regression analyses</td>
</tr>
<tr>
<td>III. Cognition and functional outcome&lt;br&gt;13 months longitudinal</td>
<td>Table analyses, bivariate analyses, multivariate linear regression analyses</td>
</tr>
<tr>
<td>IV. Depressive symptoms and outcome&lt;br&gt;13 months longitudinal</td>
<td>Table analyses, bivariate analyses, multivariate logistic regression analyses</td>
</tr>
</tbody>
</table>

### 2.8 Ethical consideration

The study protocol was approved by the Regional Committee for Ethics in Medical Research in Norway, and the Privacy Ombudsman. Oral and written informed consent was obtained from all subjects.

The concept of informed consent, however, is clearly problematic in a stroke rehabilitation population, as several patients temporarily or permanently have reduced capacity due to different cognitive impairments, such as reduced consciousness, moderate/serious dementia, delirium, and aphasia. In such cases, we consulted a next of kin before the patient was included in the project. Any objection from a next-of-kin was respected. One could question if such a procedure is ethical correct, but the alternative would be to exclude these patients from
the study, and thereby reduce the representativeness of the results for a stroke rehabilitation population. Stroke research, in general, have frequently omitted these patients from the samples, and one thereby runs the risk that previous findings could be biased. Inclusion of serious cognitively disturbed patients was therefore deemed important.

The examinations did not contain any harmful procedures, and the author’s clinical impression is that most patients were positive to participate, and experienced the interviewing and testing as a valuable part of their rehabilitation. In fact, several patients expressed a wish for regular cognitive training; an aspect which was regarded as important but presently is missing in the rehabilitation. On the other hand, the examinations were comprehensive, usually lasting 2-3 hours, and were experienced as exhausting for many. A few patients also developed headache during the examinations. The problem of fatigue and pain necessitated a flexible examination procedure, implicating that the interviewing and/or testing were split into shorter sessions, either on the same day or over several days.
2.9 Results - Abstracts of the four papers

2.9.1 Paper 1
Title: Association between ApoE ε4 and Cognitive Impairment after Stroke

Background and purpose: The understanding of the contribution of genetic factors to cognitive impairment after stroke is incomplete. The aim of the study was to examine whether the Apolipoprotein E ε4-allele (ApoE ε4) is a risk factor for cognitive impairment in the early phase after stroke.

Methods: The sample comprised 152 Norwegian stroke rehabilitation in-patients (mean age 76.8, s.d. 10.5) examined at a mean of 18.3 days (s.d. 13.4) after hospital admission. Post-stroke cognitive impairment was assessed with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The following proposed risk factors were analysed: ApoE-genotype, demographics (age, sex, education), pre-stroke cognitive reduction, (the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)), pre-stroke vascular factors (including previous stroke), stroke characteristics (type, location), and neurological stroke-related impairment (The National Institute of Health Stroke Scale (NIHSS)). Cognitive impairment was defined as a RBANS Total Index Score ≤1.5 s.d. below mean. Multiple logistic regression analyses were performed to find risk factors for post-stroke cognitive impairment.

Results: Four variables were found to be independent risk factors for cognitive impairment after stroke: ApoE ε4 (OR=3.7; 95% CI 1.2-11.6), IQCODE 3.44+ (OR=9.2; 95% CI 2.3-37.2), total or partial anterior stroke syndromes (OR=3.2; 95% CI 1.3-8.0), and NIHSS Total score>5 (OR=7.3; 95% CI 2.7-19.7). No association between ApoE ε4 and pre-stroke cognitive reduction (IQCODE) was found.

Conclusions: The presence of one or two ApoE ε4-alleles may be a significant independent risk factor for cognitive impairment in the early phase after stroke.
2.9.2 Paper 2

Title: Cognitive impairment and the role of the ApoE ε4-allele after stroke – a 13 months follow-up study

Objective: To examine the relationship between the ApoE ε4 allele and cognitive impairment 13-months after stroke.

Methods: One hundred four stroke rehabilitation patients were cognitively tested on average 18 days after hospital admission and again 13 months later with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The following potential risk factors for post-stroke cognitive impairment (defined by a RBANS total index score below 77.5 points) at 13 months follow-up were analyzed in bivariate and logistic regression analyses: ApoE-genotype, socio-demographic variables, pre-stroke cognitive reduction (The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)), vascular factors, lesion characteristics and neurological impairment (The National Institute of Health Stroke Scale (NIHSS)). Differences in general cognitive performance (pre-stroke, baseline and follow-up) across patients with different ApoE-genotypes were analyzed, and lastly differences between ε4-carriers and non-carriers for changes in performance in various cognitive domains over the 13 months period were examined.

Results: Significant risk factors for cognitive impairment at 13 months were ApoE ε4, pre-stroke cognitive reduction (IQCODE 3.44+), previous stroke, and neurological impairment (NIHSS Total Score >5). A significant dose-dependent effect of the ApoE-genotype in relation to overall post-stroke cognitive functioning was found at baseline and follow-up, but not pre-stroke. The ε4-carriers showed a significant decline in tests related to verbal learning and memory compared to the non-carriers.

Conclusions: The ApoE ε4-allele constitutes an independent risk factor for cognitive impairment at 13 months post-stroke, and is associated with progression of cognitive decline in tasks related to verbal learning and memory.
2.9.3 Paper 3

**Title:** Early post-stroke cognition in stroke rehabilitation patients independently predicts functional outcome at 13 months.

**Objective:** To identify prognostic factors associated with functional outcome at 13 months in a sample of stroke rehabilitation patients. Specifically, we hypothesized that cognitive functioning early post-stroke would predict long-term functional outcome independently of other factors.

**Methods:** One hundred sixty three stroke rehabilitation patients underwent a structured neuropsychological examination two to three weeks after hospital admittance, and their functional status were subsequently evaluated thirteen months later with the modified Rankin Scale (mRS) as outcome measure. Three predictive models were built using linear regression analyses: A biological model (sociodemographics, ApoE-genotype, pre-stroke vascular factors, lesion characteristics, and neurological stroke-related impairment); a functional model (pre and early post stroke cognitive functioning, personal and instrumental ADL, and depressive symptoms); and a combined model (including significant variables from the biological and functional model).

**Results:** A combined model of four variables best predicted long-term functional outcome with explained variance of 49%: Neurological impairment (The National Institute of Health Stroke Scale) ($\beta=0.402$, $p<0.001$), age ($\beta=0.233$, $p=0.001$), post-stroke cognitive functioning (The Repeatable Battery of Neuropsychological Status (RBANS)) ($\beta=-0.248$, $p=0.001$), and pre-stroke personal ADL (Barthel Index) ($\beta=-0.217$, $p=0.002$). Further linear regression analyses of which RBANS Indexes and subtests best predicted long-term functional outcome showed that Coding ($\beta=-0.484$, $p<0.001$) and Figure Copy ($\beta=-0.233$, $p=0.002$) raw scores at baseline explained 42% of the variance in mRS-scores at follow-up.

**Conclusions:** Early post-stroke cognitive functioning as measured by RBANS is a significant and independent predictor of long-term functional post-stroke outcome.
2.9.4 Paper 4

**Title:** Depressive symptoms in stroke patients – a 13 month follow-up study of patients referred to a rehabilitation unit.

**Background:** Although depression is known to be frequently associated with stroke, it is nonetheless under-diagnosed and under-treated in this patient population. Its effect on outcome for stroke patients is thought to be substantial, but prediction is complicated by other pre- and post stroke factors. The aims of this study was to describe changes in depressive symptoms in elderly stroke patients across a time span of one year, to examine risk factor for such changes and to explore whether depressive symptoms have any independent impact upon one year mortality and nursing home placement.

**Methods:** 194 patients diagnosed with an ischaemic or hemorrhagic stroke was recruited from the Stroke Rehabilitation Unit, Ullevaal University Hospital, Oslo, Norway during the period between March 2005 and August 2006 and followed up for a period of 13 months. Pre-stroke assessment was accomplished by means of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), the Frenchay Activities Index (FAI), the Barthel ADL Index and patient's medical history. Post-stroke assessment at inclusion and follow-up examination was performed with the Mini Mental State Examination (MMSE), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Star Cancellation Test, the Barthel ADL Index, the modified Rankin Scale (mRS) and the National Institute of Health Stroke Scale (NIHSS). Information was collected from the patients' records.

**Results:** Institutionalization at 13 months was predicted by more depression (MADRS) and cognitive impairment (RBANS) at baseline, together with lower pre-stroke social activity levels (FAI). Two factors predicted death at 13 months: Cognitive impairment (MMSE) and greater age. The prevalence of depression was relatively unchanged from baseline (56 %) to 13 month follow-up (48 %). Among the patients who were depressed at baseline 55 % still had a MADRS score above six (persistent depression) at 13 months, while 35 % in the non-depressed group at baseline had developed depression (incident depression). Persistent depression was significantly predicted by lower pre-stroke social activity levels (FAI) together with a more severe stroke (NIHSS) and worse overall function (mRS) at baseline. Incident depression was predicted by receipt of municipal home help before the stroke and a lower score on the delayed memory tasks on RBANS at baseline.
2.10 Discussion

This project has studied cognitive functioning and depressive symptoms in a stroke rehabilitation population over a 13 months period. We are of the opinion that a clear focus on these symptoms are lacking in many Norwegian stroke rehabilitation units today, and deserve greater attention considering their impact on rehabilitation and outcome. Inclusion of a clinical psychologist in the multidisciplinary rehabilitation team of the specialized stroke unit would be one way to set these topics on the agenda.

It seems obvious that a stroke rehabilitation patient routinely should be assessed for cognitive and depressive symptoms, but, unfortunately, this is not the truth today. Cognitive testing of the patients is carried out, but the methods used are in most cases broad, and shown to be insensitive to several deficits commonly seen in this patient group. Formal screening for depressive symptoms is seldom done, and the diagnosis is usually based on clinical impression only.

In the present project, we have demonstrated that testing for cognitive and depressive symptoms in a stroke rehabilitation population is feasible, and that these symptoms occur frequently in the patients both in the subacute phase while in the hospital and later.

Approximately 60% of the patients were cognitively impaired and 56% had clinically significant symptoms of depression on average two to three weeks post-stroke, decreasing slightly to 50% and 48%, respectively, at 13 months. The results suggest stability or a minor improvement in the frequency of cognitive impairment and symptoms of depression over time in the stroke survivors as a group. However, there were notable individual differences in the post-stroke course of the patients, especially with respect to symptoms of depression: About one in two of the patients classified as having significant symptoms of depression at baseline were classified as free from significant symptoms of depression at 13 months. Cognitive performance followed a more stable pattern over time: About three in four of the subjects classified as cognitively impaired at baseline were also classified as cognitively impaired at 13 months. In the years ahead of the stroke, 18% had experienced marked cognitive reduction. This confirms previous findings that post stroke cognitive impairment in many cases is influenced by an already pre-existing cognitive reduction (Henon et al. 1997; Pendlebury and Rothwell 2009).
The present results indicate that cognitive impairment and symptoms of depression are related to different risk factors and prognosis. Probably, the most interesting research finding is how genetic vulnerability through the presence of the ApoE ε4-allele is a significant risk factor for cognitive impairment both in the short and long term after a stroke, and that it is associated with reduced performance on tasks related to verbal episodic learning and memory over the 13 months follow-up period. To our knowledge, this association has only been reported in one previous study (Ballard et al. 2004), but, in that study, the researchers did not control for pre-stroke cognitive functioning, as we did. Our finding strongly suggests a degenerative process in the patients carrying the ApoE ε4-allele, stimulated or reinforced by the present stroke, and resembling the disease process seen in patients with AD. The presence of the ApoE ε4-allele may explain why some patients do not recover after a stroke, but slowly decline cognitively, and, we hypothesize, that they may finally end up with a dementia diagnosis. The message to stroke rehabilitation personnel, patients, and their families is that rehabilitation outcome probably is not only a matter of the well-known factors, like stroke severity, age and specialized stroke unit care with focus on early mobilization and training, but that genetics also influence the post-stroke cognitive course.

The identification of early post-stroke factors which bear prognostic meaning is important in a stroke rehabilitation unit both to plan for the rehabilitation and to guide the patient and the family. We have shown that cognitive and depressive symptoms in the early post-stroke phase are significant predictors of long term stroke outcome measures, like functional outcome, institutionalization and death at 13 months, even when well-established sociodemographic variables and biological factors are controlled for.

Specifically, we have demonstrated that the RBANS is a neuropsychological test battery which may be considered relevant to apply in a stroke rehabilitation unit as a tool to predict the long-term prognosis. The RBANS Total Index Score at two to three weeks after hospitalization predicted both functional outcome and nursing home residence at 13 months. Among the twelve RBANS subtests, Coding and Figure Copy, were the two subtests with the best predictive power in relation to long-term functional outcome. We therefore recommend that particular attention should be paid to early performance on these two subtests in questions related to functional prognosis. To our knowledge, the independent effect of early performance of RBANS in relation to long-term outcome has never been shown before,
although strong bivariate correlations have been reported earlier (Larson et al. 2005; Larson et al. 2003).

More than half of the patients expressed clinically significant depressive symptoms at baseline, but the symptoms were in the mild range in most cases (86%), and, in fact, none of the patients expressed symptoms in the severe range. Still, depressive symptoms at baseline, together with lower pre-stroke social activity level and cognitive impairment at baseline, were demonstrated to predict nursing home residence at 13 months. Our finding indicates that even milder types of depressive symptoms in the rehabilitation setting should be taken seriously as a negative prognostic factor of functional long-term performance.

2.10.1 ApoE ε4 and post-stroke cognitive impairment (paper 1 and 2)

The results of paper 1 and 2 strongly suggest that ApoE ε4 is a significant risk factor of post-stroke cognitive impairment both in the subacute phase and after 13 months. Furthermore, while ApoE ε4 non-carriers showed an improvement in cognitive performance during the follow-up period, the ε4-carriers declined, especially in tasks related to verbal episodic learning and memory. The results point to a restorative capacity still being preserved in the ApoE ε4 non-carriers, but not in the ε4-carriers. Rather, the decline over time in the ε4-carriers suggests a neurodegenerative process resembling the one seen in AD, manifested or exaggerated in its expression as a consequence of the present stroke. Of particular interest is the dose-dependent effect found in our material, which to our knowledge has not been reported before: Non-carriers had less risk of post-stroke cognitive impairment compared to carriers of one copy of the ε4-allele, who in turn had less risk than carriers of two copies of the ε4-allele. In fact, all carriers of two copies of the ε4-allele fell in the cognitive impairment group at follow-up, but the number of these were very low (n=4).

Previous studies have given conflicting results presumably because of differences in methodology and composition of study samples. More sensitive cognitive tests than the frequently applied MMSE, is probably required to detect the cognitive decline in the ApoE ε4-carriers, and the RBANS may be such an alternative. Our sample comprised mainly elderly patients, and, due to the patient screening procedure used at the Stroke Rehabilitation Unit at the Oslo University Hospital, Ullevaal, a high proportion of moderate/severe strokes were recruited as compared to an unselected stroke population. It may well be that the ApoE ε4-
allele exerts a stronger effect in elderly patients with moderate/severe strokes than in younger patients with less severe trauma, possibly as a consequence of less cognitive reserve (neurological redundancy) in the more severely afflicted patients.

A critical question is the extent to which the documented ApoE ε4-effect reflects a disease process already in progress before the time of the present stroke. This question is relevant as the impairments in episodic learning/memory functions resemble the profile seen in patients with AD. In the absence of a better method, we relied on the IQCODE to estimate the frequency of pre-stroke cognitive reduction. We found that the ApoE ε4 carriers had a higher frequency of pre-stroke cognitive reduction, but that the difference was non-significant. Still, this tendency could reflect a process already in effect before the stroke occurred, manifesting as part of the total post-stroke symptomatology. As seen in this context, the present IQCODE-results agree with the literature on normal aging, which suggests that there are differences in cognitive performance between healthy elderly ApoE ε4-carriers and non-carriers, but that these differences are moderate and restricted to the domains of global cognitive functioning, episodic memory and executive functions only (Small et al. 2004). In support of the validity of the pre-stroke IQCODE data, IQCODE was found to be an independent, significant predictor of post-stroke cognitive impairment at both baseline and at 13 months follow-up examination in our study. Still, the IQCODE should be properly validated as a tool to estimate pre-stroke cognitive functioning in retrospect.

The present data points to a link between ApoE ε4 and episodic memory impairment. A central component of this link may be temporal lobe dysfunction. A recent functional magnetic resonance imaging (fMRI) study of stroke patients examined 6-8 weeks after stroke found reduced medial temporal lobe functionality in patients with deficits in episodic memory (Snaphaan et al. 2009). Even non-demented stroke patients with deficits in episodic memory are characterized by medial temporal lobe atrophy on MRI-scans (Jokinen et al. 2004). Episodic memory performance is related to an extensive functional network of interacting structures in the medial temporal lobe, parietal cortex, thalamus and prefrontal cortex, and it is hypothesized that any disconnection in this network, e.g. due to a stroke, can reduce functionality in the medial temporal lobe (Simons and Spiers 2003). Carriers of the ApoE ε4-allele demonstrate reduced glucose metabolism in brain areas related to episodic memory (temporal, parietal, prefrontal cortex, and posterior cingulate) even as young adults (Reiman et al. 2004; Scarmeas and Stern 2006) and non-demented elderly ApoE ε4-carriers possibly
have a reduced hippocampal volume (Jak et al. 2007; Lind et al. 2006). These genetically related functional and possibly structural changes in brain areas of central relevance for memory could represent vulnerability-markers for increased functional impairment caused by trauma, also vascular crises. The increased severity of deficit could derive from reduced neuronal and functional redundancy in the afflicted regions. Interestingly, medial temporal atrophy is considered one of the strongest markers of Alzheimer-pathology as related to ApoE ε4 (Gold 2009). In consequence, the present findings of reduced episodic memory performance across time in the ApoE ε4-carriers may point to an identical or similar disease process being exposed as an effect of stroke pathology.

In conclusion, there is strong evidence for the validity of the ApoE ε4-effect found in our study, but further research is needed to determine whether the ApoE ε4-allele should be included among the risk factors of cognitive impairment after a stroke.

It may be objected that the negative ApoE ε4-effect is an artefact, created by a higher proportion of subjects with aphasia and paresis in dominant hand in the ApoE ε4-carriers, and consequently reducing their abilities to perform cognitive testing. A new analysis of the baseline data was therefore carried out (paper 1), excluding all subjects with aphasia (NIHSS item 9 > 0) and impaired motor function of the dominant hand (NIHSS item 5b > 0). Of the 91 patients remaining, 42 subjects (46%) were classified as cognitively impaired (RBANS total index score ≤ 77.5). An univariate logistic regression analysis with the 91 remaining subjects and cognitive impairment/no impairment as the dependent variable showed the same results as in the previous analysis with regard to significant variables (ApoE ε4, IQCODE 3.44+, Total or partial anterior stroke syndromes, and NIHSS Total score >5). Adjusted OR of the four variables were ApoE ε4 (OR 5.1; 95% CI=1.4-19.0; p=0.014), IQCODE 3.44+ (OR 7.9; 95% CI=1.7-37.6; p=0.009), Total or partial anterior stroke syndromes (OR 4.3; 95% CI=1.2-14.9; p=0.022), and NIHSS Total score>5 (OR 5.4, 95% CI=1.3-23.3; p=0.023). A similar analysis of the follow-up data was precluded because of the high drop-out rate.

Could the negative ApoE ε4-effect seen in the stroke patients be prevented or cured? At present, there is no effective medical therapy (Mahley and Huang 2009) and whether post-stroke life-style changes may have a particular benefit on the ApoE ε4-carriers is unknown. However, there are indications of lifestyle-genotype interactions, suggestive that avoiding smoking, increasing physical activity and antioxidant intake, and reducing alcohol intake,
total fat and saturated fat intake, at least in part, may reduce the elevated risk of cardiovascular disease in persons carrying the ε4-allele (Jofre-Monseny et al. 2008; Minihane et al. 2007). At what age such life style changes need to be introduced is uncertain.

If our findings are confirmed, should ApoE-genotyping be recommended as a standard screening method in the stroke unit to determine prognosis? The question has been much debated in relation to Alzheimer’s disease, and the answer has been clear: As long as there is no effective cure to prevent or treat AD, standard screening is not recommended. ApoE genotyping is useful for studying disease risk in large groups of persons, but not for determining an individual’s risk (Lovestone et al. 1996). The same arguments seem justified in relation to ApoE-genotyping and post-stroke cognitive impairment.

2.10.2 Early post-stroke cognitive performance (RBANS) as predictor of long-term functional outcome (mRS) (paper 3)

This is the first study to evaluate the predictive value of early performance of RBANS in relation to long-term functional outcome measured with mRS in a sample of stroke rehabilitation patients. The results suggest that early performance on RBANS is a strong and important predictor of mRS-scores at follow up (at 13 months). Our results thereby support the existing literature of RBANS, indicating that it may be an attractive cognitive screening battery to apply in a stroke rehabilitation setting in questions related to functional prognosis.

In our study, we found that functional outcome at 13 months varied considerably among the stroke rehabilitation patients. Approximately 34% of the patients could be defined as having a favourable outcome with no symptoms or slight disability (mRS=0-2), 21% as having a moderate disability (mRS=3), 22% as having a severe disability (mRS=4-5), while 23% were dead (mRS=6). Among the 126 stroke sufferers alive at follow-up, 91 subjects (72%) were living at home and 35 subjects (28%) in nursing homes. With the exception of one subject, all living in nursing homes had a mRS-score>2.

According to the literature, an improvement in ADL-functioning and global handicap can be expected for the majority of stroke patients, at least for the first three to six months post-stroke. However, this does not accord with our data, which showed that 31% improved, 25 remained stable, while 44% declined in mRS-score during the follow-up period. Reason for
the discrepancy could be due to differences in study samples, as previous studies generally have comprised younger patients with first-ever strokes only, while 70% of our sample were above 75 years of age and 33% had suffered a previous stroke. Another reason could be that some studies exclude dead persons (mRS-grade 6) from the analysis. In our view, this may be misleading with respect to revealing the complete range of prognosis.

The multivariate linear regression analysis revealed that a combination of sociodemographic, biological, and functional baseline variables better predicted mRS-scores at follow-up, rather than a pure biological or functional model alone. In order of importance, these baseline variables were NIHSS Total score (neurological stroke severity), RBANS Total Index (cognitive overall performance), age in years, and pre-stroke Barthel Index total score (personal ADL-performance before the present stroke). These four variables explained 49% of the variance in mRS-scores at follow-up, underlining that stroke outcome is not only a matter of stroke severity, but that multiple factors determine outcome, of which cognition is one. The importance of a multifactorial approach which includes cognitive measures is also suggested by an earlier study, which found that a combined model of medical and cognitive variables would better explain long-term dependence in daily life, than a medical or cognitive model alone (Nys et al. 2005b).

Which particular RBANS indexes and subtests are most predictive of long-term functional outcome? In fact, all RBANS Indexes and subtests were significantly associated with outcome in the unadjusted analysis. With respect to the RBANS Indexes, only the Visuospatial/Constructional Index remained significant in the adjusted analysis. Although the original five factor structure of the RBANS Indexes was not confirmed in a sample of acute stroke patients (Wilde 2006), we still find the result interesting, as visuospatial/constructional functioning earlier has been reported to be among the most important predictors of both functional outcome and quality of life after stroke in several studies (Jongbloed 1986; Kwakkel et al. 1996; Larson et al. 2003; Nys et al. 2005b; Nys et al. 2006; Sveen et al. 1996). In Larson et al. 2003, RBANS was applied in a sample of stroke rehabilitation patients, and the researchers found that only inpatient performance on the Visuospatial/Constructional Index was positively correlated with handicap, motor function, and frequency of activity six months later as measured by the FIM. Unfortunately, they did not examine the relationship between RBANS subtests and long-term outcome. Our data, however, suggest that two specific RBANS subtests, Coding (part of the Attention Index) and
Figure Copy (part of the Visuospatial/Constructional Index) may be even better predictors of long-term functional outcome than the Visuospatial/Constructional Index. Explained variance of these two subtests in the adjusted analysis was better than the Visuospatial/Constructional Index (42% vs 26%), and they remained highly significant even when controlled for age and education as possible statistical confounders. One clinical implication is that the Coding and Figure Copy tests could be relevant as easy-to-do and quick screening instruments in stroke rehabilitation units to gain long-term prognostic information. Their potential clinical utility deserves to be examined in new data. (None of them are among the recommended test in the proposed national guidelines for treatment and rehabilitation of stroke in Norway presently out for commenting (Helsedirektoratet 2009a)).

How are we to understand the Coding and Figure Copy effects in our study? The two subtests are, except from Figure Recall, the only paper and pencil tests in RBANS. Therefore, the effects attributed to them could simply reflect the test- and daily living relevance of dominant hand motor activity. However, this hypothesis was not confirmed in a regression analysis adjusting for paresis in dominant arm/hand as possible confounders. Although simple in appearance, Coding and Figure Copy are actually functionally complex tests. Predominantly tests of attention and visuospatial/constructional functions respectively, the functions involved comprise visuoperception, construction, sensomotor activity, attention, planning and visual organization (Lezak 2004). The successful execution of the tests would therefore involve the concerted cooperation of a large number of structurally distributed functions. One implication of this is that test dysfunction can derive from a large number of topologically diverse sources, as well as from extensive and gross tissue destruction like in stroke. In the latter case, the tests would appear to act like mass indicators, assessing the global character of cognitive resources; in the former case they would act as indicators of more focal damage. In a focal context, it is interesting that performance on coding tasks have also been shown to strongly and differentially predict, e.g. disability and risk of mortality in well functioning elders (Rosano et al. 2008) as well as illness risk, severity, and disability in schizophrenia (Dickinson 2008).

With respects to functions shared by both tests, visuospatial attention would appear to be a primary candidate. The neuronal substratum underlying these very complex functions comprises both prefrontal and parietal cortices as well as subcortical regions of both hemispheres, particularly the right one (Lezak 2004;Liu et al. 2003;Posner and Petersen
1990). In the case of large vascular crises, the extensive destruction of tissue would very likely affect regions of relevance for visuospatial attention, as attested by the fact that they are very common as symptoms of stroke. It is therefore to be expected that tests of these functions are sensitive to reduced performance in the present subjects. The specificity of the tests’ predictive ability also argue in favour of attentional dysfunction as the primary predictive factor, since a more global cognitive reduction would have been expected to decrease the specificity of prediction relative to the other RBANS subtests. In relation to long-term functional prognosis, it is interesting to notice the findings of Nys et al. (2005b), suggesting a link between awareness and visuoattentional mechanisms. A consequence of reduced awareness of own deficits could be lowered motivation for compensatory activities.

The outcome measure, the mRS, has been criticized for being too gross and depend too heavily on physical disabilities (Hajek et al. 1997). We have therefore examined how the mRS-scores at 13 months follow-up related to other outcome measures at follow-up, and found strong correlations with personal ADL (Barthel Index, Pearson r = -0.778, p<0.001), instrumental ADL (Frenchay Social Activity Index, Pearson r = -0.792, p<0.001), neurological stroke-related impairment (NIHSS Total, Pearson r = 0.710, p<0.001), and cognitive functioning (RBANS Total Index, Pearson r = -0.585, p<0.001). With respect to symptoms of depression, however, the association was only modest (MADRS Total, Pearson r = 0.217, p = 0.017).

A strong correlation between mRS and disability in personal ADL (Barthel Index) and neurological functioning (NIHSS) accords with previous studies, while the association with cognitive functioning and social health domains have been found to be much weaker in previous studies (de Haan et al. 1995;Hajek et al. 1997;Weisscher et al. 2008). The discrepancy could possibly support previously noted limitations of the mRS. Since the scale is only a broad-based summary measure, domains like cognition, social participation and emotions are not measured directly, but implicitly included in the score (Kasner 2006). It is therefore hardly surprising that inter-observer variability in mRS scores have been reported (Banks and Marotta 2007;Quinn et al. 2009). One possibility is that the scorer’s health profession may affect the assigned score. In our study, scoring was undertaken by two clinical psychologists who may stress cognitive, social, and emotional aspects of patients functioning in particular.
Still, RBANS’ predictive validity should preferably be further explored in relation to other long-term stroke outcome measures, including social activity level, cognitive performance, symptoms of depression, and psychosocial burden of caregiver.

2.10.3 Symptoms of depression as assessed longitudinally in stroke rehabilitation patients (paper 4)

In this study, we examined changes in symptoms of depression in stroke rehabilitation patients over a 13 months period, assessed predictors of such changes, and examined the potential independent effect of symptoms of depression on stroke outcome (mortality and nursing home placement).

We found that symptoms of depression were highly prevalent both in the subacute phase (56%) and after 13 months (48%), but for most of the patients the symptoms were of a mild character on both occasions. Neither at baseline nor follow-up examination did any patients have symptoms in the severe range as measured by MADRS, and with respect to moderate symptoms, the frequency was only 14% and 8% respectively. The only predictor of post-stroke depressive symptoms at 13 months was a lower score of domestic and social levels of activity ahead of the stroke (FAI).

Independent of stroke, a depression is said to have a good prognosis (Helsedirektoratet 2009b). However, this does not seem to be true for the stroke patients in this study, as the symptoms resolved in less than half of the patients during the follow-up period. In fact, 55% of the depressed subjects at baseline where still depressed at follow-up. In a recent three year follow-up study, stroke patients who were still depressed at six months had an increased risk of developing a chronic condition (Schepers et al. 2009). In our study patients with persistent symptoms of depression were characterized by a lower score of domestic and social activity level ahead of the stroke (FAI), more severe stroke (NIHSS), and worse overall functioning (mRS). All three factors intuitively make sense. In addition, higher levels of post-stroke ADL (Barthel Index) and less cognitive impairment (MMSE) at baseline were also predictors of persistent symptoms of depression, but we have no good explanation for these findings.

We have also shown that more than one third of the patients who were not depressed in the early post-stroke phase reported significant levels of depression at 13 months examination. Our figure corresponds well with an earlier study which reports that about 1/3 of non-
depressed patients in the immediate post-stroke period become depressed between 3 months and 2 years after stroke (Robinson et al. 1987). Predictors of incident depression were reduced memory performance at baseline (RBANS Delayed Memory Index) and receiving municipal home assistance. Notably, neither vascular risk factors nor lesion location were found to be risk factors of post-stroke depression in our study. With respect to topographical location, the negative results concur with the conclusions of a systematic review (Carson et al. 2000).

A limitation of our study, however, is that we have no measure of pre-stroke depressive symptoms in the subjects. Independent of stroke, depression is quite common, and estimated to be 19% in the general population older than 60 years (Rosenvinge and Rosenvinge 2003). We must therefore assume that many of the subjects included in this study experienced depressive symptoms ahead of the present stroke, which may have reduced the chances of finding stroke-related risk factors, like lesion location.

Our study sample originally comprised 194 stroke patients, but only 163 patients were included in the analysis. Thirty one patients could not complete the MADRS interview because of total aphasia (13 patients), impaired consciousness (7 patients), or unwillingness to answer the questions (11 patients). Although these patients did not differ from the included patients on any demographic characteristics or pre-stroke informant-reported measures except that women were overrepresented, the exclusion represents a selection bias based on neurological symptoms. The selection bias may have lead to an underestimation of the true prevalence of post-stroke depressive symptoms in our study, especially as aphasia is associated with depression in previous studies (Kauhanen et al. 1999;Kauhanen et al. 2000). This methodological problem is not specific to our project though, but represents a general problem in studies of emotional symptoms in stroke patients. One way of overcoming the problem could have been to interview a next of kin of the patient’s symptoms of depression post-stroke, as the MADRS allows for such a procedure (Montgomery and Asberg 1979). However, we chose to apply information given directly from the patients only with regard to symptoms of depression.

Ideally, one would prefer to use a standardized psychiatric interview to diagnose psychiatric illness, but this is a time consuming and impractical method in a stroke rehabilitation unit. If formal assessment of depressive symptoms should be introduced as standard practice in a stroke unit, a screening instrument is probably the most realistic alternative. Therefore, we
chose to apply the MADRS, which is recommended for use in stroke patients, and has demonstrated reliability and validity. One problem with the MADRS, however, is that there is no consensus of a diagnostic cut-off score. We used the Snaith-criteria, which are commonly applied in stroke patients, and define clinical depression by a total MADRS score > 6. However, in psychiatric practice, the usually applied cut-off for a treatable depression is >12. A recent study of Norwegian stroke patients assessed the accuracy of MADRS in identifying a clinical depression according to the DSM-IV criteria (Sagen et al. 2009). At a cut-off of >6, the MADRS had a high sensitivity (0.90), but lower specificity (0.66). A cut-off of >12 resulted in a sensitivity of 0.70 and a specificity of 0.86. Although MADRS primarily assesses psychological aspects of a depression, it also comprises somatic symptoms (e.g. sleeping problems, loss of appetite), which may well mistakenly be considered symptoms of depression, rather than symptoms of the stroke itself (Sagen et al. 2009).

Despite the limitations of MADRS, it was found to predict nursing home residence at 13 months, together with reduced cognitive functioning at baseline (RBANS Total Index) and reduced domestic and social activity level ahead of the stroke. Our results thereby imply that even mild depressive symptoms at baseline should be taken seriously as a negative prognostic factor in a stroke rehabilitation unit.

Interestingly, early symptoms of depression predicted nursing home residence, but not functional outcome at 13 months (paper 3). Thus, one could hypothesize that reduced motivation and/or inadequate coping strategies may reduce the depressed stroke patient’s abilities of self-care and thereby make him or her more dependent on nursing home care. Both biological and psychosocial factors may be relevant for such a finding, and whether the symptoms are treatable remains an open question. Notably, only 31 of the 162 patients (19%) of the subjects were taking antidepressants and none received psychotherapy at discharge from the stroke unit. This may partly be due to insufficient screening, but also doubts about whether anti-depressant treatments or psychotherapy commenced early after the onset of stroke will prevent depression and improve outcome. These reservations are relevant based on the present research literature. The results of antidepressant intervention studies have been disappointing with short-term gains not being translated into long-term benefits, and psychological interventions mostly proven ineffective so far (Hackett et al. 2009; Watkins and French 2009). However, it should be noted that the number of intervention studies is low. The latest Cochrane review of interventions for treating depression after stroke comprised 17
studies (13 pharmaceutical trials, 4 psychotherapy trials, and none ECT trials) (Hackett et al. 2009) only, despite being based on searches in relevant databases from approximately 1966 until May 2006. In a recent study, (Mitchell et al. 2009; Watkins and French 2009) promising results are reported with an eight week brief psychosocial-behavioral intervention in combination with antidepressants, which were shown to be highly effective in reducing depression early post-stroke (4 months) and later (12 months). However, the subjects were younger than the present index cases (mean age 58 years), and the authors did not assess the association between recovery from depression and other outcome measures.

In principle, it is hard to understand why not stroke patients with depressive symptoms, or at least subgroups of these (probably patients with relatively intact cognitive functioning), should benefit from psychotherapy as long as there is empirical evidence for the efficacy of psychotherapy for treatment of depression among the elderly generally (Pinquart et al. 2006; Serfaty et al. 2009). According to the Norwegian national guidelines for diagnosing and treating adults with depression, treatment of depression in the elderly should follow the same principles as for younger adults (Helsedirektoratet 2009b). No specific recommendations are given for post-stroke depression. Considering the low number of high-quality psychotherapeutical intervention studies which have been carried out, further studies to clarify this issue are needed.

2.10.4 Methodological considerations

Our subject sample was recruited from the Stroke Rehabilitation Unit at the Oslo University Hospital, Ullevaal. The routines of the Stroke Rehabilitation Unit were consistent with national and international standards. The multidisciplinary rehabilitation team consisted of doctors (geriatrists/neurologists), registered nurses, auxiliary nurses, physical therapists, occupational therapists, and speech therapists. The average length of stay in the hospital was 38.3 days (sd 24.1), and during this period the patient were offered medical treatment, rehabilitation and active training tailored to his/hers specific needs.

Patients in the stroke rehabilitation unit were transferred from the hospital’s acute setting. Only patients in a stable medical condition and judged by a senior consultant to benefit from rehabilitation were admitted. In practice, this means that several patients with very mild or very severe strokes have been treated at the acute setting, but never been admitted to the
Stroke Rehabilitation Unit. The number of patients falling in this category is unknown. As a consequence of the screening procedure, our study sample is probably biased towards the middle/severe range in terms of stroke severity. (Today, the Stroke Unit at Oslo University Hospital, Ulleval has been reorganized, and all stroke patients, independently of stroke severity and medical condition, are admitted directly to the unit).

The patients in the project were recruited consecutively, except for periods were the examiners were off duty, due to holidays, illness, or academic courses and conferences. Few exclusion criteria were applied in order to secure a representative sample of the stroke rehabilitation population both with respect to age, sex, stroke severity, and pre-stroke medical and functional status. Generally, there have been a strong tendency of previous studies to include younger patients with first-ever stroke only in the samples, thereby restricting the representativeness of the results.

There is not yet a Norwegian national stroke register to compare our data, but according to a recent paper from the Swedish register, Riks-Stroke, of 79689 patients treated at Swedish stroke units from 2001 to 2005 (Terent et al. 2009), our patients characteristics concord quite well with theirs with regard to age, sex and stroke type (Table 4).

Table 4: Comparison of baseline characteristics between Swedish patients treated at stroke units and our sample at the Stroke Rehabilitation Unit, Oslo University Hospital, Ulleval.

<table>
<thead>
<tr>
<th></th>
<th>Swedish Riks-Stroke</th>
<th>Our study sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=79689</td>
<td>n=194</td>
</tr>
<tr>
<td>Age, yrs (mean, SD)</td>
<td>75.1 (11.2)</td>
<td>76.9 (10.5)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>51%</td>
<td>51%</td>
</tr>
<tr>
<td>Haemorrhagic stroke %</td>
<td>12%</td>
<td>16%</td>
</tr>
<tr>
<td>Dependency in ADL</td>
<td>12%*</td>
<td>40%**</td>
</tr>
<tr>
<td>Previous stroke, %</td>
<td>21%</td>
<td>28%</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>25%</td>
<td>11%</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>20%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Note:
* % with mRS-scores 4 or 5 in a Swedish sample of 545 patients investigated 3 months after hospitalisation.
** % with mRS-scores 4 or 5 in our sample examined at a mean of 18.7 days (sd 13.2) after hospitalisation.
However, both the proportion of patients who had experienced a previous stroke and the proportion dependent in ADL after the present stroke is higher in our sample than in the Swedish national register. The percentage dependent in ADL is not directly comparable since our data were collected 2-3 weeks post-stroke, while the Swedish figures is based on 3-months data, but still indicate that our patients have suffered more severe stroke and, thus, become more dependent in ADL-functioning than the Swedish stroke patients. In sum, due to the bias in the study sample, our results are not representative of the stroke population as a whole, but may represent a stroke rehabilitation population with an overweight of moderate/severe strokes.

Ideally, our results should have been compared to a control group, but no such exists in any of the four studies. Being in a hospital with a potential life-threatening condition represents a stressful life experience, which may affect both cognitive performance and emotional well-being negatively. Thus, comparison of our results to a hospital-based population (matched for age, sex, education) with a life-threatening disease other than stroke would probably be a better alternative than relying on a normal-community based one. This criticism is particularly relevant for the cognitive data in the present case, since the Norwegian version of RBANS has never been validated in a stroke population. We relied on American norms (adjusted for age and education) to estimate the frequency of cognitive impairment in our sample. Considering the high estimated frequency of cognitive impairment, one might argue that RBANS overestimate the impairment rate. However, a comparison of RBANS performance of our stroke patients at baseline with a sample of twenty elderly colorectal cancer patients examined at the Oslo University Hospital, Ullevaal one day before surgery or chemotherapy, support the validity of our results (Table 5).
Table 5: Comparison of RBANS performance between our stroke patients and a sample of in-hospital colorectal cancer patients. All figures as means (sd).

<table>
<thead>
<tr>
<th>RBANS-performance</th>
<th>Colorectal cancer patients (n=20)</th>
<th>Stroke patients (n=152)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate memory</td>
<td>105.5 (15.7)</td>
<td>85.5 (19.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Visuoconstructional</td>
<td>117.9 (12.3)</td>
<td>82.3 (18.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Language</td>
<td>94.8 (10.0)</td>
<td>77.2 (13.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Attention</td>
<td>102.0 (17.3)</td>
<td>70.3 (10.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delayed memory</td>
<td>100.3 (14.0)</td>
<td>80.4 (14.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Index</td>
<td>103.8 (16.2)</td>
<td>73.7 (13.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: Dr Siri Rostoft Kristjannson, Oslo University Hospital, Ullevaal, is gratefully acknowledged for supplying the colorectal data.

The patients in the two groups were of comparable age, sex, and years of education. As can be seen, there were significant differences in performance between the colorectal cancer and stroke patients on all RBANS Indexes. While the cancer-group performed in the normal range on all indexes, the stroke patients performed in the borderline/impaired range. Further validation studies need to confirm the results, but indicate that being in a hospital in a potential life-threatening situation is not a situational factor which in itself is sufficient to lower cognitive performance significantly. Still, this scepticism is frequently expressed by health personnel in hospital settings.

Aphasia and paresis in dominant hand are symptoms that could negatively affect the ability to perform cognitive testing. In our project, patients with such impairments were included, and were scored zero on tests they were incapable of performing. This procedure may produce inflated impairment estimates. In order to control for this effect in our baseline figures (paper 1), we excluded all subjects with aphasia (NIHSS item 9 > 0) and impaired motor function in dominant hand (NIHSS item 5b > 0). Only 91 of the 152 subjects were left for analysis. The frequency of cognitive impairment dropped (from 61%), but still remained as high as 46%, indicating that cognitive symptoms are clearly present in the sample independent of aphasia and paresis in dominant hand.

Our choice of cognitive test battery may be discussed. We relied on the RBANS, which has a strong focus on learning and memory functions, but less on executive functions. Preferably,
more tests of executive functions should have been included, since they may be particularly affected in stroke patients.

There was a relatively high drop-out rate during the follow-up period. Of the 194 patients originally included, 37 (19%) had died, and 31 (16%) had withdrawn at follow-up because of lack of motivation to participate (n=25) or moving to another geographical area (n=6). The high drop-out rate is not specific to our project, but represents a general problem in longitudinal studies of stroke patients with a high proportion of elderly, frail patients. Still selective dropouts may represent a threat to the validity of a study. We checked for differences between the subjects participating at follow-up and those who had withdrawn, but found no significant differences on any sociodemographics or baseline clinical variables, except for a higher proportion of women withdrawing from the longitudinal studies examining cognition and outcome (paper 3) and depressive symptoms and outcome (paper 4).

A methodological strength of our project is the longitudinal design with data of the patients’ performance at three points of time, i.e. pre-stroke, at two-three weeks after the stroke and after thirteen months. However, pre-stroke data were collected retrospectively and on the basis of structured interviews with next of kin, and one could question the validity of these data. Ideally, one would have wished to examine the patients shortly ahead of the present stroke with the same test instruments as used after the stroke, but such a study design would, of course, been impossible to perform in practical terms. Even though the IQCODE, the BI, and the FAI are all validated as outcome measures in stroke populations, their validity as tools to examine pre-stroke functioning in retrospect via a close informant is unknown.

2.11 Conclusions

- The overall aim of this project has been to examine cognitive impairment and symptoms of depression in a sample of stroke rehabilitation patients, and how these factors are related to risk factors and prognosis.
- We confirm previous findings that cognitive impairment is frequent after stroke occurring in approximately 60% of the stroke rehabilitation patients in the subacute phase and 50% after 13 months post-stroke.
The hypothesis that genetic factors may make some patients particularly vulnerable to the cognitive effects of a stroke is strengthened through the project. Not only did the presence of one or two copies of the ApoE ε4-allele constitute a significant independent risk factor for post-stroke cognitive impairment in the subacute phase and after 13 months, but it was also associated with a decline in cognitive performance over the follow-up period, particularly in tasks related to verbal episodic learning and memory. In contrast, non-carriers of the ApoE ε4-allele showed an improvement in cognitive performance over the same period.

Cognitive performance as measured by RBANS Total Index in the subacute phase was a strong prognostic factor for both functional outcome and institutionalization at 13 months even when sociodemographical, biological and functional variables were controlled for. Among the RBANS’ subtests, Coding and Figure Copy, were the strongest predictors of long-term functional performance. Both tests are easy and quick to administer, and may well be considered as attractive screening tools in clinical settings to gain long-term prognostic information.

Clinical significant symptoms of depression (as measured by MADRS) were reported by 56% of the patients 2-3 weeks post-stroke and 48% at 13 months follow-up. Our data indicate that post-stroke depression may follow different courses. Among the depressed group at baseline, 55% still reported symptoms of depression at follow-up (persistent depression), and among the non-depressed group at baseline, 35% reported symptoms of depression at follow-up (incident depression). Lower pre-stroke social activity level (FAI) was the only risk factor for depression at 13 months. Risk factors for persistent depression were lower pre-stroke social activity level (FAI), more severe stroke (NIHSS), worse overall function at baseline (mRS), and, in addition, high personal ADL-functioning (Barthel Index), and high cognitive performance (MMSE). Risk factors for incident depression were receiving municipal home help before the stroke and reduced score on the RBANS delayed memory index at baseline.

The symptoms of depression reported at baseline were predominantly in the mild range (86%), with no patients reporting symptoms in the severe range. Still, depressive symptoms at baseline were a significant independent predictor of nursing home residence at 13 months (together with lower pre-stroke social activity level and cognitive impairment at baseline). The result suggests that that even milder types of depressive symptoms in the rehabilitation setting should be taken seriously as a
negative prognostic factor of long-term performance, and that routinely screening for symptoms of depression in clinical settings may be warranted.

2.12 Proposals for future research

- The ApoE ε4-findings in relation to post-stroke cognitive functioning reported in paper 1 and paper 2 must be regarded as tentative, and should be confirmed in a new longitudinal study, and, this time, preferably by including fMRI of temporal lobe functionality.

- The Norwegian version of RBANS has not been properly validated in a stroke population, and its validity ought to be better documented if RBANS should be applied as a neuropsychological screening battery in stroke rehabilitation units for clinical or research purposes. Although our results in paper 3 gives strong support to the predictive validity of RBANS in relation to functional long-term outcome, future studies should explore its relation to other long-term stroke outcome measures, including social activity level, cognitive performance, symptoms of depression, and psychosocial burden of caregiver.

- The results of paper 4 confirm that symptoms of depression are frequent after stroke, most often of a mild or moderate character, but still are associated with an unfavourable prognosis. Despite a growing awareness of the serious consequences of post-stroke depression, few patients receive treatment. In fact, a proper knowledge of how post-stroke depression could best be treated is lacking, as reflected in the modest number of high-quality antidepressant and psychotherapeutical intervention studies carried out. The effect of cognitive behavioural therapy is well documented in the treatment of mild and moderate depression in general. Future studies should examine whether cognitive behavioural therapy is beneficial in the treatment of post-stroke depression, either alone or in combination with antidepressants.
Reference List


Early post-stroke cognition in stroke rehabilitation patients predicts functional outcome at 13 months

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Word count of the body text: 3167
Abstract

Objective

To identify prognostic factors associated with functional outcome at 13 months in a sample of stroke rehabilitation patients. Specifically, we hypothesized that cognitive functioning early post-stroke would predict long-term functional outcome independently of other factors.

Methods

One hundred sixty three stroke rehabilitation patients underwent a structured neuropsychological examination two to three weeks after hospital admittance, and their functional status were subsequently evaluated thirteen months later with the modified Rankin Scale (mRS) as outcome measure. Three predictive models were built using linear regression analyses: A biological model (sociodemographics, ApoE-genotype, pre-stroke vascular factors, lesion characteristics, and neurological stroke-related impairment); a functional model (pre and early post stroke cognitive functioning, personal and instrumental ADL, and depressive symptoms); and a combined model (including significant variables from the biological and functional model).

Results

A combined model of four variables best predicted long-term functional outcome with explained variance of 49%: Neurological impairment (The National Institute of Health Stroke Scale) ($\beta=0.402$, $p<0.001$), age ($\beta=0.233$, $p=0.001$), post-stroke cognitive functioning (The Repeatable Battery of Neuropsychological Status (RBANS)) ($\beta=-0.248$, $p=0.001$), and pre-stroke personal ADL (Barthel Index) ($\beta=-0.217$, $p=0.002$). Further linear regression analyses of which RBANS Indexes and subtests best predicted long-term functional outcome showed that Coding ($\beta=-0.484$, $p=<0.001$) and Figure Copy ($\beta=-0.233$, $p=0.002$) raw scores at baseline explained 42% of the variance in mRS-scores at follow-up.

Conclusions

Early post-stroke cognitive functioning as measured by RBANS is a significant and independent predictor of long-term functional post-stroke outcome.
Early post-stroke cognition in stroke rehabilitation patients independently predicts functional outcome at 13 months

Introduction
A stroke can have serious physical, psychological, social and cognitive consequences, and may dramatically alter a person’s life. It increases the risk of dying, becoming institutionalized, demented, dependent in activities of daily living (ADL), depressed and account for more hospital and rest-home bed days than any other condition [1]. However, research show that 30-42% of stroke patients have a favourable post-stroke outcome and continue to live an independent life without long-lasting, restraining symptoms [2-4]. It would appear important, therefore, to identify factors that predict functional outcome in order to set realistic targets for rehabilitation and to guide patients and their relatives accordingly. A large number of studies have been carried out with more than 150 demographic, radiological, neurophysiological and neurological variables reported to predict outcome [5]. Due to heterogeneity in design and setting, comparison of results across studies is difficult, but among the most substantiated predictors are age, initial severity of the stroke, previous stroke, urinary incontinence, unconsciousness at onset, disorientation in time and place, severity of paralysis, sitting balance, admission ADL score, and level of glucose outside the infarct area in hypertensive patients. In addition, female sex, diabetes, hypertension, atrial fibrillation, physical inactivity, cardiac diseases, depression, cognitive impairment, perceived social support and absence of specialized stroke unit care have been reported to increase the likelihood of a negative functional outcome [5-8].

A limitation of many of these studies is that the findings are based on simple associations between the predictor variable and the outcome measure. However, the important question, in terms of prediction, is whether a given factor remains an independent predictor for outcome when other known predictors are taken into account [4]. Although strong associations between early post-stroke performance and long-term functional outcome have frequently been reported, the independent predictive power of early post-stroke cognitive functioning is scarcely examined [1;9]. Some authors have argued against the validity of early post-stroke cognitive testing because of its closeness to acute effects, while other researchers have found that early cognitive testing provides valid information both with respect to long-term cognitive performance, ADL-functioning, risk of institutionalization and death [10-13].
The objective of this study was to evaluate functional status at 13 months in a sample of patients referred to a stroke rehabilitation unit and to identify prognostic factors associated with functional outcome. Specifically, we hypothesized that cognitive functioning two to four weeks after a stroke would predict long-term functional outcome independently of other factors.

Material

A total of 194 stroke patients were consecutively recruited from the Stroke Rehabilitation Unit at Ulleval University Hospital, Oslo, Norway during the period between March 2005 and August 2006. Inclusion criteria were patients diagnosed with an ischemic or haemorrhagic stroke. Exclusion criteria were non-fluency in the Norwegian language, severe visual or hearing impairment, alcohol or drug abuse, or previously being treated for a psychiatric illness. Thirty one subjects (16%) withdrew from the study during the follow up period, leaving 163 subjects in the study sample. The 31 subjects who withdrew did not differ significantly from the participating 163 patients regarding sociodemographical or any clinical baseline variables, except for a higher proportion of females (65%, p<0.05).

Methods

All subjects underwent a comprehensive structured examination while hospitalized in the stroke rehabilitation unit, and were subsequently re-examined in average 13 months later. Mean time between hospitalization and baseline testing was 18.3 days (s.d. 13.4), while follow-up examinations were undertaken at a mean of 408.6 days (s.d. 41.2) later. For subjects living at home, the follow-up examinations were carried out in the hospital, while subjects living in nursing homes were examined at the nursing home wards. All data collection was undertaken by two psychologists, LF and JW.

Outcome assessment (the dependent variable)

The modified Rankin Scale (mRS) [14] was administered both at baseline and follow-up to assess the outcome. The mRS is a seven-graded global disability scale with following
scoring: 0 (no symptoms at all); 1 (no significant disability despite symptoms, able to carry out all usual duties and activities); 2 (slight disability, unable to carry out all previous activities, but able to look after own affairs without assistance); 3 (moderate disability, requiring some help, but able to walk without assistance); 4 (moderate severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance); 5 (severe disability; bedridden, incontinent, and requiring constant nursing care and attention); and 6 (dead). The scale has shown acceptable psychometric properties and is widely used as a functional outcome measure in stroke research [15]. A cut-off of ≤1 or ≤2 is frequently applied to classify a favourable stroke outcome from an unfavourable one. However, dichotomization of the scale has been criticized due to reduced statistical power, increased risk of misclassification (type II errors), and because choice of cut-off may affect the results [16;17]. We therefore used the full spectrum of the mRS-scale in the statistical analysis. The scoring was done by LF and JW on the basis of a comprehensive structured clinical interview and testing of the subjects.

Prognostic variables (the independent variables)

Demographics and biological data
Demographics (age in years, sex, education in years), pre-stroke medical variables (number of medications on admission, hyperlipidemia (treated), diabetes mellitus (treated), angina pectoris (treated), atrial fibrillation, myocardial infarction, previous stroke or TIA, and cigarette smoking), were collected from medical records and/or by interviewing the subjects or next of kins at baseline examination.

The strokes were classified according to type (infarct and/or hemorrhage) and hemispheric location (left, right, bilateral, brainstem, cerebellar, unknown) based on results from CT-scans and evaluation of clinical symptoms.

Neurological stroke-related impairment was measured with the National Institute of Health Stroke Scale (NIHSS) [18].

The Oxfordshire Community Stroke Project classification (OCSP) was applied to categorize the stroke according to topographical location and lesion severity [19].
ApoE genotyping was performed on the basis of blood samples collected from the subjects at baseline examination according to method described earlier [20].

**Functional data**

The Norwegian version of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) was administered to evaluate cognitive reduction over the last 10 years preceding the stroke [21]. Due to lack of informants or subjects unwilling to involve an informant, 131 informant interviews were obtained. We found no significant differences between subjects with and without informants regarding any sociodemographic or baseline clinical characteristics.

Post stroke cognitive functioning was assessed by administering the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) – form A [22] at baseline and follow-up. RBANS is sensitive for measuring cognitive impairment after stroke both in an acute and rehabilitation setting [12;23;24]. RBANS was administered to all subjects, even those with aphasia/apraxia and/or hemiplegia in dominant side. Subjects with severe aphasia/apraxia were scored with error on tasks they were incapable of performing, while subjects with hemiplegia that affected dominant arm/hand used non-dominant hand for tests requiring writing/drawing skills (Figure Copy and Recall, Coding). For subjects aged 65 years and above, RBANS Index Scores were calculated on the basis of age- and education corrected norms for the geriatric population [25]. Original RBANS norms were applied for subjects under 65 years. These norms are corrected for age, but not for education.

Personal ADL was assessed with the Barthel Index [26] and instrumental ADL with the Frenchay Activities Index [27]. At baseline the data was collected through interviews with nurses in rehabilitation unit, at follow-up from nurses in nursing homes or directly from the subjects or a close relative.

Symptoms of depression were examined by the Montgomery Aasberg Depression Rating Scale (MADRS) [28] based on structured interviews with the patients.

**Statistical analysis**
Analyses were performed using SPSS (Statistical Program for Social Science) package, version 16.0. To identify pre-stroke and baseline predictors of stroke outcome at 13 months, bivariate and multiple linear regression analysis were carried out with mRS-score at 13 months follow-up as the dependent variable. Before performing the linear regression analyses we examined the distribution of each variable by using histograms, Q-Q and box plots. Log-transformation was not considered necessary for any variable. All variables in the bivariate analysis with a p-value <0.05 were entered one-by-one in the linear multivariate regression analysis (following the order of the variables’ β-values). All variables were checked for multicollinearity. The only variables that correlated highly (Pearson’s r>0.7) were the NIHSS Total scale and Barthel Index at baseline.

Three predictive models were built, one including pre-stroke and baseline biological data as independent variables (the biological model), one including pre-stroke and baseline functional data (the functional model) and, finally, one combined model including both biological and functional data (the combined model).

The following variables were analyzed in the biological model: NIHSS total score (neurological impairment), OCSP-classification (topographical location/severity), lesion type (ischemic, haemorrhagic, ischemic with haemorrhagic transformation), lesion site (right, left, other), pre-stroke vascular risk factor (previous hypertension (treated), previous hyperlipidemia (treated), previous diabetes mellitus (treated), previous angina pectoris (treated), previous atrial fibrillation, previous myocardial infarction, previous stroke, previous TIA, and cigarette smoking), number of medications on hospital admission, and genetic vulnerability through the presence of ApoE ε4-allele (yes vs no).

In the functional model, the following variables were examined: pre-stroke ADL functioning (Barthel Index Total score and Frenchay Activity Index score), pre-stroke cognitive impairment (IQCODE total score), baseline ADL functioning (Barthel Index total score), baseline cognitive functioning (RBANS total index), and baseline symptoms of depression (MADRS total score).

All significant variables of the biological and functional models were used as the combined model.
In all three models, age, sex, and years of education were included in the analyses.

Finally, to identify specific cognitive predictors of stroke outcome at 13 months, two additional models were built; one with RBANS Index scores and one with RBANS subtests raw scores at baseline as independent variables respectively.

**Ethical and juridical considerations**

The Regional Committee for Ethics in Medical Research in Norway and the Privacy Ombudsman approved the study protocol. Oral and written informed consent was obtained from the subjects.

**Results**

**Subjects’ characteristics**

The mean age of the patients was 76.9 yrs (s.d. 10.7), 75 subjects (46%) were females, and the mean years of education was 11.5 (s.d. 3.7). Of them 109 (67%) suffered a stroke for the first time, whereas 54 (33%) had suffered a stroke before. Characteristics of the subjects at baseline are presented in table 1.

**Functional outcome at 13 months follow-up**

At 13 months follow-up-examination, 14 (9%) subjects were assigned a mRS score of 0 (no symptoms), 20 (12%) score 1 (no significant disability), 21 (13%) score 2 (slight disability), 35 (21%) score 3 (moderate disability), 28 (17%) score 4 (moderate severe disability), 8 (5%) score 5 (severe disability), and 37 (23%) score 6 (dead).

Compared to the mRS-scores at baseline, 50 subjects (31%) had improved, 42 subjects (26%) remained stable, and 71 subjects (44%) had worse mRS-score at follow up.

Of the 126 subjects alive at follow-up, 35 lived in nursing homes and 91 at home. Except for one subject, all living in nursing homes had a mRS-score >2, and compared to patients living
 Predictors of functional outcome at 13 months follow-up
The results of the unadjusted and adjusted linear regression analysis of the three models are presented in table 2.

In the biological model, the strongest predictor of functional outcome at 13 month was NIHSS Total score at baseline ($\beta=0.499$; $p$-value $<0.001$), while the strongest predictor in the functional model was Barthel Total score at baseline ($\beta=-0.393$; $p$-value $<0.001$. As NIHSS Total score and Barthel Index total correlated highly (Pearsons $r=-0.804$), it was decided to run these two predictors in two separate multivariate analysis in the combined model. When including Barthel Index (and excluding NIHSS total) the result was identical with the result of the functional model. The results of the combined model including NIHSS total (and excluding Barthel Index) are shown in table 2.

Thirteen subjects (8%) experienced a new stroke during the follow-up period. In order to eliminate the effect of a new stroke on functional outcome at 13 months, we performed an additional multivariate linear regression analysis (combined model) excluding the subjects with a new stroke. The result did not change (NIHSS Total scale baseline $\beta=0.421$, $p$-value $<0.001$; RBANS Total index baseline $\beta=-0.229$, $p$-value $=0.003$; Age, yrs baseline $\beta=0.224$, $p$-value $=0.002$, Barthel Index prestroke $\beta=0.224$, $p$-value $=0.001$; explained variance 49%).

To illustrate the numerical influence of the significant predictors in the combined model on the mRS-scores we calculated their scores at baseline and related these scores to the mRS-scores, table 3.

Relations between cognitive functioning early post-stroke and functional outcome at 13 months
As overall cognitive level at baseline turned out to be a significant predictor of long-term stroke outcome, we wanted to explore this relation further. Table 4 presents results of the unadjusted and adjusted linear regression analysis with mRS-score at 13 months as the dependent variable and RBANS indexes and subtests entered as independent variables. The
unadjusted analysis showed that all baseline RBANS Indexes and subtests were individually highly associated with mRS-score at 13 months, but only the Visuospatial/Constructional Index (p<0.001), and the two subtests Figure Copy (p=0.002) and Coding (p=<0.001) remained significant in the adjusted analysis.

Discussion

The functional long-term outcome differed markedly among the patients. At 13 months post-stroke only 34% of the patients could be defined as having a favourable outcome (no symptoms-slight disability), 43% of the patients were classified with moderate-severe disability, and 23% were dead. Our results are in line with figures from previous in-hospital and population-based studies which have examined functional long-term outcome between 6 and 12 months post-stroke using the mRS [29-31].

The multiple linear regression analysis revealed that a combined model using sociodemographical, biological and functional baseline variables best predicted functional outcome at 13 months with explained variance of 49% (table 3). This finding accords with previous results showing multiple-factor models to be the best predictors of long-term stroke outcome [9]. Our results are also in line with previous studies showing that severity of neurological impairment, age, and pre-stroke ADL-functioning are major determinants affecting post-stroke outcome [7;32-35]. Neurological stroke-related impairment, as measured by NIHSS, may be viewed as a direct expression of stroke severity, and in previous studies, a baseline score equal to or lower than 6 points was strongly associated with a favourable functional prognosis at 3 months [33] and a score equal to or below 5 highly increasing the chance of being discharged to home rather than to a rehabilitation or nursing facility [36]. With respect to age, there are several explanations why younger patients probably have a better functional prognosis, including less co-morbidity, less post-stroke complications, a better physical and cognitive restorative capacity. On these grounds, it has been suggested that age per se should not be considered isolated in issues related to rehabilitation and prognosis [37].

Cognitive functioning at baseline (RBANS Total Index) was found to be an independent predictor of long-term functional outcome. To our knowledge, this is the first study which
has used mRS-scores as outcome measure in evaluating the impact of RBANS on long-term functional outcome, and our results are therefore not easy to compare with results of previous studies. However, earlier studies of stroke rehabilitation in-patients did find RBANS Index scores to predict functional outcome at hospital discharge [38], self-reported cognitive disability at six months [12], and self-reported cognitive disability, instrumental ADL-functioning, and participation restrictions in domains of physical independence, mobility, occupation, social integration and economic self-sufficiency twelve months post-stroke [23]. Although none of these studies examined the independent effect of RBANS-performance on long-term outcome, they still attest to the predictive utility of RBANS in stroke rehabilitation settings.

Since cognition in the early phase after a stroke proves to be a powerful predictor of long-term functional outcome, it is important to understand the nature of this relationship. In the present study, all RBANS Indexes and subtests were significantly associated with outcome in the unadjusted linear regression analyses. However, in the adjusted analyses, only the Visuospatial/Constructional Index and two subtests Coding (part of the Attention index) and Figure Copy (part of the Visuospatial/Constructional Index), remained significant (table 4). This in general accord with Larson et al. (2003), who found performance on the Visuospatial/Constructional Index at a subacute stage to be the only RBANS-measure to correlate significantly with handicap, motor function, and frequency of activity at six months. Unfortunately, these researchers did not carry out an analysis of subtests.

Coding and Figure Copy are dependent on motor dexterity and speed for their final execution; they are pen and pencil type of tasks. They are also visuospatial of nature. Compromised motor and visual functioning, ADL and symptom load as an effect of primarily right hemisphere lesions could explain the correlations. This, however, was not brought out in a regression analysis where motor dysfunction and right hemisphere stroke was adjusted for (data not shown). The implication appears to be that there is a functional specificity to the tests in question at least beyond the motor execution part, co-varying with increasing symptom load at follow-up. Based on a functional decomposition of the two tests, visuospatial attention would appear to be a common denominator [39;40]. This type of function is likely to be especially vulnerable to the kind of vascular insult induced by the stroke, since vast territories of parietal and prefrontal regions are affected. Especially the
right-hemisphere expanses of these regions comprise central parts of the mechanisms responsible for activation and attention [41-43]. The functional integrity of these areas would also be affected by left-hemisphere strokes. As the severity of the stroke increases, so does the risk of recruiting visuospatial dysfunction as well as mRS-type of symptoms.

Our results may have implications for which cognitive test instruments should be recommended in clinical and research settings of stroke patients. Broad screening measures, like the Mini Mental Status Examination (MMSE), are often the preferred choice, but have been criticized for being insensitive to varying impairments, including visuospatial/constructive and executive functions [44]. We would suggest that both Coding and Figure Copy beneficially could be added in clinical settings, especially as both tests are easy and quick to administer. We further suggest that more complex neuropsychological test batteries like RBANS should be used in research to study long-term functional outcomes.

Our study has limitations. The outcome variable mRS is a summary tool that assesses physical disabilities with less emphasis on cognition, emotion and social activity [45]. Our sample is of moderate size and recruited from a single Norwegian hospital-based stroke rehabilitation unit, limiting its relevance for other settings. Furthermore, RBANS has not been validated for Norwegian-speaking stroke patients. However, preliminary validation of RBANS in a Norwegian psychiatric population has shown the test battery to have adequate psychometric properties [46].

On the strong side, the study patients were recruited consecutively and with limited use of exclusion criteria. Based on their sociodemographic characteristics, they are representative of older stroke patients fulfilling inclusion criteria for rehabilitation at a university hospital. Only two administrators of tests and scales have been involved, both adhering strictly to instructions.
Reference List


Weisscher N, Vermeulen M, Roos YB, de Haan RJ: What should be defined as good outcome in stroke trials; a modified Rankin score of 0-1 or 0-2? J Neurol 2008;255:867-874.


Terryberry-Spohr L, Gordon K, List Kalnins T: Prediction of Functional Outcomes in the Acute Rehabilitation Setting Using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); 2000, pp 663-664.


42 Liu T, Slotnick SD, Serences JT, Yantis S: Cortical mechanisms of feature-

43 Egner T, Monti JM, Trittschuh EH, Wieneke CA, Hirsch J, Mesulam MM: 
Neural integration of top-down spatial and feature-based information in visual search.

44 Nys GM, van Zandvoort MJ, de Kort PL, Jansen BP, Kappelle LJ, de Haan 
EH: Restrictions of the Mini-Mental State Examination in acute stroke. Arch Clin

45 Kasner SE: Clinical interpretation and use of stroke scales. Lancet Neurol 
2006;5:603-612.

46 Løberg EM, Langeland M, Jørgensen HA: Reliability and validity of a
Norwegian translation of the Repeatable Battery for the Assessment of 
Neuropsychological Status in patients with psychosis; 10-year Anniversary of the
Norwegian Neuropsychological Association, Oslo, Norway, Aug 24th 2006, poster 
presentation. 2006.
Table 1: Basic characteristics of the subjects ($n=163$)

<table>
<thead>
<tr>
<th>Pre-stroke functioning:</th>
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<tbody>
<tr>
<td>Cognition</td>
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<tr>
<td>IQCODE</td>
<td>3.24 (0.34)</td>
</tr>
<tr>
<td>ADL</td>
<td></td>
</tr>
<tr>
<td>Barthel Index</td>
<td>19.0 (1.7)</td>
</tr>
<tr>
<td>Frenchay Social Activity Index</td>
<td>36.4 (9.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stroke characteristics:</th>
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<tbody>
<tr>
<td>Type, $n(%)$</td>
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<tr>
<td>- Ischemic</td>
<td>134 (82)</td>
</tr>
<tr>
<td>- Haemorrhagic</td>
<td>26 (16)</td>
</tr>
<tr>
<td>- Ischemic with haemorrhagic transformation</td>
<td>3 (2)</td>
</tr>
<tr>
<td>OCSP-classification, $n(%)$ *</td>
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</tr>
<tr>
<td>- TACS</td>
<td>36 (22)</td>
</tr>
<tr>
<td>- PACS</td>
<td>64 (39)</td>
</tr>
<tr>
<td>- LACS</td>
<td>50 (31)</td>
</tr>
<tr>
<td>- POCS</td>
<td>13 (8)</td>
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<tr>
<td>Lesion site, $n(%)$</td>
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</tr>
<tr>
<td>- Right</td>
<td>69 (42)</td>
</tr>
<tr>
<td>- Left</td>
<td>67 (41)</td>
</tr>
<tr>
<td>- Other (bilateral, brainstem, cerebellar, unknown)</td>
<td>27 (17)</td>
</tr>
<tr>
<td>Neurological impairment</td>
<td></td>
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<tr>
<td>- NIHSS Total score at baseline</td>
<td>7.8 (7.5)</td>
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<th>Baseline functioning:</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Cognition</td>
<td></td>
</tr>
<tr>
<td>RBANS Index Scores</td>
<td></td>
</tr>
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<td>- Immediate Memory</td>
<td>85.3 (19.1)</td>
</tr>
<tr>
<td>- Visuospatial/Constructional</td>
<td>80.9 (18.1)</td>
</tr>
<tr>
<td>- Language</td>
<td>76.6 (13.2)</td>
</tr>
<tr>
<td>- Attention</td>
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<td>- Delayed Memory</td>
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<tr>
<td>mRS</td>
<td>2.8 (1.5)</td>
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<tr>
<td>Symptoms of depression</td>
<td></td>
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<tr>
<td>MADRS</td>
<td>9.7 (7.9)</td>
</tr>
</tbody>
</table>

Mean (s.d.) if not otherwise stated.

* IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly; MADRS = Montgomery Aasberg Depression Rating Scale; OCSP-classification=Oxfordshire Community Stroke Project-classification; TACS=Total anterior circulation syndrome; PACS=Partial anterior circulation syndrome; LACS=Lacunar syndrome; POCS=Posterior circulation syndrome; NIHSS=National Institute Health Stroke Scale; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; mRS=Modified Rankin Scale.
Table 2: Predictors of mRS-outcome at 13 months (n=163)

<table>
<thead>
<tr>
<th>Biological model</th>
<th>Unadjusted linear regression analysis</th>
<th>Adjusted linear regression analysis</th>
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<tr>
<td></td>
<td>( \beta )</td>
<td>( p )-value</td>
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<tr>
<td>NIHSS Total scale</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, yrs baseline</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>OCSP-classification</td>
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<td>No of medications on hospital admission</td>
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<td>Atrial fibrillation (treated)</td>
<td>0.183</td>
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<td>Education, yrs</td>
<td>-0.202</td>
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<td>Diabetes mellitus (treated)</td>
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<td>0.026</td>
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<td>Explained variance</td>
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<td>( p )-value</td>
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<tr>
<td>Barthel Index baseline</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>RBANS Total index baseline</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, yrs baseline</td>
<td>0.364</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MADRS baseline</td>
<td>0.364</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Barthel Index prestroke</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>Frenchay Social Activity Index prestroke</td>
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<td>IQCODE prestroke</td>
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<td>Education, yrs</td>
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<td>Explained variance</td>
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<table>
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<th>Combined model</th>
<th>Unadjusted linear regression analysis</th>
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<td>( \beta )</td>
<td>( p )-value</td>
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<tr>
<td>NIHSS Total scale baseline</td>
<td>0.493</td>
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<td>RBANS Total index baseline</td>
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<td>&lt;0.001</td>
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<td>Barthel Index prestroke</td>
<td>-0.334</td>
<td>&lt;0.001</td>
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<tr>
<td>Explained variance</td>
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Table 3: Distribution of mRS-scores at 13 months follow-up in relation to scores of significant predictor variables at baseline (n=163)

<table>
<thead>
<tr>
<th>Modified Rankin Scale-score at 13 months follow-up</th>
<th>0 No symptoms (n = 14)</th>
<th>1 No significant disability (n = 20)</th>
<th>2 Slight disability (n = 35)</th>
<th>3 Moderate disability (n = 28)</th>
<th>4 Moderate/severe disability (n = 8)</th>
<th>5 Severe disability (n = 8)</th>
<th>6 Dead (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline predictor variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Age, yrs baseline</td>
<td>70.4 (14.5)</td>
<td>72.9 (10.8)</td>
<td>72.1 (14.5)</td>
<td>76.6 (9.4)</td>
<td>77.8 (9.1)</td>
<td>79.3 (8.1)</td>
<td>82.4 (6.0)</td>
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<tr>
<td>- NIHSS total baseline</td>
<td>1.3 (1.1)</td>
<td>3.1 (1.8)</td>
<td>4.2 (4.0)</td>
<td>6.7 (6.9)</td>
<td>10.9 (6.4)</td>
<td>20.0 (8.2)</td>
<td>10.8 (8.0)</td>
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<tr>
<td>- RBANS total baseline</td>
<td>91.1 (15.7)</td>
<td>80.5 (12.6)</td>
<td>74.7 (13.5)</td>
<td>72.6 (10.2)</td>
<td>66.9 (7.7)</td>
<td>66.0 (5.7)</td>
<td>69.1 (12.7)</td>
</tr>
<tr>
<td>- Barthel Index pre stroke</td>
<td>19.9 (0.3)</td>
<td>19.5 (0.9)</td>
<td>19.7 (0.6)</td>
<td>18.7 (1.7)</td>
<td>18.6 (2.0)</td>
<td>18.4 (2.4)</td>
<td>18.3 (2.2)</td>
</tr>
</tbody>
</table>

Mean (sd)
Table 4: Cognitive predictors of mRS-outcome at 13 months (n=163)

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted linear regression analysis</th>
<th>Adjusted linear regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta )</td>
<td>( p )-value</td>
</tr>
<tr>
<td><strong>RBANS Indexes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Immediate memory</td>
<td>-0.353</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Visuospatial/Constructional</td>
<td>-0.459</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Attention</td>
<td>-0.391</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Language</td>
<td>-0.369</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Delayed memory</td>
<td>-0.405</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Explained variance</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RBANS subtests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- List Learning</td>
<td>-0.473</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Story Memory</td>
<td>-0.422</td>
<td>&lt;0.001</td>
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<tr>
<td>- Figure Copy</td>
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<tr>
<td>- Line Orientation</td>
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<tr>
<td>- Picture Naming</td>
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<tr>
<td>- Semantic Fluency</td>
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<tr>
<td>- Digit Span</td>
<td>-0.317</td>
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<tr>
<td>- Coding</td>
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<td>- List Recall</td>
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<tr>
<td>- List Recognition</td>
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<tr>
<td>- Story Memory</td>
<td>-0.381</td>
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<tr>
<td>- Figure Recall</td>
<td>-0.576</td>
<td>&lt;0.001</td>
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<tr>
<td>Explained variance</td>
<td></td>
<td></td>
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</table>