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Thesis for the Degree of
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The Life Early After Stroke (LEAST) study

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Sammendrag på norsk

Hvert år får ca. 15 000 mennesker slag i Norge. Insidensen av både førstegangs hjerneslag og gjentatte slag ser ut til å avta noe på grunn av bedre primær og sekundær forebyggelse.

En stadig eldre befolkning med større risiko for hjerneslag vil imidlertid føre til en økning i det totale antall hjerneslag, og dette sammen med bedret overlevelse vil føre til en sterk økning i antallet personer som lever med store eller små konsekvenser etter gjennomgått hjerneslag. Kunnskapsbasert akutt slagenhetsbehandling har for mange slagpasienter bidradd til å redusere følgetilstandene av hjerneslaget. Hittil har det meste av forskningen tydet på at behandling i slagenhet med tidlig mobilisering og rehabilitering har vært viktige faktorer for å oppnå disse gode resultatene. Aktivitetsnivået hos pasienter innlagt ved ulike slagenheter rundt omkring i verden ser imidlertid ut til å variere mye.

Lammelser og kognitive problemer er de mest vanlige og kjente konsekvenser av hjerneslag, men de senere årene har mer oppmerksomhet blitt rettet mot den høye forekomsten av fatigue (ekstrem tretthet) og også redusert helse relatert livskvalitet (HRQoL) etter hjerneslag.

Fysisk aktivitet synes å være viktig for å bedre funksjon og HRQoL etter hjerneslag. Hvilke faktorer som er involvert i utviklingen av fatigue etter hjerneslag har vært mer usikkert, men noen av hypotesene er at den nevrologiske omorganiseringen i hjernen, andre samtidige sykdommer og fysisk dekondisjonering er medvirkende.

Fysisk aktivitet ser ut til å være viktig i de fleste faser etter hjerneslag for å bedre funksjon, og forskning viser stort sett at bedringen blir større med økte aktivitetsnivåer, og at oppgaveorientert aktivitet gir best resultat.

Den nylig publiserte, randomiserte og kontrollerte "A Very Early Rehabilitation Trial " (AVERT-studien),viser imidlertid at for tidlig og intensiv trening kan forsinke rehabiliteringsprosessen.

Hovedmålet med denne doktoravhandlingen var å øke kunnskapen om hvordan aktivitetsnivået varierer hos pasienter med hjerneslag som er innlagt ved norske sykehus og hvilke faktorer som eventuelt påvirket en slik variasjon. Sekundære mål var å undersøke sammenhengen mellom tid til første mobilisering og aktivitetsnivået i akutt fase og funksjon, helserelatert livskvalitet (HRQoL) og fatigue 3 måneder senere, samt sammenligne forekomsten av fatigue etter hjerneslag med forekomsten av fatigue hos en tilsvarende gruppe friske eldre fra den generelle befolkningen og hvilke faktorer som påvirket utviklingen av fatigue etter hjerneslag. Vi gjennomførte derfor en prospektiv observasjonsstudie hvor pasienter med akutt hjerneslag innlagt ved 11 norske slagenheter ble inkludert i løpet av de første 14 dager etter slaget og fulgt opp 3 måneder senere. I tillegg sammenlignet vi forekomsten av fatigue hos pasientene med hjerneslag med en alders- og kjønnstilpasset populasjon fra Helseundersøkelsen i Nord-Trøndelag (HUNT3-studien).

Ved inklusjon ble funksjon før slaget og slagets alvorlighetsgrad registrert og alle inkluderte pasienter ble observert hvert tiende minutt gjennom en arbeidsdag. Aktivitetsnivå, hvem de var sammen med og lokalisasjon ble notert. I alt 394 slagpasienter ble observert.

Antall sykepleiere og pasienter til stede på observasjonsdagen ble registrert i tillegg til om måltider ble servert i pasientrom eller på spisestue.

Tre måneder senere ble pasientene kontaktet enten per telefon eller på poliklinikken og funksjon, HRQoL, fatigue, smerte og depresjon ble kartlagt med spørreskjemaer.

Fra observasjonsdataene analyserte vi tre aktivitetskategorier: tid i seng, tid sittende ut av seng og tid i stående/gående stilling. Deretter analyserte vi forskjeller mellom sykehusene og hva aktivitetsnivået hadde å si for funksjonsnivået 3 måneder etter hjerneslaget.

Pasientene ble i gjennomsnitt observert på dag 5 etter slaget. Resultatene viser at det er statistisk signifikante forskjeller mellom sykehusene i alle aktivitetsnivåene. Forskjellene i tid i stående/gående var i stor grad forklart av om slagenhetene hadde eget spiserom eller serverte mat på pasientrommene, og av hvor mye tid som ble tilbrakt med fysioterapeut.

Økt tid i stående/gående var assosiert med bedre funksjon og helserelatert livskvalitet ved 3 måneder. Tid til første mobilisering hadde ingen betydning for utkomme.

Omtrent 30% av pasientene med hjerneslag hadde fatigue 3 måneder etter slaget mot 10% av HUNT3 populasjonen. Fatigue før hjerneslaget, smerte og depresjon var assosiert med fatigue. I tillegg var det en trend til sammenheng mellom mer tid i seng i akutt fase og fatigue 3 måneder senere.

Avhandlingen viser stor variasjon i fysisk aktivitetsnivå mellom norske sykehus. Mer tid i stående og gående under sykehusoppholdet den første uken etter hjerneslag er positivt for bedring av funksjon og HRQoL 3 måneder senere. Fatigue var hyppigere hos pasientene med hjerneslag enn i en alders- og kjønnstilpasset populasjon uten gjennomgått hjerneslag. Fatigue før slaget i tillegg til smerte og depresjon etter slaget øker risikoen for fatigue ved hjerneslag.

A poem about stroke

One day I felt that I wasn't really me,
Parts of my body weren't as they should be.
My arms wouldn't work and my leg went dead,
And the words just wouldn't come out of my head.
Send for the doctor 'A stroke' he declares,

A clot on the brain caught us all unawares
No headaches, no warning signs, how can this be?

I don't understand what has happened to me...

("Unknown author, poem found at a hospital ward")

To my grandmother Ågot,

who suffered from a severe stroke in 1987 at the age of 79, lost her speech and the use of the right side of her body, and never had the opportunity to take advantage of the evidence-based stroke unit treatment. She died after 3 months of bed rest.

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Summary

Every year, 15 000 people in Norway have a stroke. The incidence rate of first-ever and recurrent strokes seem to be falling slightly due to better primary and secondary prevention. However, more people survive their strokes and the prevalence is increasing. An increasing older population at greater risk of stroke also contributes to this. Evidence-based acute stroke unit treatment has helped to decrease the consequences of stroke. Up to now, all research has shown that early mobilization and rehabilitation have been important factors contributing to the good results. However, activity levels seem to vary widely in acute stroke units across the world.

Paresis and cognitive problems are the most common problems after stroke, but in recent years more attention has been drawn to the high prevalence of fatigue and reduced health related quality of life (HRQoL) after stroke.

There is increasing evidence that physical activity is important for improving functional outcome and HRQoL. Factors contributing to the development of fatigue are more uncertain, but the hypotheses are that they include cerebral reorganization, comorbidity and physical deconditioning.

Physical activity seems to be important to promote recovery in most phases after stroke, and most research shows greater improvement with increased levels of activity. However, the recent "A Very Early Rehabilitation Trial "(AVERT) shows that starting too early and with too high intensity may delay the recovery process.

The overall aim of this thesis was to increase knowledge of how the activity levels during hospital stay differs in stroke patients admitted to Norwegian hospitals and to assess which factors were associated with these differences. A further aim was to assess the association between time to first mobilization and the amount of activity early after stroke and functional

outcome, HRQoL and fatigue three months later. Finally, we wanted to compare the prevalence of fatigue in patients after stroke to the prevalence in the general population and to explore which factors were associated with fatigue after stroke.

We conducted a prospective observational study where acute stroke patients admitted to 11 Norwegian stroke units were included within 14 days after onset of stroke and a follow-up assessment was performed 3 months later. In addition we compared the prevalence of fatigue among the stroke patients with the prevalence of fatigue in an age and sex-matched population from the Nord-Trøndelag Health Study (HUNT3 survey).

At baseline, we recorded details of pre-stroke function, stroke severity, age and gender. All patients were observed every ten minutes during a working day, and activity levels, people present and location were recorded. We also recorded the number of nurses at work and the total number of patients admitted to the stroke units on the day of observation. Finally, we recorded whether the meals were served in the common areas or in the bedroom.

Three months later, those who were alive were contacted if possible, either by phone or in person for collection of data. Disability, HRQoL, level of fatigue, pain and depression were measured using questionnaires.

We finally explored 3 activity levels at baseline: time in bed, time sitting out of bed and time upright. Furthermore, we analyzed the differences in activity levels between the hospitals and the relation between activity level and outcome 3 months later.

In addition we used data from the HUNT3 survey to assess the differences in fatigue perceived between an age matched population not suffering from stroke and our stroke cohort.

A total of 394 stroke patients were observed on average 5 days poststroke. The results from the study showed that the activity levels differed significantly between the hospitals for all three activity categories. The differences in time spent upright were largely explained by hospitals serving meals in common areas, and different amounts of time spent with a physical therapist.

The amount of time spent in upright activity was associated with significantly better functional outcome and better HRQoL at 3-month follow up. Time to first mobilization did not show any association with either of the outcomes.

Fatigue was experienced by approximately 30 % of the 257 stroke patients able to answer the HUNT3 survey fatigue questionnaire, and 10% of the age-matched HUNT3 population.

Factors associated with fatigue were pre-stroke fatigue, pain and depression. There was also a trend toward an association between increasing amount of time spent in bed and fatigue three months later.

In conclusion, this thesis shows that physical activity levels vary among patients admitted to Norwegian hospitals and that increasing amount of physical activity in the acute phase after stroke is associated with better functional outcome and HRQoL 3 months later. Fatigue is more frequent among stroke survivors than in a non-stroke population. Pre-stroke fatigue, post-stroke pain and depression were associated with post-stroke fatigue.

Acknowledgements

The present work was carried out at the Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology in Trondheim, Norway between March 2012 and July 2015. The Liaison Committee between the Central Norway Regional Health Authority and NTNU funded the work in this thesis.

The Research Group of Geriatrics, Movement and Stroke (GeMS) was created during this period, and has been part of my life since January 2014, and added an enriched environment for science and collaboration.

This thesis had not been possible without all the patients and their families that have volunteered to participate in the study, and not possible without all the stroke units, willing stroke nurses and other staff at the hospitals helping us with the inclusion process.

I am very grateful to be given the opportunity to study the stroke patients' activity levels early after stroke, and explore if this was linked to outcome later, since movement and starting the process of finding ways to recover and master the life after suffered stroke is important.

First I thank my main supervisor Associate Professor Torunn Askim, who truly has survived all my fussing all these years, and has let me take advantage of her research skills. She has always been available and mostly enthusiastic, though she sometimes might have been a bit tired of me. But without you I don't know how I would have finished. We have had some awesome journeys together, just mention two weeks in Australia, doing a lot of work with the data, but also time to look at the inner sides of Australia. We have also made Lisbon, Singapore, Istanbul, London and Glasgow as part of the journey to my PhD.

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Finally, thanks to my husband Jan, who supported me in the decision to do this research, and to all the rest of the extended family for being interested and supportive when necessary.

Selected abbreviations

ADL	Activities of daily living
AVERT	A Very Early Rehabilitation Trial
BI	Barthel Index
CSU	Comprehensive or Combined Stroke Unit
EE	Enriched Environment
EQ-5D-5L	EuroQuol 5 Dimension 5 Level (HRQoL instrument)
ESD	Early supported discharge
HADS(-D)	Hospital Anxiety and Depression Scale (-depression domain)
HRQoL	Health related quality of life
HUNT	Helseundersøkelsen i Nord-Trøndelag (The Nord-Trøndelag Health Study)
HUNT3	HUNT survey part 3 conducted 2006-2008
ICF	International Classification of Functioning, Disability and Health
LEAST	Life Early After STroke
mRS	modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
NRS	Norwegian Stroke Registry
OSC	Oxford Stroke Classification
PA	Physical activity
PSD	Post-stroke depression
PSF	Post-stroke fatigue
PT	Physical therapist
SSS	Scandinavian Stroke Scale
SU	Stroke Unit
VAS	Visual Analog Scale
WHO	World Health Organization

List of papers

I Hokstad A Indredavik B, Bernhardt J, Ihle-Hansen H, Salvesen Ø, Seljeseth YM, Schüler S, Engstad T, Askim T. Hospital Differences in Motor Activity Early after Stroke. A Comparison of 11 Norwegian Stroke Units. J Stroke Cerebrovasc Dis. 2015; 24: 1333-1340.

II Anne Hokstad, MD, Bent Indredavik, MD, PhD, Julie Bernhardt, PhD, Birgitta Langhammer PhD, Mari Gunnes MSc, Christine Lundemo MSc, Martina Reiten Bovim, medical student, Torunn Askim, PhD. Upright activity within the first week after stroke is associated with better functional outcome and Health Related Quality of Life. Results from a Norwegian multi-site study. Journal of Rehabilitation Medicine (In press).

III Thorlene Egerton, Anne Hokstad, Torunn Askim, Julie Bernhardt, Bent Indredavik. Prevalence of fatigue in patients 3 months after stroke and association with early motor activity: A prospective study comparing stroke patients with a matched general population cohort. BMC Neurology. 2015; 15:181

1 Introduction

1.1 The Burden of stroke

Stroke is one of the leading causes of death, after heart disease and cancer, and a leading cause of severe disability in Norway and the rest of the Western world (Bonita et al., 1997; Statistisk Sentralbyrå, 2012; Stegmayr & Asplund, 2003). Globally, lower national income is associated with even higher relative mortality and burden of stroke (Kim & Johnston, 2011). In Norway, the annual incidence of first ever stroke is reported to be 3.1 per 1000 in persons aged 15 years and older, proportion of first ever stroke and recurrent stroke is estimated to 75% and 25% respectively (Ellekjaer et al., 1997; Ellekjaer & Selmer, 2007). Adjusted to the Norwegian population we would expect 11 000 first-ever strokes and 3500 recurrent strokes yearly (Ellekjaer & Selmer, 2007). In high income countries mortality rates were falling by 21-38% 1990-2010 (Sarti et al., 2003; Stegmayr & Asplund, 2003). Whether this trend is caused by lower incidence or reduced case fatality, explained by better stroke care, decline in stroke severity and detection of milder strokes because of better diagnostics with CT and MRI scanning is not known (Sarti et al., 2003). The decline in first ever stroke rates might be attributed to improvement of risk factor control (Hong et al., 2011). There has also been a reduction in recurrent stroke rates in recent decades, and this is also attributed to better secondary prevention (Eriksson & Olsson, 2001; Hardie et al., 2003). Stroke risk increases with age; the increased birth rate after the second world war has already led to increased numbers of people above the age of 65 and the number of strokes is expected to increase proportionally (Waaler, 1999). In the coming years the prevalence of stroke in Norway therefore probably will increase due to an aging population. This means that more people will have to live their life with the consequences of stroke.

1.2 Definition of stroke

Stroke is defined by the World Health Organization (WHO) as:

"A syndrome of rapidly developing symptoms and signs of focal, and at times, global, loss of cerebral function lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin" (Hatano, 1976)

Transient episodes of cerebral ischemia are excluded by the definition. In the original definition, vascular lesions discovered without having shown clinical manifestations were not registered as stroke, and this definition is used in this thesis.

The definition comprises three main pathological types of stroke: ischemic, primary intracerebral hemorrhage and subarachnoid hemorrhage.

1.3 Types of stroke

In Norway the proportions of the different types of stroke are: cerebral infarctions (85 % of the cases), intracerebral hemorrhage (12% of the cases) and subarachnoid hemorrhage (3% of the cases), of those patients admitted to hospital (Ellekjaer et al., 1997).

1.3.1 Hemorrhagic stroke

Hemorrhagic strokes can be classified as subarachnoid hemorrhage and intracerebral hemorrhage. Subarachnoid hemorrhages are extra-cerebral, have another etiology than intracerebral hemorrhage and are usually treated in neurosurgery departments. Subarachnoid hemorrhages and intracerebral bleeds due to trauma are outside the scope of this thesis.

Intracerebral hemorrhages can be classified mainly in two categories: hypertensive bleeds located deep in the subcortical areas, and the more superficial amyloid angiopathy.

1.3.2 Ischemic stroke

Ischemic stroke can be classified according to symptoms or etiology. The most frequently used classification systems are:

Classification based on symptoms:

The Oxfordshire Community Stroke Project (OSCP) classification, also known as the Bamford classification system, is a simple bedside method of classifying acute ischemic strokes. It uses the patient's symptoms to classify which region of the brain has been affected, and once classified it allows for prediction of a patient's prognosis (Bamford et al., 1991). The four categories of stroke are as follows:

Total Anterior Circulation Infarct (TACI): All three of the following categories must be present: Higher cerebral dysfunction, homonymous hemianopia and ipsilateral motor and/or sensory loss of at least 2 areas of the face, arm and leg.

Partial Anterior Circulation Infarct (PACI): Two of the categories of TACI must be present.

Lacunar circulation Infarct (LACI): Pure motor stroke or pure sensory stroke or sensorimotor stroke or ataxic hemiparesis. Absence of cortical or brainstem signs.

Posterior Circulation Infarct (POCI): Isolated hemianopia, cerebellar ataxia, brainstem signs including ipsilateral cranial nerve palsy with contralateral motor/sensory deficit, or bilateral motor/sensory loss, or coma.

Some clinicians also use a category for strokes which are difficult to put into one of the four main categories. The OCSP classification was useful when there were no radiologic devices available, and is still useful in developing countries with limited imaging resources and for evaluating upcoming problems regarding cognitive deficits and disability. The OCSP classification is shown to be reasonably valid in predicting the site and size of cerebral infarctions (Mead et al., 2000), except for discrimination between lacunar and small-volume cortical infarcts (Asdaghi et al., 2011).

Classification according to etiology:

Strokes have different etiologies, and finding the etiology of the stroke is essential to prevent recurrence. In addition to clinical findings, stroke diagnosis based on etiology requires diagnostic tools such as CT, MR, ultrasound/Doppler and cardiac monitoring and blood samples.

The TOAST (The Trial of ORG 10172 in acute stroke treatment) classification denotes five sub-types of ischemic stroke according to the most probable etiology: 1. Large-artery atherosclerosis (embolus/thrombosis), 2. Cardioembolic, 3. Small-vessel occlusion (lacuna), 4. Stroke of other determined etiology and 5. Stroke of undetermined etiology (Adams et al., 1993).

Classification according to the underlying etiology is more useful for management, both for acute treatment and secondary prevention.

1.4 Stroke symptoms

Stroke symptoms might be focal or global:

Definite focal signs: unilateral or bilateral motor impairment (including dyscoordination), unilateral or bilateral sensory impairment, aphasia, hemianopia, diplopia, gaze deviation, and dysphagia, ataxia, apraxia or perception deficit of acute onset.

Not acceptable as sole evidence of focal dysfunction: Dizziness, vertigo, localized headache, blurred vision, dysarthria, impaired cognitive function, impaired consciousness, and seizures.

Global signs: this applies to patients with SAH or deep coma, excluding coma of systemic origin such as shock, Stoke-Adams syndrome or hypertensive encephalopathy (The WHO MONICA Project, 2007).

1.5 Mechanism of ischemic stroke

Cerebral infarction usually occurs after gradual or sudden occlusion of a brain artery, and is usually caused by intra-arterial embolism or thrombosis (Hossmann, 2006), but could also be caused by external compression from tumors (Nguyen & DeAngelis, 2006), hemorrhagic strokes (Naranjo et al., 2013) or vasospasm (Otite et al., 2014). Infarction might also be induced by reduced cerebral blood flow due to extra-cerebral vascular constriction or occlusion of cerebral blood flow. Usually the circle of Willis is responsible for redistribution of blood supply under these conditions. With decreased flow to the vessels, the blood perfusion pressure falls, and the flow first declines in the peripheral branches of the brain arteries. This will induce changes in the watershed areas, a border zone between the large supplying arteries of the brain. There are also anastomoses (Heubner's anastomoses) distal to the circle of Willis, with individual capacity determining the variations in cerebral tissue damage due to a vascular occlusion. When the reduction in blood flow reaches a critical point, the intracellular energy metabolism and protein synthesis is inhibited, the ion channels cannot maintain the homeostasis, and the cell membrane starts to leak. The injury is established within a few minutes after the onset of ischemia. The damage is greatest in the middle of the infarction core. This area is surrounded by an area called the penumbra, which has a critically low blood flow level, but is able to survive a little longer. If the blood flow is recaptured this area has potential for recovery within 4-6 hours. If the blood supply is not re-induced the injury might progress, including the penumbra and also inducing secondary damage to brain tissue due to edema and inflammation (Astrup et al., 1981).

1.6. Evidence-based stroke treatment

Treatment of stroke has changed radically in the last two decades, with the introduction of evidence-based specialized stroke unit care (Indredavik et al., 1991; Stroke Unit Trialists, 2013). Evidence-based medicine is the process of reviewing available clinical evidence from systematic research, integrated with individual clinical expertise in making decisions for the care of an individual patient, integrated with the patients' needs and choice. The bases of evidence-based medicine and thereby evidence-based stroke unit care are summarized in Figure 1 (Sackett DL, 1996).

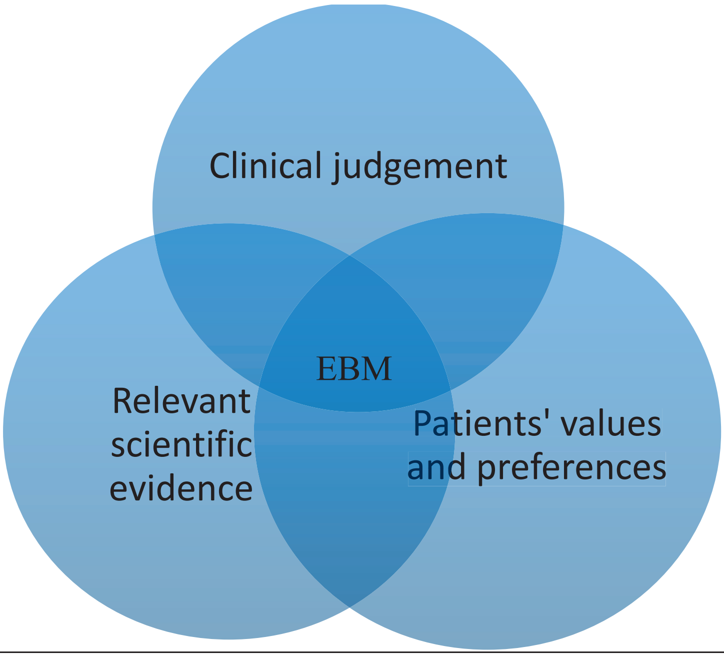

Figure 1. Evidence-based medicine (EBM) summarized (Sackett DL,et al.BMJ.1996;312:71-72).

1.6.1 Organized inpatient (stroke unit) care

Stroke unit treatment

"Organized stroke unit care is a form of care provided in hospital by nurses, doctors and therapists who specialise in looking after stroke patients and work as a coordinated team. Patients who receive this care are more likely to survive their stroke, return home and become independent in looking after themselves. A variety of different types of stroke unit have been developed. The best results appear to come from those which are based in a dedicated ward." (Stroke Unit Trialists' Collaboration, 2013)

Stroke unit (SU) treatment is now recommended for all stroke patients. It reduces death and dependency in the short and long term compared to treatment in a general medical ward, and should now be the treatment of choice (Indredavik et al., 1999; Stroke Unit Trialists, 2013). Many aspects of stroke unit care probably contribute to the better outcome, and include fast track diagnosis and medical treatment, secondary medical prevention (Kernan et al., 2014), discharge planning, and follow up (Fisher et al., 2011; Indredavik et al., 1999). Early and frequent mobilization has also been considered one of the key factors in improving outcome (Chan et al., 2013). Factors influencing further recovery and stroke recurrence are rehabilitation (Pollock et al., 2014) as well as lifestyle changes including increased levels of physical activity, weight reduction and smoking cessation (Billinger et al., 2014; Galimanis et al., 2009). In data published in 2014, based on registrations from 1995-2010, including 320 000 from the Swedish Riks-Stroke registry, the authors found that the proportion of patients treated in a stroke unit rather in a general medical ward had increased from 53.9% to 87.5%. More patients were discharged directly home and a greater proportion of patients were on secondary prevention such as warfarin, statins and anti-hypertensive medicine. They also found a slightly better functional outcome 3 months post-stroke regarding independent walking, dressing, and toileting. However, case fatality rates increased from 18.7 to 20.0 % from 2001 to 2010. The increasing death rates were among severe strokes, although the proportion of severe strokes did not increase. Plausible explanations for this increased case fatality were shorter hospital stay and rehabilitation, and lack of institutional care after discharge, due to change in the Swedish health care system. It was also a trend that milder strokes might benefit more from the stroke unit rehabilitation (Appelros et al., 2014). A Finnish study found that 1-year death rates decreased between 1999 and 2007 (Meretoja et al., 2011). Studies on other European stroke populations also show the tendency to better outcome with organized multidisciplinary team treatment in a stroke unit (Ayis et al., 2013; Turner et al., 2015)

In Norway 53 hospitals are treating stroke patients, of which 45 have dedicated, stroke units. According to data from the Annual Report from the Norwegian Stroke registry 2013, 84% of stroke patients are admitted directly to a stroke unit, and a total of 91% are treated in a stroke unit during their stay in hospital ("Årsrapport Norsk hjerneslagregister 2013/Annual Report Norwegian Stroke Registry 2013," 2014).

Comprehensive or combined stroke units

Stroke unit care can be organized in different ways. The three most common types of stroke units are the acute admission stroke unit, the comprehensive stroke unit (CSU) combining acute treatment with rehabilitation, and the delayed admission or rehabilitation stroke unit (Stroke Unit Trialists' Collaboration, 2013). The acute admission stroke units focus on acute treatment including an acute assessment and allocation to treatment according to the main type of stroke (e.g. hemorrhage or infarction), starting thrombolysis, endovascular treatment or antithrombotic medication if indicated, together with focus on physiologic homeostasis to reduce further damage to the brain tissue. However, treatment in a stroke unit combining acute treatment and early rehabilitation, a CSU, is the model with most evidence from randomized trials. CSU treatment is shown to reduce complications, disability and mortality and might now be the treatment of choice (Chan et al., 2013; Stroke Unit Trialists' Collaboration, 2013). Early mobilization seems to be one of the most important factors for the beneficial effect of CSU treatment, followed by stabilizing the blood pressure (Indredavik et al. 1999). Patients treated in a CSU are more likely to be physically active and are also more often discharged directly home (Stroke Unit Trialists' Collaboration, 2013; West et al., 2013).

An enriched environment with increased stimulation and social support is also hypothesized to be an important component of a CSU (Indredavik et al., 1999). Patients in need of prolonged inpatient rehabilitation are admitted to rehabilitation stroke units.

The stroke units in Norway are organized as CSUs in accordance with the Norwegian National Guidelines for Stroke Treatment and Rehabilitation, published in 2010.

Early supported discharge (ESD)

ESD is suitable for mild and moderate strokes and demonstrates significantly improved outcome and shorter institutional stay compared to a standard treatment group; it can be regarded as an extension of stroke unit treatment (Fisher et al., 2011; Fjaertoft et al., 2011). The multidisciplinary ESD team plans and coordinates discharge from hospital and provides rehabilitation in the community. Several studies have shown the health benefits of ESD, and ESD is still evident when evidence-based models of these services are implemented in practice (Fisher et al., 2015). However, implementation of ESD seems to be difficult and most hospitals in Norway have still not established an ESD service.

1.6.2 Early rehabilitation

In general, physical rehabilitation is shown to be more effective than usual care in improving motor function in all phases after stroke. A recent Cochrane review concludes that all kind of physical rehabilitation is beneficial for recovering after stroke in contrast to no rehabilitation, and significant benefit is associated with starting rehabilitation soon after stroke for independence in activities of daily living (ADL) (Pollock et al., 2014). Effects of physical training are mostly restricted to the functions trained and preferably motor training should be task-oriented (Veerbeek et al., 2014). But how early and intensive the rehabilitation should be is still the subject of discussion (AVERT, 2015).

Time to first mobilization

Early mobilization after stroke has been thought to contribute to the powerful effect of CSU treatment (Govan et al., 2007; Indredavik et al., 1999). The term “early” is not clearly defined, but in the Norwegian guidelines of stroke care and rehabilitation it is defined as mobilization out of bed within 24 hours of stroke onset if the patient is stable (Helsedirektoratet, 2010). Time to first mobilization should preferably be defined as the time from onset of stroke to the first mobilization out of bed. Time from hospital admission to first mobilization out of bed is also used as a measure of early mobilization in one recent mobilization study (Sundseth et al. 2012). Probably this also can be regarded as a surrogate measure if the exact time for stroke onset is not known. Approximately 50 % of stroke patients with known onset time are admitted to hospital within 4.5 hours after stroke onset (Norsk hjerneslagregister, 2014). Up to 25% of stroke patients may have unknown onset time, and tend to have more severe strokes, but we do not know if they have longer median time from stroke onset to admission. Recent studies indicate that there is circadian morning predominance of stroke onset and that many patients with unknown stroke onset probably wake up shortly after the event (Wouters, et al., 2014).

The rationale for early mobilization is based on three main arguments. First, it is believed to prevent secondary complications associated with sustained bed rest (Diserenset al., 2006). Second, it might improve recovery by improving the musculoskeletal and cardiovascular system and finally it is thought to utilize the narrow window of brain plasticity early after stroke (Ivey et al., 2009). Based on these arguments is has been hypothesized that an early start and more frequent out-of-bed activity would improve outcome even more. However, the recent AVERT trial, including more than 2000 acute stroke patients in 3 continents, found that more intensive rehabilitation starting out of bed activity within 24 hours after stroke onset was associated with delayed recovery compared to standard care (AVERT, 2015). This is also in line with the results from a Norwegian trial showing that mobilization within 48 hours after hospital admission for acute stroke was superior to mobilization within 24 hours (Sundseth et al., 2012). It is worth mentioning that 60 % of the patients randomized to standard care in the AVERT trial also were mobilized within 24 hours and the average time to first mobilization was 19 hours in the intervention group versus 22 hours in the control group, hence the differences between the groups were greater regarding frequency and amount of mobilization than for timing. Even if the Norwegian guidelines recommend mobilization within 24 hours of stroke onset, we do not know if the hospitals adhere to the guidelines. Since too early mobilization is associated with less favorable outcome, and optimal timing of mobilization is unknown, it also will be of interest to illuminate the association between timing of first mobilization and outcome. This is explored in **Paper II** of this thesis.

Amount of early activity

Earlier observational studies across Australia and Europe have shown that patients in stroke units spend 30-98% of their daytime in bed and 0-66% of daytime in moderate to high activity (sitting out of bed or upright (Figure 2) (Askim et al., 2012; Askim et al., 2014; Bernhardt et al., 2008; Bernhardt et al., 2004; Wellwood et al., 2009). More detailed studies by Askim et al. found that time spent in bed was 30.3-30.6 % of daytime, time spent sitting out of bed was 46.4-48.0% of daytime, and time upright was 18.0-19.9% of daytime between 8 am to 5 pm in the stroke unit in Trondheim, Norway (Askim et al., 2012; Askim et al., 2014).

One of these studies also showed a strong association between more time spent in bed during the daytime in the early phase after stroke and poorer outcome three months later (Askim et al., 2014),

Most studies on activity observation report time in different activities and not frequency. However, results from phase II of the AVERT trial showed that frequent mobilization was associated with better walking abilities and earlier discharge home (Cumming et al., 2011), so probably not only timing and duration of mobilization influence outcome, but also frequency.

All stroke units in Norway are regarded as CSUs with a focus on early rehabilitation; however, we do not know the amount of activity for acute stroke patients in Norwegian stroke units and whether there are variations in activity levels for hospitalized stroke patients in the acute phase after stroke. This is explored in **Paper 1** of this thesis.

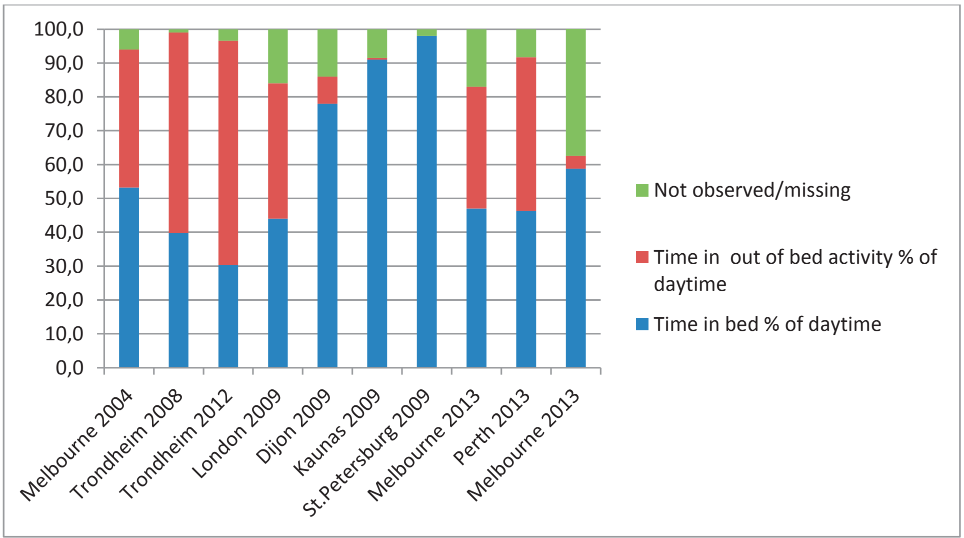

Figure 2. Time spent in different motor activities in acute stroke units across the world. Observed by behavioural mapping.

1.6.3 Enriched environment

Enriched Environment (EE) describes living conditions which promote engagement in physical, cognitive and social activity (Nithianantharajah & Hannan, 2006), and EE has shown better recovery of limb function in animal models (Madinier et al., 2014). Both environmental facilities (Janssen et al., 2014) and facilitating activities (van de Port et al., 2012) might increase the activity levels among acute and subacute stroke patients. An Australian qualitative study among nursing staff in a rehabilitation unit found that nurses were willing to facilitate patients' activities; however, barriers to overcome were workload, routine and attitude (White et al., 2014). Patient-related factors that influenced patients' ability to drive their own recovery were lack of opportunities to do things in addition to therapy and a place to go for activity, as well as a passive rehabilitation culture and environment (Eng et al., 2014). Access to communal areas is shown to increase activity levels in a rehabilitation setting (Janssen et al., 2014). Factors such as an increased nurse:patients ratio may also influence activity levels (Bernhardt et al., 2008), while a recent study found that increased time with a physical therapist did not necessarily translate into a meaningful increase in physical activity (English et al., 2014). In one of our studies we focus on environmental factors and their relationship to activity levels (**Paper I**).

1.7 Recovery after stroke

1.7.1 Brain plasticity and motor recovery

Motor deficit is the most prominent symptom after stroke, and spontaneous recovery of motor function, with a first fast initial phase the first six weeks, and a slower recovery for the next six weeks is usually observed after stroke. Recovery from paresis usually levels off substantially 3 months after onset of ischemic stroke (Jorgensen et al., 1995). Motor recovery after stroke is due to several mechanisms including the brain's plasticity with cortical reorganization, which include increased recruitment of contralateral motor areas, increased activity in non-primary motor areas, and recruitment of ipsilateral sensorimotor areas as shown by functional neuroimaging studies (Li et al., 2014; Riecker et al., 2010; Tombari et al., 2004). These alterations are shown to be modified by behavioural experience in animal models (Nudo, 2007).

The brain's plasticity seems to be heightened in the first month after stroke. The best period for improving recovery after stroke onset is unclear, but in animal models very early and intense training (less than 5 days after stroke onset) may lead to increased brain tissue damage, while late onset rehabilitation (more than 30 days after stroke onset) is less effective in terms of brain plasticity and outcome (Krakauer et al., 2012).

The mechanism of recovery may also comprise three general changes within the sensorimotor network: restitution, substitution and compensation.

Restitution includes reduction of edema, absorption of hematoma, restoration of axonal transport and ionic currents. This process is relatively independent of external variables such as physical and cognitive stimulation, while substitution depends on external stimuli such as practice with the paretic arm or leg during rehabilitation. Substitution includes the functional adaptation of diminished but partially restored neuronal networks that compensate for components lost or disrupted by the injury. Substitution may add a cost to the mental and/or physical energy needed to carry out a relearned motor skill. For example, stroke patients may have problems with walking and talking at the same time because walking is no longer automatically performed. Compensation aims to improve the mismatch between the patients' impaired skills and the demand from the environments, and may include increased time or effort to maintain basic aspects of an affected skill, or develop a new skill that replaces an affected one (Dobkin, 2005).

1.7.2 Consequences of stroke

Up to 40-50 % of stroke survivors have difficulties with basic self-care 3-6 months post-stroke because of physical and cognitive impairments. Walking ability and higher degree of independence is a predictor for discharge home either directly from acute hospital or after rehabilitation (Brauer et al., 2008; West et al., 2013). In addition, urinary incontinence and cognitive impairment are two of the most significant predictors for poor functional outcome three and six months after stroke (Eriksson et al., 2008; Kwakkel et al., 2010; Muir et al., 1996; Sato et al., 2014; Stroke Unit Trialists' Collaboration, 2013). Approximately 10-20 % of the patients are dead 3 months poststroke (Appelros et al., 2014; Gattringer et al., 2014).

Stroke patients also rate their HRQoL lower than healthy controls of the same age, and lower than people with other medical diseases (Wikman et al., 2011). Reduced function, especially dependency in ADL, is associated with poorer health-related quality of life (HRQoL) (Lopez-Espuela et al., 2015; Sprigg et al., 2012), and mRS is shown to be strongly correlated with HRQoL (Ali et al., 2013).

Fatigue seems to be one of the most distressing symptoms poststroke, affecting around 40% (Wu et al., 2015) of stroke survivors and the underlying mechanisms that cause fatigue are still poorly understood. There may be both physical and cognitive factors involved in the development and perception of fatigue, as well as morphological changes in the brain (Kuppuswamy et al., 2015).

Approximately one third of stroke survivors experience depression either early or late after the stroke onset, and depression impedes the rehabilitation and recovery process (Gaete & Bogousslavsky, 2008; Kutlubaev & Hackett, 2014).

Pain also is a frequent symptom after stroke, and may affect up to half of the patients 4-12 months poststroke; stroke-related pain is associated with more severe strokes and sensory disturbances (Jonsson et al., 2006; Lundstrom et al., 2009)

Depression, pain and fatigue often coexist, and are associated with poorer HRQoL and increased mortality (Carod-Artal & Egido, 2009; Naess et al., 2012a; Visser et al., 2014)

1.7. 3 Factors influencing outcome after stroke

The consequences of a stroke depend on several factors, including the location of the vessel occlusion and how much brain tissue is affected. The most common symptoms of stroke are hemiparesis, swallowing problems, aphasia, neglect and other cognitive problems (Flowers et al., 2013; Lawrence et al., 2001; Sinanovic, 2010) .

Demographic factors such as gender, higher age (Bhalla et al., 2013; Sato et al., 2014; van de Port et al., 2006), living conditions and level of social support influence the prognosis for outcome after stroke. Female patients tend to have lower ADL functioning 6 months poststroke; contributing factors may be higher age, lower prestroke functioning and depression (Lai et al., 2005). More women tend to deteriorate to dependency over the first year poststroke (Ullberg et al., 2015), and dependency is associated with higher mortality rates (Eriksson et al., 2008). Prestroke disability and comorbidity such as previous stroke (Tyson et al., 2007), depression, fatigue, diabetes mellitus, atrial fibrillation (Bhalla et al., 2013) have been identified as factors negatively influencing recovery from stroke. However, the initial stroke severity and degree of paresis still represent the most important prognostic factors for motor recovery (Adams et al., 1999; Hendricks et al., 2002).

Patients with depression are at higher risk of developing pain post-stroke (Jonsson et al., 2006; Lundstrom et al., 2009; Naess et al., 2012c), while pain is shown to delay the rehabilitation and recovery process poststroke (Aprile et al., 2015).

1.8 Definition and measurements of the different dimensions of outcome poststroke

WHO has developed the International Classification of Functioning, Disability and Health (ICF) to provide a standard language for characterization of domains that address the concepts of medical and social disability as a composite of body structures, functions, activity and participation. It also includes environmental factors (WHO, 2013). This means that in stroke, neurological deficit, loss of ability to perform tasks, loss of ability to function in normal roles and activities, and quality of life should be addressed. These domains overlap to some degree and no assessment tool in general use in stroke care covers all dimensions. Several measurement tools exist to assess the different domains. Some of the most frequently used are mentioned in the next sections and will be described in more detail in the methods section. The different domains of ICF are illustrated in Figure 3.

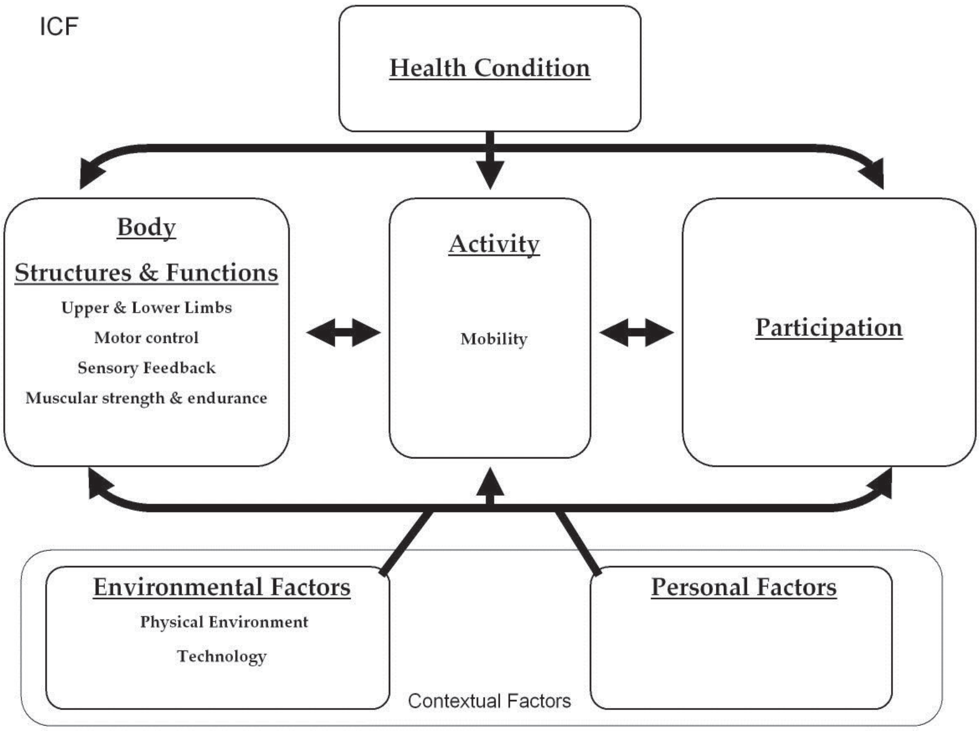

Figure 3.World Health Organization international classification.

1.8.1 Classification of neurological and functional impairments after stroke

The National Institute of Health Stroke Scale (NIHSS) is a widely used tool to assess neurological function (or impairment) in patients with signs and symptoms of stroke in the acute phase and for further decision making in the acute phase regarding therapy, evaluating the acute therapy, and also to evaluate any signs of deterioration in the acute phase and predicting prognosis (Brott et al., 1989). The NIHSS consists of 11 items assessing consciousness, orientation, motor deficits, sensibility, language, coordination, inattention and homonymous hemianopia.

Functional disabilities and daily functioning are often measured by the modified Rankin Scale (mRS) (Kasner, 2006). It is regarded as a global stroke scale and scoring of daily functioning from 0 (no symptoms) to 5 (severe disability, in need of constant care) and 6 (death). mRS is widely used to assess global outcome (or dependency) in stroke studies.

1.8.2 Health, Quality of life and Health-related quality of Life after stroke

Health is defined by the World Health Organization (WHO) as a "*state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*." (WHO, 1948) This definition is a statement impossible to fulfill, but it overcame the earlier definition defining health as the absence of disease. As the population ages and many live their life with chronic diseases WHO has developed several classification systems measuring gradations of health, that assess aspects like disability, functioning and perceived quality of life and wellbeing (Huber et al., 2011).

Quality of life (QoL) has been defined by the WHO-QOL group as "*individuals' perceptions of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns*" ("Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group," 1998).

The concept of HRQoL has been defined as "*the value assigned to duration of life as modified by the impairment, functional state, perceptions and social support that are influenced by the disease, injury, treatment or policy*" (Patrick, 1993). HRQoL is assumed to be a broad multi-dimensional construct referring to the aspects of life related to health. QoL is a larger construct also referring to other aspects of life (Fuhrer, 2000; Salter et al., 2008; "SHARE Survey of Health, Aging and Retirement in Europe, Wave 4," 2013). These constructs should not be used interchangeably.

Traditionally, outcome measures in stroke focus on disability and mortality. However, in recent decades more attention has been directed toward patient-reported outcome measures (PROMS), such as health status, participation and quality of life (Carod-Artal & Egido, 2009; Fitzpatrick et al., 1998). A clinically significant difference in symptoms or function for the patient might be clarified better by patient-reported outcomes of HRQoL (Guyatt et al., 1993).

There exist both generic and specific stroke measures of HRQoL. EuroQol-5Dimension-5Level (EQ-5D-5L) is a generic HRQoL measure that will be described more thoroughly in the methods section. In the framework of ICF, the EQ-5D-5L assesses some aspects of participation, but also involves disability and body functioning (Alguren et al., 2012; Salter et al., 2007)

Physical activity (PA) and exercise in all phases after stroke seem to have a positive impact on function and have also been shown to improve HRQoL (Fjaertoft et al., 2004; Rand et al., 2010). This is explored in greater depth in chapter 1.10.3.

1.8.3 Fatigue in the general population and after stroke

Fatigue could be both physiological and pathological. There is no consensus on how to define fatigue. Physiological fatigue is considered to be normal after a prolonged effort as a feeling of general tiredness; it occurs rapidly and is of short duration (i.e. after an exercise session or after a long walking tour in the mountains), and improves after rest (De Groot et al., 2003).

Pathological fatigue on the other hand is described as a "'*constant weariness unrelated to previous exertion levels and not usually ameliorated by rest' or as 'a feeling of physical tiredness and lack of energy that is described as pathological, abnormal, excessive, chronic persistent or problematic'* " (De Groot et al., 2003).

Fatigability is another construct that may be confused with fatigue, but fatigability is defined as the magnitude or rate of change in a performance criterion relative to a reference value over a given time of task performance (Kluger et al., 2013), or, in other words, one gets worn out earlier in performing the same task as in a former state.

The present thesis aims to assess the prevalence of pathological fatigue in the stroke population compared to the general population.

Fatigue in the general population. The prevalence of fatigue in the general population has been variably reported from 5%–47%, depending on the population studied, the questionnaire used, and the threshold score used to identify those with fatigue from those (Fukuda et al., 1997; Jason et al., 1999; Lerdal et al., 2005; Loge et al., 1998; Tennant et al., 2012). Despite the inconsistent results, prevalence appears to increase with increasing age (Hinz et al., 2013; Loge et al., 1998) and number of chronic diseases (Gron et al., 2014; Wright et al., 2014), and to be higher in women (Jason et al., 1999).

Post-stroke fatigue (PSF). Fatigue is one of the most common complaints after stroke and is reported to affect 35-92% of stroke survivors early after stroke with a tendency to persist over a longer period (Duncan et al., 2012). Most studies report a fatigue rate higher than 50% (Appelros, 2006; Lerdal et al., 2011; Schepers et al., 2006). The large range of reported prevalence of PSF probably mirrors the lack of a definition of fatigue, heterogeneity in the study population, time since stroke, use of several different scales or questionnaires for measuring fatigue (Duncan et al., 2014; Lerdal et al., 2009), and the fact that the symptoms seem to be of multi-dimensional origin (De Groot et al., 2003; Lerdal et al., 2009).

PSF is described as physical, mental (or central), or performance based or a combination of these (Staub & Bogousslavsky, 2001). People with neuropsychological deficits may experience mental fatigue due to additional mental effort to produce motoric and mental skills, and also physical fatigue as a consequence of motor deficits, even if they appear totally recovered (Staub & Bogousslavsky, 2001). There is no conclusive evidence on the association between PSF and lesion site (Kutlubaev et al., 2012). Although some studies report an association with basilar artery infarction (Naess et al., 2005), basal ganglia infarction (Tang et al., 2010) and subcortical white matter infarcts (Tang et al., 2014), others find no such association (Appelros, 2006; Choi-Kwon et al., 2005). It is also hypothesized that fatigue is related to the extra costs of energy expenditure related to the network changes that appear in the brain along with motor recovery after stroke (Askim et al., 2009). Reduced spontaneous neuronal firing rates in the lesioned hemisphere and subsequent decrease of cortico-motor excitability is also a plausible mechanism for this phenomenon (Kuppuswamy et al., 2015),

Those with fatigue shortly after stroke are also likely to report fatigue in the long term (Schepers et al., 2006; van de Port et al., 2007), while those not reporting fatigue early most likely will not develop fatigue (Christensen et al., 2008).

PSF and its association with poorer functional outcome is conflicting, with some studies reporting an association (Christensen et al., 2008; Glader et al., 2002; Naess et al., 2005), while another reported no association (van de Port et al., 2007). There also seems to be an association between PSF and increased mortality (Glader et al., 2002; Mead et al., 2011; Naess & Nyland, 2013). A recent review finds no clear association between type and severity of stroke and PSF (Ponchel et al., 2015).

Emotional disturbance such as depression is significantly associated with PSF in several studies (Appelros, 2006; Choi-Kwon et al., 2005; Duncan et al., 2015; Schepers et al., 2006) however depression and fatigue have many coexisting and shared experiences, and fatigue is one of the main symptoms of depression (ICD 10, 2015). This makes it difficult to differentiate between fatigue and depression as independent conditions. Patients with pain also report more PSF than others (Appelros, 2006; Glader et al., 2002).

Few studies on stroke patients and fatigue seem to have explored the association between coexisting morbidities and PSF. Two studies reported no association to cardiovascular diseases or diabetes mellitus (Appelros, 2006; Choi-Kwon et al., 2005), while one study reported association with diabetes mellitus, cardiovascular disease and migraine in young adults (Naess et al., 2005).

Some recent studies found an association with prestroke fatigue (Chen et al., 2015; Duncan et al., 2014; Lerdal et al., 2011). In addition, demographic factors such as increasing age (Feigin et al., 2012), living alone, and female sex (Glader et al., 2002) are associated with more fatigue. Most studies on fatigue and HRQoL after stroke find that fatigue has a negative impact on HRQoL (Chen et al., 2015; Feigin et al., 2012; Mead et al., 2011; Naess et al., 2012a).

1.8.4 Depression after stroke

Depression is defined by ICD 10 (ICD 10, 2015) as mild, moderate or severe depending on the number of symptoms. The individual usually suffers from depressed mood, loss of interest and enjoyment, and reduced energy leading to increased fatigability and diminished activity. Marked tiredness after only slight effort is common. Other common symptoms are reduced concentration and attention; reduced self-esteem and self-confidence; ideas of unworthiness; pessimistic views of the future; disturbed sleep.

The prevalence of poststroke depression (PSD) is indicated to range from 20-65% depending on the population studied, assessment tools, and definition applied (Andersen et al., 1994;

Burvill et al., 1995; De Ryck et al., 2013; Kotila et al., 1999). Depressive symptoms may be misdiagnosed as cognitive problems or fatigue and vice versa.

Prevalence of PSD is strongly related to cognitive impairments such as memory and executive dysfunction and aphasia (De Ryck et al., 2013; Hommel et al., 2015), stroke severity, functional impairment and social support (Choi-Kwon et al., 2012; De Ryck et al., 2014) . Remission of PSD positively influences ADL and recovery after stroke (Chemerinski, et al., 2001).

1.8.5 Post-stroke pain

Pain is defined by the International Association for the Study of Pain (IASP) as : "*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."*("International Association for the Study of Pain IASP,").

Pain is always subjective, and individuals learn application of the word through experiences of pain related to injury in early life. Pain is also usually associated with an unpleasant feeling and an emotional experience. Pain could be classified by location, pathophysiology or duration. Pain sensation is a vital function of the nervous system to avoid potential injury, while pain persisting beyond the phase of healing and lasting more than 3 months is defined as chronic ("International Association for the Study of Pain IASP,").

Pain is reported to be experienced in approximately 50 % of patients poststroke (Indredavik et al., 2008; Langhorne et al., 2000; Lundstrom et al., 2009). New pain after stroke is lower, with prevalence reported from 11 - 21% (Lundstrom et al., 2009; O'Donnell et al., 2013). Poststroke pain is associated with stroke severity, especially sensory and motor deficits, and depressive symptoms (Harrison & Field, 2015; Lundstrom et al., 2009; O'Donnell et al., 2013).

Central poststroke pain is common and affects up to a third of those reporting pain (O'Donnell et al., 2013; Widar et al., 2002), thereafter peripheral neuropathic pain, pain following spasticity, and pain from shoulder is reported most frequently. Headache and other musculoskeletal pain are also common (Harrison & Field, 2015).

Chronic pain poststroke is associated with increased disability and dependency (O'Donnell et al., 2013), negative influence on recovery and rehabilitation (Aprile et al., 2015) as well as reduced HRQoL (Aprile et al., 2015; Choi-Kwon et al, 2006; Naess et al., 2012a).

1.9 Stroke and physical activity

1.9.1 The concept of physical activity

Physical activity, exercise and physical fitness are terms describing different concepts (Caspersen et al., 1985).

Physical activity (PA) is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" (Caspersen et al., 1985). The term comprises different dimensions of PA such as frequency, duration and intensity, and can also comprise type and amount of activity. The definition of physical activity embraces any motor activity and these terms are used interchangeably in the present thesis.

Exercise is "physical activity that is planned, structured, and repetitive for the purpose of conditioning any part of the body" (Howley, 2001).

Physical fitness is defined as “A measure of the body’s ability to function efficiently and effectively in work and leisure activities, resist hypokinetic diseases (diseases from sedentary lifestyles), and to meet emergency situations.”(Caspersen et al., 1985).

Effort conducted during the activity may be measured by specific energy expenditures values (MET multiples of basal resting energy expenditure) known to be associated with specific activities. Activities may be classified as light, moderate or vigorous based on their assigned METs (Ainsworth et al., 2011).

1.9.2 Measurements of physical activity

To measure PA is important in order to increase the understanding of the relationship between PA and a range of different outcomes like physical health, mental health and recovery (Bauman et al., 2006). Measuring PA is also important in order to measure the impact and effectiveness of health promoting programs and interventions designed to increase PA (Lohne-Seiler et al., 2014). Several methods are available for collecting data on PA.

Questionnaires: PA has traditionally been assessed by self-administered questionnaires. These are suitable and easy to administer in large groups and can be performed at low cost (Sallis & Saelens, 2000). Questionnaires should capture the frequency, duration and intensity dimensions of PA, and be easy to administer and understand (van Poppel et al., 2010). However, use of questionnaires has been associated with recall bias, and this is pronounced in stroke patients (Mudge & Stott, 2009; Resnick et al., 2008). Most generic instruments assess leisure time physical activity, and activities performed as part of daily life most often have not been assessed (Taraldsen et al., 2012). This is a limitation because physical activity in older people is mostly performed as part of daily life activities. Questionnaires may not be suitable for measuring PA in a hospital setting due to short stay and illness.

Body-worn sensors: PA can be measured objectively with body-worn sensors. By use of such methods it is possible to collect and store information about PA performed by a person over longer periods, and to distinguish between different activities such as time spent supine, standing/walking, or sitting. However, most of these devices tend to underestimate step counts particularly in older people with gait problems and slow walking speed (Cyarto et al., 2004; Storti et al., 2008).

Observational methods: In many stroke studies over the past 10 years, observational methods have been used. In a recent review including papers from 1980 to 2014, 91 papers were assessed, for both device and observation. Thirty-one of these studies were observational, and most observational studies were performed within 14 days poststroke in a hospital setting. Devices were moreover used in the sub-acute and in the chronic phase to monitor activity in the community setting. The different observational methods used to measure physical activity were behavioural mapping (25 studies), videotape observation (4 studies) and counting repetitions of activities (2 studies). Most studies had three major activity categories of interest: sitting out of bed, standing or in bed. Observational periods ranged from 30 minutes to 12 hours on 1 to 10 days, and observations were performed from every 8 to every 30 minutes, most often every 10 minutes (Fini et al., 2015).

Observational methods suit inpatient settings where more patients can be observed at a time, but these methods are time- and labor-intensive. However, the benefits of observational methods are the abilities to report type of activity, people attending them, interaction with other people, and location registration (i.e. in bedroom, communal areas or therapy areas) (Fini et al., 2015).

1.9.3 Physical activity after stroke; influence on functional outcome, HRQoL and fatigue

PA and influence on functional outcome: Up to half of stroke survivors are dependent in activities of daily living 3 months post-stroke (Eriksson et al., 2008). Activity limitations are often a consequence of disability and dependency (Gadidi et al., 2011). Patients at risk of more deconditioning are those of higher age, having more severe strokes, less activity pre-stroke (Baert et al., 2012) and balance problems (Michael et al., 2005). Even physically well recovered stroke survivors with ability to undertake higher activity levels stay sedentary, and tend to be more physically inactive than age-matched controls (Danielsson et al., 2014). Barriers to participation in PA were lack of motivation, health concerns, and stroke impairments. Motivational factors for PA were social support and the need to be able to perform daily tasks (Nicholson et al., 2013). Stroke survivors also tend to prefer more structured exercise and activity than healthy controls, maybe because of decreased confidence and the need for observation and instruction for relearning an exercise (Banks et al., 2012). There is strong evidence that physiotherapy interventions favoring intensive high repetitive task-oriented and task-specific training in all phases after stroke improves motor recovery , and that effects are mostly restricted to the actually trained functions and activities (Pollock et al., 2014; Veerbeek et al., 2014). In a recent Danish trial, acute stroke patients were allocated either to intensive task-oriented training at home 3 days poststroke while they were still hospitalized or to standard care. The treatment group showed a significantly better outcome than the standard care patients 3 months poststroke on mRS and specific ADL measures (Rasmussen et al., 2015). However, too early and intensive mobilization may have a negative influence and may delay the recovery process after stroke (AVERT, 2015; Sundseth et al., 2012).

PA and HRQoL after stroke: In general, stroke patients rate their HRQoL lower than other patient groups and healthy people at the same age (Burstrom et al., 2001; Janssen et al., 2013). Dependency is strongly associated with reduced HRQoL (Carod-Artal & Egido, 2009; Lopez-Espuela et al., 2015), while enhanced physical activity levels have been associated with better HRQoL in stroke survivors (Langhammer et al., 2008; Lopez-Espuela et al., 2015; Rand et al., 2010; Tyedin et al., 2010). A number of studies in recent years have shown that chronic stroke patients participating in organized and unorganized PA improve their HRQoL compared to their more inactive counterparts (Aidar et al., 2011; Langhammer et al., 2008; Rand et al., 2010). The reason for this might be multifactorial because both improving physical function and social participation have been shown to improve HRQoL.

Few studies so far have explored the relationship between PA and rehabilitation in the acute phase after stroke and HRQoL later. However, one small trial looking at early rehabilitation in hospital with an increased amount of activity in the intervention groups showed a trend toward and association with better HRQoL in the long term (Tyedin et al., 2010) and one with dependent patients recruited to a home-based training program with a multidisciplinary team in addition to inpatient treatment (Rasmussen et al., 2015), showed a trend toward and association with better HRQoL in the long term.

However, knowledge about the association between amount of early rehabilitation after stroke and outcome in the chronic phase is still sparse. In Paper II we have tried to address some of these associations.

PA and fatigue after stroke: It is shown that energy consumed per covered distance is 1.7 times greater than normal in hemi-paretic adult stroke patients during walking. Cardiorespiratory fitness in patients suffering from mostly mild strokes is estimated to vary between 26-87% of that in healthy age-matched individuals. The smaller gap between energy expenditure and maximal cardiorespiratory capacity could explain at least fatigability in stroke survivors, but also the experience of fatigue (Smith et al., 2012).

Only a few studies have explored the relationship between physical fitness and fatigue among stroke patients. A review from 2012 concluded there was no association between economy of gait (rate of oxygen consumption), peak exercise capacity (VO2 peak) and fatigue, and there were no associations between ambulatory activity intensity, step counts or participation in PA sessions of more than 20 minutes (Duncan et al., 2012). Later, Duncan et al. found an association between lower step count by body-worn sensors 1 month poststroke and increased levels of fatigue at 6 and 12 months poststroke (Duncan et al., 2015).

Only one small intervention trial has so far explored the relationship between an exercise/cognitive therapy group (COGRAT) versus a cognitive therapy group (CO), and found an alleviation of fatigue after a 12-week program in both groups. However, the effect was most pronounced in the COGRAT group, indicating that graded PA could be a therapeutic target for poststroke fatigue (Zedlitz et al., 2012).The conflicting findings regarding the association between fatigue and PA may mirror the problems in defining the concept of fatigue as well as the problem with distinguishing physical and mental fatigue, and its relation to muscle fatigue and other conditions such as cognitive problems.

There is a lack of studies investigating the impact of early rehabilitation on fatigue in the long term after stroke.

In Paper III we explored the relationship between early rehabilitation and fatigue in the chronic phase after stroke.

1.9.4 Rationale for the study

There is evidence that treatment in a stroke unit focused on rehabilitation within the first days after stroke is of importance for recovery and good outcome. However, the amount of out-of-bed activity differs significantly between stroke units worldwide and it would be of great interest to investigate how activity levels differ between stroke units within Norway. It would also be of great interest to investigate which factors explain these potential differences. Hence, this is the topic of Paper I in the present thesis.

In recent years, guidelines for stroke care and rehabilitation worldwide have focused on the disadvantages of prolonged bedrest, and the importance of starting mobilization and rehabilitation within a few days post-stroke. Recommendations in Australia, UK, and Scandinavia have been to start mobilization out of bed within 24-48 hours if the patient is medically stable. However, the recently published AVERT trial revealed that patients receiving very early, frequent and intensive mobilization showed a delayed recovery curve compared to patients receiving standard care. Still, the impact of out-of-bed activity applied during hospital stay in the Norwegian CSUs is unknown. It would therefore be of great interest to investigate the association between early upright activity and outcome 3 months later in multiple Norwegian stroke units. The outcomes of interest would be disability and HRQoL. Hence, this is the topic of Paper II in the present thesis.

Fatigue is a common but neglected symptom after stroke. Prevalence of fatigue in the general population and in the stroke population varies considerably. Multiple factors such as comorbidity, pre-stroke fatigue, pain and depression have been shown to increase the risk of developing fatigue after stroke, and there is some evidence that physical activity might reduce the risk of developing fatigue. However, the impact of upright activity during hospital stay on fatigue 3 months later is still unknown. Hence, this is the topic of Paper III in the present thesis.

2 Aims of the thesis

The overall aim of the thesis was to increase knowledge about activity levels across multiple Norwegian comprehensive stroke units and its association to outcome 3 months later, and to evaluate which factors influenced activity levels. A further aim was to compare fatigue levels in stroke patients with a cross section of age-matched people from the general population and factors influencing fatigue development.

The specific aims were:

Paper 1: The aims were to determine the amount of early motor activity in patients admitted to different Norwegian stroke units and to explore which factors explained the variation in activity between hospitals, and to assess where and with whom patients spent most of their daytime.

Paper 2: The aims were to assess the association between the timing and amount of upright activity applied in clinical practice in patients admitted to multiple Norwegian stroke units and degree of disability and health-related quality of life three months later.

Paper 3: The primary aim was to determine the prevalence of fatigue among a less selective stroke population 3 months after stroke, and to directly compare prevalence with an age- and gender-matched general population sample from a similar region (HUNT3 survey). The secondary aim of this study was to investigate the relationship between motor activity early after stroke and post-stroke fatigue.

3 Material and methods:

This thesis is based on two studies: one multi-center prospective observational study including stroke patients within 2 weeks post-stroke (Paper I, II and III) and a follow up assessment three months later (Paper II-III), the Life Early After Stroke (LEAST) study. In addition, data from the large cross-sectional Nord-Trøndelag Health Study (HUNT3) are reported in Paper III, as an age-matched reference group from the general population.

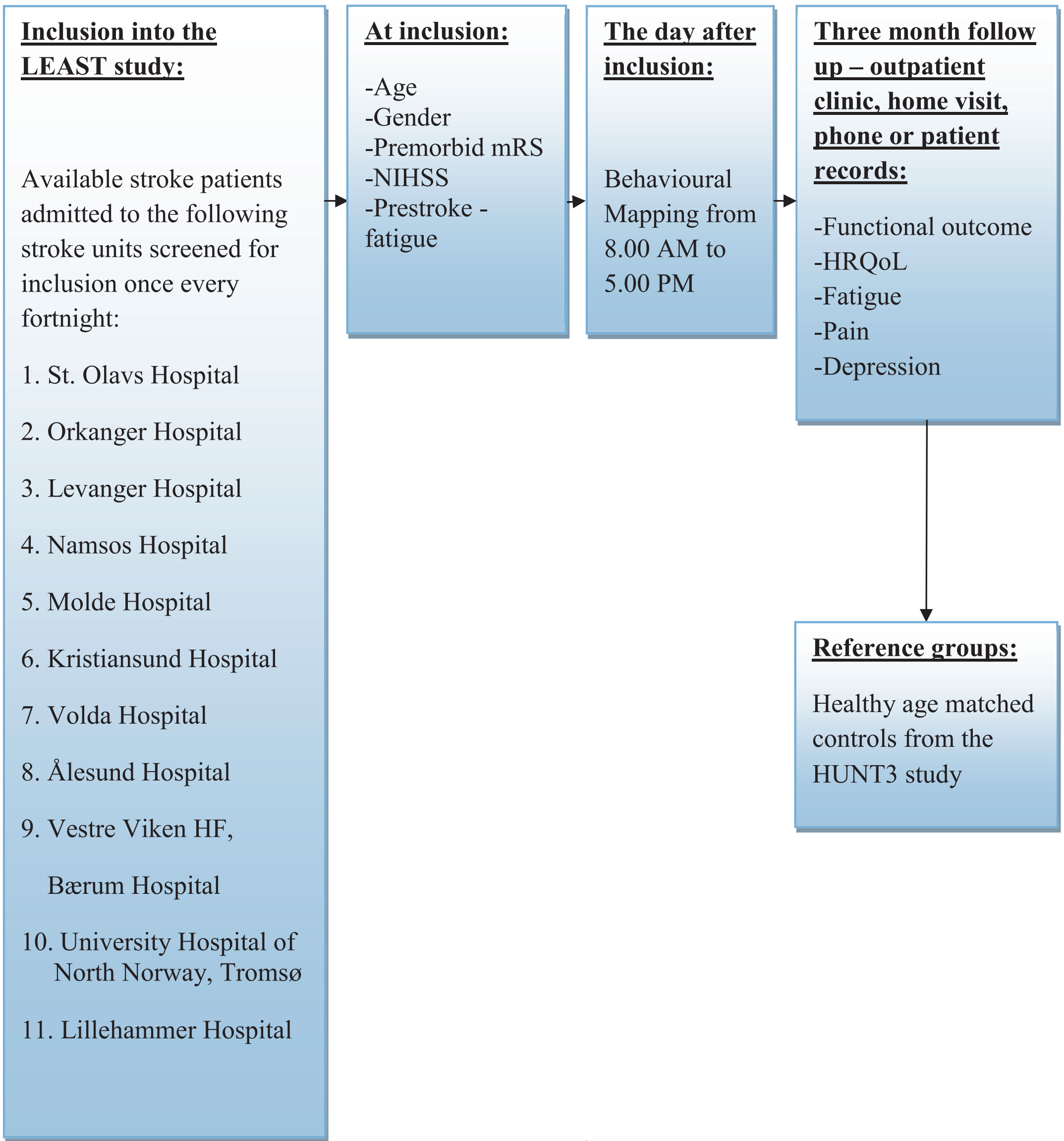

Figure 4. Study design.

3.1 Study design and setting

3.1.1 The LEAST study

This was a prospective observational study that recruited patients from 11 Norwegian stroke units between December 2011 and June 2013. The 3-month follow-up assessment was completed by the end of September 2013. The participating hospitals were located in three out of four Norwegian Health Authorities: eight hospitals from the Central Norway Health Authority, one hospital from the Northern Norway Health Authority, and two hospitals from the South-East Norway Health Authority. Of the hospitals, 2 were university hospitals, 2 were small (treating less than 100 stroke patients per year) and 7 were middle-sized (treating between 100 and 400 stroke patients per year). The hospitals are listed in Figure 4.

3.1.2 HUNT 3 study

The Nord-Trøndelag Health Study (the HUNT Study) is a longitudinal population health study and includes large total population-based cohorts from the 1980s, covering 125 000 Norwegian inhabitants in the county of Nord-Trøndelag; HUNT1 (1984-86), HUNT2 (1995-97) and HUNT3 (2006-08). The study was primarily set up to address arterial hypertension, diabetes, screening of tuberculosis, and quality of life. Every citizen of Nord-Trøndelag County in Norway aged 20 years or older has been invited to all the surveys for adults. The county of Nord-Trøndelag has been found to be representative of the Norwegian population except for slightly lower education and income than average (Holmen, 2003).

Data were collected through self-reported questionnaires, interviews, clinical examinations and measurements performed by specially trained nurses using standardized protocols and equipment. Only data from the HUNT3 study will be used in the present thesis. For a detailed description of the sample and design of the project see Krokstad et al, 2013, (HUNT, 2015; Krokstad et al., 2013).

3.2 Participants

3.2.1 The LEAST study (Paper I-III)

The stroke patients were recruited from 11 Norwegian comprehensive stroke units (CSU).

All participants were referred to the stroke units with an acute onset stroke, either infarcts or intracerebral hemorrhage. Patients were eligible if they had been diagnosed with a stroke (according to the WHO definition) within the last 13 days (e.g. 14 days at the day of observation), age >18 years, Norwegian speaking and not receiving palliative care. Patients were excluded if they were likely to be discharged from hospital with less than five hours of observation. Informed consent was obtained from those able to agree. Patients who were not able to give informed consent were included if their next of kin gave oral consent to participation.This is in keeping with Norwegian consent procedures for patients unable to consent.

A total of 547 patients were screened for inclusion. Reasons for exclusion and missing are summarized in Figure 5. A total of 411 patients were observed; however, 16 patients were later excluded because they did not have a stroke diagnosis and 1 patient withdrew. At 3-month follow up, we were unable to get any information about 3 of the patients due to wrong phone number or not answering the phone, and no data at 3 months in patient records, and 39 patients had died.

Of the remaining 352, four patients only had data from the patient record about function, and 77 patients were not able to answer any questionnaires because of cognitive decline or severe illness, thus 271 were able to answer at least one questionnaire at 3-month follow up. Of these, 262 patients were available for answering EQ-5D-5L, 261 answered FSS7, and 257 answered the HUNT3 questionnaire at 3 months. One patient was found to have too few observations on activity and was only included in the fatigue analyses that did not require activity data in Paper III.

Some of the patients declined to answer more than one or two questionnaires because of tiredness, cognitive problems or unwillingness to answer more questions.

The baseline characteristics are presented in Table 1.

3.2.2 The HUNT population (Paper III)

The HUNT3 population was used as a reference group for data on fatigue obtained in the stroke survivors. Data from The HUNT3 study were obtained from a data file transferred from the HUNT Research Centre.

In the HUNT3 survey a total of 50807 people participated, a participation rate of 54.1% of those invited. Of these, 2 had withdrawn and were excluded from the data file delivered to us. Of those remaining, 1298 had a previous history of stroke and 9908 had not answered the fatigue questionnaire; these were excluded from further analysis. Eligible for age and gender matching were 39599. Stroke patients were matched by age (up to a maximum of 2 years difference) and gender to respondents from the HUNT3 survey. The number of participants with available data in the stroke cohort determined the sample size for the study.

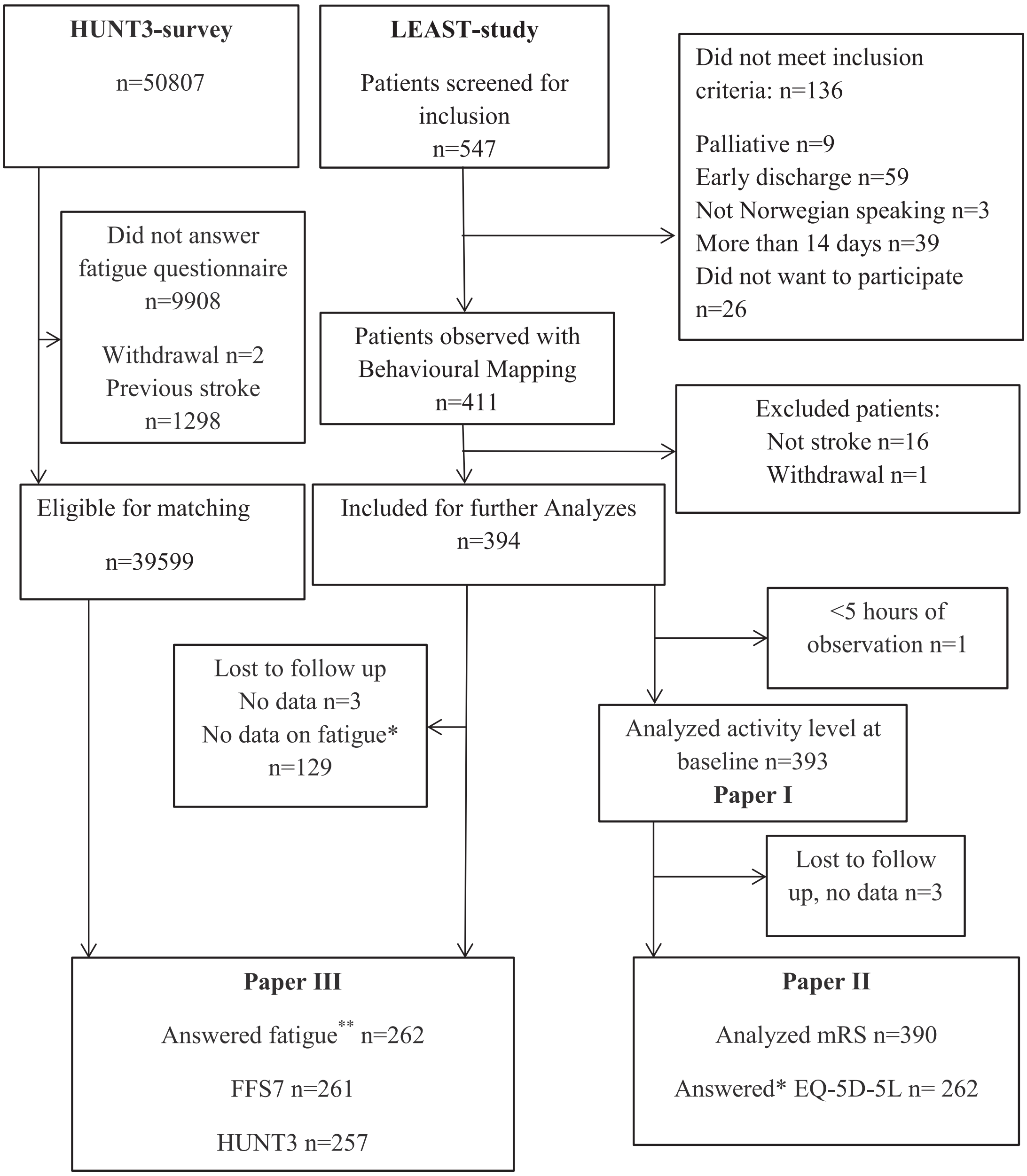

Figure 5. Flow of patients and participants through the study.

* Those not answering were not able to respond per telephone or in person because of cognitive decline, tiredness, aphasia or severe illness

**Answered at least one of the fatigue questionnaires (total 262, answered FSS7 n=261, answered HUNT3 n=257)

Table 1. Baseline characteristics of stroke patients, and age and gender matched participants from the HUNT3

Paper	I	II	III	
Study participants	Stroke	Stroke	Stroke	HUNT3
n	393	390	257	257
Age mean (SD)	76.8 (11.2)	76.8 (11.3)	74.8 (11.4)	74.8 (11.5)
Gender (male) %	48.1	48.5	53.7	53.7
Home dwelling %	89.3 %	89.2 %		100%
Premorbid mRS median (IQR)	1 (1-3)	1 (1-3)	1 (1-2)	
NIHSS at inclusion, mean (SD)	7.9 (7.7)	7.9 (7.7)	5.0 (5.0)	
mRS at inclusion, median (IQR)	4 (3-5)	4 (3-5)	3 (2-4)	
Stroke type-n (%)*				
TACI	62 (15.8)		17 (6.6)	
PACI	143 (36.4)		103 (40.1)	
LACI	59 (15.0)		47 (18.3)	
POCI	73 (18.6)		58 (22.6)	
Haemorrhage	56 (14.2)		32 (12.5)	

*unpublished data

Table 2. Overview of questionnaires and data collected for stroke patients and age and gender matched participants from the HUNT3 study

Paper	I	II	III	
Participants	Stroke	Stroke	Stroke	HUNT3
Premorbid fatigue			x	
Fatigue				
FFS-7			x	
HUNT3-question			x	x
HRQoL				
EQ-5D-5L		x		
EQ-5D-VAS		x		
Depression HADS-D			x	x
Pain				
Pain questionnaire			x	
HUNT3-head, body				x
Comorbidity (listed in 3.3.1)			x	x

x data collected, reported in the results of the different papers

3.3 Measurements

An overview of data collected and used in the different papers is shown in Table 2.

3.3.1 Data collection for stroke patients

3.3.1.1 Data collection at baseline

The hospitals were contacted every second week and observation was performed if there were 2 or more eligible patients. At the day of observation the total number of patients admitted to the ward, number of stroke patients and nurses and nurse assistants were recorded. We also noticed if the wards had shared dining and living facilities outside the bedrooms and if the meals were served in the dining room or bedside for the included patients. The patients and the staff at the wards were informed about the monitoring throughout the day and that they should do nothing different on the day of observation. We also noticed if physical therapists (PTs) were available.

Demographic data on age, gender, residence, dependency and comorbidities (hypertension, heart failure, myocardial infarct, lung disease (including asthma and COPD), kidney disease, diabetes mellitus, cancer and connective tissue disease (including rheumatoid arthritis and spondylitis).

Pre-stroke fatigue was measured at inclusion retrospectively by two items: ‘Did you experience fatigue before you had your stroke’ (yes/no), and, ‘If yes, how long did you experience fatigue’ (less than a week, less than 3 months, 3–6 months and more than 6 months). Patients who reported fatigue lasting longer than 3 months before the stroke were defined as having pre-stroke fatigue in accordance with another stroke survey assessing pre-stroke fatigue (Lerdal et al., 2011).

The National Institute of Health Stroke Scale (NIHSS) assesses neurological function (or impairment) in patients with signs and symptoms of stroke in the acute phase, and may also be used to evaluate any signs of deterioration in the acute phase as well as outcome.

The NIHSS has been well validated and shown reliable both for physicians and for other health workers (Brott et al., 1989; Goldstein & Samsa, 1997). Further, NIHSS has established reliability and validity for use in prospective clinical trials, validity for predicting long-term outcome after stroke (Adams et al., 1999), and has shown an excellent inter- and intra-rater reliability with a weighted kappa of 0.93 and 0.95 (Goldstein & Samsa, 1997). Although later studies have shown that individual rating of some of the items may interfere with the overall result (Josephson et al., 2006), and a modified NIHSS scale has been developed (Meyer et al., 2002) the original NIHSS is recommended in clinical use, it is straightforward and takes only few minutes to perform with no need for additional equipment (Harrison et al., 2013). Most large trials and studies seem to choose NIHSS as a severity measure at stroke onset (AVERT, 2015; Berkhemer et al., 2015; Mullen et al., 2012).

The NIHSS neurologic examination includes 15 individual elements that measure motor and sensory function, language and speech production, vision, level of consciousness, attention, and neglect. The elements are summed to provide an overall assessment of stroke severity, with the score ranging from 0 to 42.

The NIHSS score strongly predicts the likelihood of a patient's recovery after stroke. A score of ≥16 is associated with a high probability of death or severe disability whereas a score of ≤6 forecasts a good recovery (Adams et al., 1999). However, NIHSS might underestimate impairment from posterior circulation strokes, which will lead to considerable disabilities (e.g. balance problems, truncal ataxia) (Martin-Schild et al., 2011).

NIHSS is now implemented as the scale of choice for estimating stroke severity at admission to hospital in all Norwegian Hospitals and is also reported to the Norwegian Stroke Registry (Helsedirektoratet, 2010; "Årsrapport Norsk hjerneslagregister 2013/Annual Report Norwegian Stroke Registry 2013," 2013).

Observational methods: For observation the method of Behavioural Mapping was used. The method was developed and tested in an acute stroke population and has been shown to be reliable and acceptable to stroke patients (Bernhardt et al., 2008; Bernhardt et al., 2004). Validity was not specifically examined in different papers on behavioural mapping, but the method is considered to have good face validity over short periods and is often used as a criterion measure to validate devices. Behavioural mapping over a single day has been shown to be valid in an acute setting as the behavior was very similar over 2 days (p 0.97) (Bernhardt et al., 2004). Inter-rater reliability of behavioural mapping studies are shown to be good, with most intraclass correlation coefficients (ICC) ranging over 0.8 for outcomes relating to location and interaction with others as well as time spent in specific activities. ICC comparing observation to a device (dual-axis accelerometer) also was fairly good with ICC in different positions as lying, sitting and upright varying from 0.68 to 0.74 (Kramer et al., 2013).

Observations were conducted every 10 minutes from 8 am to 5 pm on one single day or alternatively across two consecutive days. At each time point, the observer recorded patient activity, who was attending the patient, and the patient's location. When patients were out of view (e.g. in the bathroom or off ward), the patient or carer was contacted retrospectively and data were added if possible, or they were marked as not observed. The patients were observed for approximately 1 minute at each time point. If more than eight patients were eligible for inclusion, those with the shortest time from onset of stroke were prioritized for inclusion.

Categories of physical activity: At each observation, 12 prescribed activities could be recorded. More than one activity could be recorded at each observation. The 12 activities were 1) no active motor supine; 2) no active motor on left side; 3) no active motor on right side; 4) sit support in bed; 5) sit support out of bed; 6) transfer with hoist; 7) roll and sit up; 8) sit with NO support; 9) transfer with feet on floor; 10) standing; 11) walking; 12) stairs. For analyses 3 main activity categories were explored: In bed (activity 1, 2, 3 and 4), sitting out of bed (activity 5, 6, 7 and 8), and upright activity (activity 9 to 12) (Askim et al., 2012; Bernhardt et al., 2004).

Categories of location: 1. Bedroom, 2. On ward communal area (hall and patients lounge), 3. Therapy area, 4. Bathroom, 5.Off ward not observed (doctor's room, radiological imaging, Doppler, echo, and other)

Categories of people present: 1. Alone, 2. Nurse (nurse and/or nurse assistant), 3. Physical therapist (PT), 4. Family, and 5. Others

Time to first mobilization: Time to the first mobilization out of bed from hospital admission was registered prospectively. The nurses and PTs were asked to register time for first mobilization in their records before study onset, and this was also routine in many hospitals already.

3.3.1.2 Data collection and assessment tools at three months follow up:

Patients were contacted 3 months poststroke for follow-up assessment either in person or by telephone interview. Information about death was if possible intercepted through the patient record. Otherwise most of the patients who were dead before three months were discharged to nursing homes and information assessed from the nursing staff or from next of kin. For patients alive but not able to meet in person or answer a telephone call, information on functional status and living conditions was collected from next of kin, nursing staff or patient records.

Function and disability: The Rankin scale was developed in 1957 (Rankin, 1957) for assessment of stroke outcomes, and was modified in 1988 to improve its comprehensiveness (van Swieten et al., 1988). The modified version, or mRS, has ever since been commonly used to assess disability after a stroke, and can also be applied in the earliest stages after the acute event to define a baseline status and clinical decision-making such as to plan discharge destination and rehabilitative interventions and to measure improvement/deterioration in function over time. The mRS measures the disability component of ICF, including activity and participation (Kasner, 2006).

The modified Rankin Scale (mRS) is the most prevalent functional outcome measure in stroke trials and has been used in several studies. The mRS quantifies disability using an ordinal hierarchical grading from zero (no symptoms) to 5 (severe disability) with some adding a category of mRS 6 (death). Earlier studies have proven excellent construct and convergent validity of the scale (Banks & Marotta, 2007; Kwon et al., 2004). However, estimates of mRS reliability have been less favorable with substantial inter-observer variability (Quinn et al, 2009).

Table 3. Measurement tools used in this thesis, at baseline and 3-month follow up

Measurement	Purpose	Test parameters	Reliability	Validity	Paper/ time
National Institute of Health Stroke Scale (NIHSS)	To assess neurological impairment after stroke	Summary score of 15 individual elements measuring different aspects of bodily and cognitive impairment. Range 0-42	Test-retest reliability K= 0.93, stable stroke patients rerated at 3 months interval Inter-rater reliability K=0.95	Content validity: Most items measure what they are intended to do (Meyer et al., 2002) Predictive accuracy of outcome at 3 months =0.83 (Muir et al., 1996) However, for posterior infarction, NIHSS may underestimate impairment (Martin-Schild et al., 2011) NIHSS is sensitive to changes (Harrison et al., 2013)	I,II,III Baseline
The modified Rankin Scale (mRS)	Assess overall independence in stroke patients (or disability)	Degree of disability rated on a 0-6 scale. 0-2 is independent, 6 dead	Test retest reliability: _K =0.72 with reassessment at 3 months interval (video) Inter-rater reliability K =0.57 (moderate) different raters rating stroke of varying severity (Quinn et al., 2009) Face vs phone *k*=0.72-0.82 (Savio et al., 2013)	Criterion validity: Good agreement with other stroke scales and to stroke volume (infarct size)(J. L. Banks & Marotta, 2007) Excellent agreement with BI (r=-0.89) and FIM (r=-0.89) (Kwon et al. 2004) Content validity: There are evidence for the association between mRS and type of ischemic stroke and	I, II, III Pre-morbid, 3 months

				acute neurological impairment (Banks & Marotta, 2007) Not sensitive to small changes (Wade, 1992)	
HRQoL EQ-5D-5L	Assess Health related Quality of life. Generic		Test-retest reliability: Good with an ICC 0.75-0.81(with the exception of ICC 0.38 for pain in one period of three)(Hunger et al., 2012):	Validated for stroke patients Criterion validity : moderate to good compared to 3L Construct validity: moderate to strong correlations between 5L dimensions and mRS, BI (Golicki, Niewada, Buczek, et al., 2015)	II 3 months
EQ-VAS	Total perceived health		Test-retest reliability: Good ICC 0.67-0.81(Hunger et al., 2012)	Construct validity: moderate to strong BI vs EQ-VAS 0.43-0.86 (Spearman correlation coeffsient)	II 3 months
Fatigue FSS-7	Assess perception of fatigue. Commonly used in patients with neurological symptoms	Scores 7 items of experienced fatigue in a 7 point Likert scale. Scores 7 to 49, ≥ 28 fatigue	Cronbach's alpha for the person-reliability FSS-7 varied between 0.87 and 0.93 at four measurement times (compared to FS-36) (Lerdal & Kottorp, 2011)	Criterion (concurrent) validity: The Rasch-equivalent Cronbach's alpha statistic was calculated as 0.91, compared with SF-36 vitality scores at 4 measurement times (Lerdal & Kottorp, 2011)	III 3 months

HUNT3 fatigue questionnaire	Assess fatigue	One question, 7 response categories	Not tested	Not tested	III 3 months
Pain					
a.First question from the Brief Pain Inventory Short form b.One question about new pain after stroke	Assess pain or not pain	Yes or no. a.One question about present pain b. one question if this is new pain after stroke onset	Not tested. Only tested for the numeric scales which we did not use (Cleeland & Ryan, 1994).	Not tested. Only tested for the numeric scales which we did not use (Cleeland & Ryan, 1994)	III 3 months
HADS-D	Screening depression prevalence. Generic.	7 items scored 0-3, HADS-D score ≥ 8 depression	Test-retest reliability, few studies, one recent among cognitive intact nursing-home residents (Haugan & Drageset, 2014), show good for most of the items except HADS-D 8 and 10 and R^2= 0.38-0.62 for the rest, but overall composite reliability (different dimensions scored) was 0.76 and 0.69 respectively, means the internal consistency is good.	Construct validity: Review (stroke patients) 2002 Cronbach's alpha for HADS-D varied from 0.67-0.90 (mean 0.82). The sensitivity and specificity for HADS-D of approximately 0.80 were very similar to the sensitivity and specificity achieved by the General Health Questionnaire. Correlations between HADS and other commonly used questionnaires were in the range 0.49 to 0.83 (Bjelland et al., 2002).	III 3 months

Abbreviations: K, Kappa; ICC, Intraclass correlation coefficient; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale; NIHSS, National Institutes of Health Stroke Scale; mRS, The modified Rankin Scale; r, Spearman correlation coefficient; BI, Barthel Index; FIM, Functional Independence Measures; HRQoL, Health related quality of life; EQ-5D-5L, EuroQol 5Dimension 5Levels scale; EQ-VAS, EuroQol Visual Analog Scale; HUNT3, Helseundersøkelsen i Nord-Trøndelag del 3; FSS7, Fatigue Severity Scale 7 item version; BI, Barthel Index, SF-36, Short-Form Health Survey; R^2, Squared multiple correlations

There are several studies assessing inter-observer reliability that have been found to show substantial variability (Wilson et al., 2005) even if a structured interview of the patient or carer is applied. Quinn et al. found that agreement was moderate (k=0.57). Intra-observer variability was good (k=0.72) but less than expected from previous literature (Quinn et al., 2009). Measuring the mRS by telephone with the structured interview has provided good agreement compared to face-to-face interview with weighted k=0.82 (Savio et al., 2013) and k=0.71 (Janssen et al., 2010) (The latter in subarachnoid hemorrhage patients).

Health Related Quality of Life Questionnaire:

European Quality of Life Questionnaire (EQ-5D) (Golicki, Niewada, Karlinska et al., 2015; Torrance etal., 1995) is an internationally developed, generic index used to assess HRQoL. “EQ-5D™ is a standardized instrument for use as a measure of health outcome” (EuroQol, 2015) and measures aspects of quality of life that are highly relevant for stroke patients. It was developed to evaluate HRQoL in the general population, but appears to be valid also in stroke patients (Dorman et al., 1997; Golicki, Niewada, Buczek, et al., 2015). A new version of the EQ-5D was developed and tested recently to reduce ceiling effect observed in the earlier EQ-5D-3-level version (Herdman et al., 2011).The EQ-5D-5L index, based on the crosswalk value set, is shown to be appropriately responsive in patients with stroke, the corresponding EQ-VAS showed a bit less responsiveness (Golicki, Niewada, Karlinska, et al., 2014). The test-retest reliability is rated good for both EQ-5D and EQ-VAS (Hunger et al., 2012). The EQ-5D-5L is also applicable for telephone interview (EuroQolGroup, 2015), and is shown to have good measurement properties with lower ceiling effect and better discriminatory power than EQ-5D-3L also applied by telephone in different patient populations (Agborsangaya et al., 2014).

The questionnaire consists of two parts. The first part; EQ-5 Dimension-5 Level (EQ-5D-5L) assesses HRQoL in five dimensions: mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Each dimension scores on five levels reflecting five levels of difficulty in each; 1 = I have no problem with performing the activity; 2= I have some problems with performing the activity, 3=I have moderate problems with performing the activity, 4= I have severe problems with performing the activity, and 5=I am unable to perform the activity. These ratings are combined into a 5-digit response rate, which is converted to an index value in a value set developed by the EuroQol Group. There are value sets developed for approximately 10 countries, but not for Norway. We chose to use the Danish value set, because this will presumably be most close to the Norwegian society. The index value indicating best health is 1.000 (digit combination 11111), and the worse index-value in this set is -0.624 (digit combination 55555). The number 0 indicates "dead"; however because we only used self-rating and not proxies, this is not used in our study. In concordance with the EQ-5D-5L we used a Visual Analogue Scale (EQ-VAS). The patients rate their own health in a range from 0 to 100 (0 = worst health and 100 = best health).

Fatigue: Because of the subjective character of fatigue, and the fact that no objective signs have been identified, self- report is considered the most valid way to measure fatigue.

There are several fatigue questionnaires developed to measure fatigue experienced and our choice of fatigue questionnaires was based on earlier studies performed, and psychometric properties for use in stroke patients and the aim of comparing PSF with the HUNT3-participants. In our study three questionnaires were applied.

At 3-month follow-up the Fatigue Severity Scale (FSS-7) was applied in the stroke cohort. The 9-item FSS is the most commonly used scale to measure fatigue in stroke patients (Lerdal et al., 2009; Naess et al., 2006; van de Port et al., 2007). Nevertheless, the shorter 7-item version of FSS, FSS-7, has shown better psychometric properties in patients with stroke than the original 9-item version (Lerdal et al., 2005), and we considered FSS-7 the most suitable questionnaire. Scores from the 7-point Likert scale response options were averaged to yield a score from 1 to 7, where higher scores indicate higher fatigue levels. Most studies recommend a cut-off score of ≥ 4.0 as indicative of fatigue (Lerdal et al., 2005).

Finally, the same fatigue question as used in the HUNT3-survey was applied (HUNT, 2015). This question is to our knowledge not validated in stroke patients or other population groups. The single question was: "Do you feel, for the most part, strong and fit or tired and worn out?". There were seven response categories, which ranged from "very fit and healthy" to "very tired and worn out", with the middle option as neutral. Since there is no former definition of fatigue for this questionnaire, we chose to define fatigue as a score ≥ 5, since this value represents the mildest value of feeling tired and worn out most of the time. These results could be compared directly with the HUNT3 population.

Depression screening poststroke: Depression was assessed by Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). The validity for HADS to detect PSD was rated as good in two recent studies (Kang, 2013; A. Turner et al., 2012). HADS is a very common mood screening instrument and was also applied among the HUNT3 participants, making it possible to compare prevalence of depression in both groups. HADS is a self-assessment questionnaire, and can also be administered verbally. It has also been applied by telephone in several studies; however, validation for telephone application seems to be lacking. HADS comprises 2 subscales, HADS-anxiety and HADS-depression (HADS-D) each with 7 items scored from 0 *(*no symptoms) to 3 (maximum impairment), considering emotional state over the last 7 days. The scores are summed to give a total score ranging from 0 – 21 in each subscale. Recommended diagnostic thresholds are ≥ 8 for doubtful cases and

≥11 for definite cases for each subscale (Zigmond & Snaith, 1983). We used a cut-off of 8 for caseness.

Pain: No specific pain questionnaire has been developed for stroke patients; however, for patients with cognitive or language problems who are not able to self-rate pain, several observational tools have been developed to measure pain (Husebo et al., 2010; Torvik et al., 2010). Because we used a telephone interview and people need to be able to answer questions by telephone, we had to use simple questions to assess pain. Two simple questions were asked: "Throughout life we experience pain such toothache, light headache and so on, do you experience pain other than this everyday pain?", and "Is the pain experienced new after stroke onset?". The response categories for both questions were yes or no. The first question was adapted from the Brief Pain Inventory Short Form (Cleeland & Ryan, 1994). There is no validation or reliability testing for the single questions available. However, the numeric scales of the Brief Pain Inventory, which we did not use, have been tested for psychometric properties such as validity and reliability across different languages and show high reliability and validity (Kumar, 2011) .

3.3.2 Data collected from the HUNT3 Survey

Data collected from the HUNT-3 survey population were age, gender, fatigue question and HADS-D, and information about comorbidities such as hypertension, heart failure, myocardial infarct, lung disease (including asthma and chronic obstructive pulmonary disease), kidney disease, diabetes mellitus, cancer and connective tissue disease (including rheumatoid arthritis and spondylitis).

3.4 Statistics

3.4.1 Estimation of power (only for comparison of the fatigue groups).

Paper III. When looking at the outcome for the fatigue question, we estimated fatigue in the general group of 25% as an average, and fatigue among stroke patients varying from 30% to more than 50%, then estimated that with 90% power, and a significance of 5% we needed approximately 200 patients in each group.

3.4.2 Baseline data processing and analysis (all papers)

Demographic data: Descriptive statistics were used to report the mean and proportion of baseline variables, the distribution of the mRS score before onset of stroke and at baseline,.

Behavioural Mapping data: The highest level of activity in every 10-min interval was recorded in the database (Microsoft Access 2007). The recorded activity levels were put into one of the three pre-defined categories, and the proportion of time spent in each category was calculated.

When patients were not able to be directly observed for 1-2 observations due to privacy, eg patients were in the bathroom, missing activity data were imputed and activity classed as sitting out of bed. If more than two observations were missing it was maintained as not observed. Missing activity data because of CT/MR scan or because the patient was undergoing ultrasound of heart and blood vessels or in the doctor's room were also imputed as in bed as patients are required to lie flat for these procedures. All other occasions of 'not observed' were recorded as missing.

When time from admission to first mobilization was missing, this was imputed as the time from admission to the end of observation.

Descriptive statistics were used to report the mean and 95% confidence intervals (CIs) in each motor activity category.

3.4.3 Analyses of each paper

Paper I

The Kruskal-Wallis nonparametric test was used to compare differences in variables between hospitals.

A mixed logistic regression model was used to determine which of the independent variables were associated with activity levels. The independent variables tested were (1) nurse:patient ratio (the number of nurses divided by the total number of patients admitted at the day of observation); (2) number of stroke patients treated per year in each hospital; (3) if the meals were served in communal areas or not; and the amount of time spent with (4) a nurse/nurse assistant, (5) a PT, and (6) a family member. Patient ID and hospital ID were included as random effects in the mixed logistic regression model. Three models were tested with time spent in upright activity, sitting out of bed, and in bed as dependent variables. All analyses were adjusted for age and stroke severity.

General linear mixed model analysis was used to assess the association between high activity level and nurse per patient, nurse with patient, PT and PT in team with patient, number of stroke patients treated per year in each hospital, and if the meals were served in the dining areas or not for the mobilized patients.

Paper II

Descriptive statistics were used to report the mRS score and the EQ-5D-5L at 3-month follow-up. T-test statistics and Mann-Whitney U test were used to compare mean and median between the subgroups answering and not answering EQ-5D-5L at follow-up.

To determine which variable was the strongest predictor for good functional outcome (mRS at three months) among a set of possibly correlated variables, we used the proportional odds model recommended by the OAST collaboration (Williams, 2006). In the proportional odds model, the odds ratios (ORs) are assumed to be equivalent across all mRS cut-points (for example 0 versus 1-6, then 0-1 versus 2-6, and so on). This is a straightforward generalization of the logistic regression model. We used the 'Brant test' to analyze if this assumption was fulfilled.

To determine the strongest predictor for good HRQoL (EQ-5D-5L and EQ-VAS), a linear regression model was used. The standardized residuals of EQ-VAS and EQ-index were normally distributed except for a few outliers of EQ index value.

The independent variables of interest were: (i) time spent in bed, (ii) time spent sitting out of bed, (iii) time spent in upright activity and (iv) time from admission to first mobilization. Age, NIHSS score, premorbid mRS, gender, and hospital site were added as covariates. The independent variables were tested in both one simple and one comprehensive multivariable model. In the simple model, each independent variable was evaluated one at a time. In the comprehensive model, time in bed and time upright were entered simultaneously and the third category (time sitting out of bed) was kept out of the analysis because it is co-dependent on the other two activity categories. This means that changes in one activity category keeping the second category constant were at the expense of sitting out of bed, which was not added to the model. Time to first mobilization was also entered in the comprehensive model.

Paper III

Stroke patients were matched by age (up to a maximum of 2 years difference) and gender to respondents from the HUNT3 survey (HUNT.) who had all the outcome measures of interest to this study and no history of previous stroke. The HUNT participant of the same gender with the closest age (in 0.1 year increments) to each stroke participant was selected, with the matching procedure carried out blinded to any other outcome measure. The number of participants with available data determined the sample size for the study.

FSS scores from the 7-point Likert scale response options were averaged to yield a score from 1 to 7. The FSS-7 questionnaires were excluded if fewer than 4 items were answered. For FSS-7, imputation was done for four questionnaires.

Fatigue prevalence was examined in both groups using the HUNT3-survey questionnaire. The proportion of participants from each group reporting fatigue ≥ 5 on this question was compared using the chi-square test. Fatigue prevalence among the stroke patients was also reported using the FSS-7 with cut-off of ≥ 4.0.

The association between early motor activity and post-stroke fatigue was tested using logistic regression models with fatigue dichotomized using FSS-7 score ≥ 4.0. Proportion of daytime in bed, sitting out of bed and upright were each tested in separate simple models. Stroke severity (NIHSS score) and pre-stroke function (mRS) were included as covariates. A single comprehensive multivariable logistic regression model also including HADS-D score, pain, pre-stroke fatigue, age and gender as additional independent variables was also examined. In this model, both time in bed and time upright were included, but time sitting out of bed was excluded as it is co-dependent on the other two activity categories.

3.5 Ethical considerations

The LEAST study was approved by the Regional Committee of Medical and Health Research Ethics (REC no 2011/1428) and the HUNT3 survey as a part of it (REC midt no 2012/675).

The observational method had been used in different studies across the world and was also tested in previous studies at St. Olavs Hospital, showing that the approach was very feasible (Askim et al., 2012; Bernhardt et al., 2008; Wellwood et al., 2009).

It has been shown that severely affected stroke patients also benefit from early mobilisation, but since the optimal time for first mobilisation and subsequent rehabilitation is still not clear, it was important to include patients with all severities in this study.

Informed consent was obtained from those able to agree. Some of the most severely affected patients were not be able to sign the informed consent because of unconsciousness or aphasia. and for those not able to consent we asked REC for permission to inform their next of kin and included the patients if the next of kin gave their consent. However, patients were able to withdraw from the study at any time and to have their data deleted.

The most possible harmful effect in the present study was that some of the patients could experience the observation every 10 minutes as a strain. To decrease this strain, the observer acted as discreetly as possible and protected privacy by not observing when the patient was behind a locked door in the bathroom, in the doctor's room, or in other places associated with a need for privacy.

At the 3-month follow-up in person or by phone, many of the participants commented that they appreciated talking about their experience and feelings after the stroke. A few did not want to answer all the questionnaires and this was respected.

4 Results and summary of papers

4.1 Paper I

Hospital differences in activity levels early after stroke. A Comparison of 11 Norwegian stroke units.

Early rehabilitation is recommended in most guidelines on acute stroke treatment. Activity levels in patients early after stroke vary across the world. The primary aim of this study was to assess the variation in motor activity in patients admitted to multiple Norwegian stroke units and to identify factors which explained the variation between hospitals.

A prospective observational study including patients from 11 Norwegian hospitals was conducted. Eligible patients were those <14 days post-stroke, >18 years, not receiving palliative care. Activity levels, people present, and location were recorded by use of a standard method of observation between 8 a.m. and 5 p.m. Hospital policy on serving meals in communal areas was also registered. A mixed general binominal model was used to analyse which factors explained variation in activity levels between hospitals, after adjusting for age and stroke severity.

A total of 393 patients from 11 stroke units were included. The patients spent 44.1% of the day in bed, 43.2% sitting out of bed, 8.3 % in higher motor activities (4.4% was not observed). Patients also spent 74.4% of their day in their bedroom, 14.0 % of their day in communal areas, 2.7 % of their day in the bathroom and 2.7 % of their day in therapy areas. They spent 55.9 % of the daytime alone. Nurses were present 14.9% of the daytime, and 3.3 % was spent with a physical therapist.

Increased physical activity was associated with spending more time with a physical therapist, OR 1.05 (95% CI 1.03-1.08, $p < 0.001$) and being admitted to a hospital serving the meals in communal areas, OR 1.46 (95% CI 1.09 -1.95, $p=0.011$). Spending time with a nurse did not increase physical activity levels, but was associated with more time in sitting out of bed OR 1.02 (95% CI 1.00 to-1.03, p=0.018).

In conclusion; despite variation between the hospitals, patients admitted to Norwegian stroke units spend most of the day out of bed. Time spent with a physical therapist and hospitals having a policy of serving meals in communal areas explained most of the variation in activity between hospitals.

4.2 Paper II

Upright activity within the first week after stroke is associated with better functional outcome and health related quality of life. Results from a Norwegian multi-site study

Early rehabilitation with a focus on mobilization and increased physical activity probably contributes to better outcome after stroke. The aim of this study was to assess the amount of physical activity early after stroke and its association with functional outcome and health related quality of life (HRQoL) three months later.

This was a prospective observational study. Patients were recruited from 11 Norwegian stroke units. All patients <14 days poststroke were eligible, except those receiving palliative care. Time spent in different activity categories (in bed, sitting out of bed, upright) was recorded using a standard method of observation. Outcome was assessed by modified Rankin Scale (mRS), and health-related quality of life by EuroQol-5 dimension 5 level (EQ-5D-5L) three months later. A partial proportional odds model was used to analyze the association between motor activity and mRS, while linear regression analysis was used to analyze the association between motor activity and the EQ-5D-5L. For analysis, EQ-5D-5L was converted to an EQ-index value. The independent variables were tested in both one simple and one comprehensive multivariable model. In the simple model, each independent variable was evaluated one at a time. In the comprehensive model, time in bed and time upright were entered simultaneously and the third category (time sitting out of bed) was kept out of the analysis because it is co-dependent on the other two activity categories. Time to first mobilization was also entered in the comprehensive model. The analyses were adjusted for age, sex, pre-stroke function obtained by mRS and stroke severity obtained by National Institutes of Stroke Scale and hospital site.

A total of 390 patients (mean age 76.8 years, 48.1% male) were included. In the simple multivariate model, the OR for poorer functional outcome (e.g. higher mRS score) was 0.96 (95 % CI 0.94 to 0.99, p=0.010) as time in upright activity increased, and in the comprehensive multivariate model the odds for poorer functional outcome decreased as time in upright increased, OR 0.97 (95% CI: 0.94 to 1.00, p=0.048) . There was also a significant positive association between time in upright activity and higher EQ index three months later for both the simple multivariate model, Beta 0.178 (95% CI 0.067 to 0.289, p 0.002) and in the comprehensive multivariate model, Beta 0.184 (95% CI: 0.055 to 0.312, p=0.005). The same associations were found between time in upright activity and EQ-VAS with Beta 0.185 (95% CI 0.060 to 0.307, p=0.004) in the simple multivariate model, and Beta 0.153 (95% CI 0.008 to 0.294, p=0.038) in the complex multivariate model.

In conclusion more time in upright activity early after stroke was associated with better functional outcome and health-related quality of life 3 months later. These results confirm that the amount of upright activity early after stroke is important.

4.3 Paper III

Prevalence of fatigue in patients 3 months after stroke and association with early motor activity: A prospective study comparing stroke patients with a matched general population cohort

Fatigue is a common complaint post-stroke. Reasons for higher prevalence are still unclear. This study aimed to determine if fatigue prevalence in stroke patients is different to that of age- and gender-matched general population controls, and to explore whether early motor activity after stroke was associated with reduced likelihood of fatigue at 3 months post stroke.

This was a prospective cohort study of stroke patients admitted to 11 regional Norwegian hospitals, within 14 days post-stroke. Stroke patients (n=257) were age- and gender-matched to participants in a general population health survey (HUNT3 survey) carried out in a regional county of central Norway. The single-item fatigue questionnaire from the HUNT3 survey was administered to both groups to compare prevalence. The association between early motor activity (*time in bed, time sitting out of bed*, and *time upright)* and fatigue at 3 months post-stroke (Fatigue Severity Scale) was tested with logistic regression. Simple models including each activity outcome in turn, with adjustment for stroke severity and pre-stroke function, were tested, as well as a comprehensive model that included additional independent variables of depression, pain, pre-stroke fatigue, age and gender.

Prevalence was higher post-stroke compared with the general population: 31.1% versus 10.9%. In the simple regression models, none of the early motor activity categories was associated with fatigue at 3 months post-stroke. In the comprehensive model, depression, pain and pre-stroke fatigue were significantly associated with post-stroke fatigue. Time in bed through the daytime during hospital stay almost reached statistical significance (p=0.058) with an odds ratio for experiencing fatigue of 1.02 (95% CI 1.00-1.04) for each additional 5.4 minutes in bed.

In conclusion, stroke patients have higher prevalence of fatigue 3 months after stroke than the age- and gender-matched general population, which may be partly explained by the stroke population being in poorer health overall. The relationship between early motor activity and inactivity remains unclear and further research which may help drive development of new treatments to target this challenging condition is needed.

5 Discussion

5.1 Main findings

In the present thesis we wanted to explore different aspects of early rehabilitation after stroke and relation to functional outcome, HRQoL and fatigue 3 months later.

Firstly, this thesis has found that amount of activity differs significantly between the participating Norwegian stroke units. These differences could be explained by differences in the policy of serving meals in communal areas or in the bedroom, and the amount of time spent with a physical therapist.

We also have shown that more time in higher motor activity early after stroke was associated with better functional outcome and health-related quality of life 3 months later. Time to first mobilization after hospital admission did not show any association with either of the outcomes.

Finally, we showed that fatigue was prevalent in stroke patients, and this was related in particular to experienced pre-stroke fatigue, pain after stroke, and depression. There was also a trend toward more fatigue with more time spent in bed, but it did not reach statistical significance. The prevalence of fatigue among the stroke patients was approximately 3 times higher than in an age- and gender-matched general population from the HUNT3 survey.

5.2 General methodological considerations

5.2.1 Internal validity of a study

Internal validity is the degree to which observed changes in a dependent variable can be attributed to changes in an independent variable or to what extent the results are representative for the cohort studied. First, the study design is important, where RCTs are considered to have greater strength because any confounding factors are minimized (Concato, 2013; Juni et al., 2001). The study may be affected by random and systematic bias or errors. Random error is due to chance and can be minimized by larger sample size. Selection bias not at random is related to, for instance, more affected participants included than those eligible (Tripepi et al., 2010). Missing data and confounding factors (Skelly et al., 2012) are also possible sources of bias that may be a threat to the internal validity of a study.

5.2.1.1 Stroke patients

Study design: Generally every research method will have strengths and weaknesses (Concato, 2013). The LEAST study was a prospective observational study. The patients were assessed for functional level and stroke severity at inclusion, then observed for an exposure (here activity levels). Outcome was then collected after the exposure. In this case we did not have a control group. The controls are the patients themselves, but they were compared according to the differences in activity levels, holding known confounders constant.

A limitation of an observational study is that it is not possible to adjust for all confounders. It is possible to claim that the most active patients are more active because the strokes were milder and they did not have stroke-related complications in the acute phase, or the patients were healthier before the stroke, and that this was the true predictor of outcome at 3 months, and not the activity level by itself.

Another limitation of this study was that some of the hospitals were quite small, and very few patients were included, which may give a bias in activity levels between the hospitals, even if there were no significant differences in NIHSS, premorbid mRS, mRS at inclusion or days since stroke between the hospitals. Differences in number of staff per patient may also influence activity levels. Off ward activity may also represent a bias, since those on home visits and off ward other than for therapy/investigation probably achieve more upright activity.

However, even if an observational study method is weaker than a RCT, the strength of our study was the broad enrollment criteria with a fairly large cohort covering a wide range of neurological impairment.(Berger et al., 2012).

Selection: Patients in the present study were included prospectively, and at each hospital at least two eligible patients were needed for the observer to perform the observation.

Thus some patients were lost because only one acute stroke patient was admitted in the week assigned for observation and no observation was performed.

There also might be a selection bias where patients with very mild strokes were not included, because they were more likely to be discharged earlier from hospital than those with moderate and severe strokes. Data from the patient-reported outcome questionnaires were not missing at random because the more severely affected patients were more likely to be missing questionnaire data both at inclusion and at three-month follow-up. This may lead to an underestimation of the results for overall perception of fatigue, since more affected patients may have more comorbidities, which may lead to increased fatigue perception even if the relation is not clear (Appelros, 2006; Choi-Kwon et al., 2005). However, higher level of disability is clearly related to reduced HRQoL (Harrison et al., 2013), and this will more clearly represent a bias toward better HRQoL.

All severity groups were included if consent was provided, and also the most severe stroke patients when consent was received from next of kin. The only patients not eligible for inclusion were those who were on palliative treatment or who were not Norwegian speaking. All diagnoses were checked from the patient's record to verify the stroke diagnosis and 16 patients were later excluded because their symptoms and findings were due to other diagnoses mimicking stroke (e.g. epileptic seizure, infections and stroke sequel, and stroke symptoms interpreted as TIA). The few mimics in our study probably reflect that most patients had a verified diagnosis at inclusion. On the other hand, we might have lost a few patients with transient symptoms regarded as stroke mimics, but most of those would have been classified as TIAs and were then not eligible.

The major strength was the large sample size including almost 400 patients from 11 Norwegian stroke units and the naturalistic study design investigating clinical practice as usual. The study sample seems to be slightly older, with more severe strokes, compared to the average Norwegian stroke population ("Årsrapport Norsk hjerneslagregister 2013/Annual Report Norwegian Stroke Registry 2013," 2014).

Observation of early activity : The patients were observed using the method of Behavioural Mapping described in section 3.3.1. The observational method has been shown to be both valid and reliable (Kramer et al., 2013; West & Bernhardt, 2012).

Observation could of course be a bias to mobilize the patients more, but our subjective impression was that the staff became used to the observers and continued with their clinical practice as usual. Additionally, the observers tried to be very discreet.

Even though the amount of missing data was very small, the most common reason for missing was off-ward activity. Because off-ward activity such as home visits is likely to be upright activity, this limitation represent a risk of underestimation of upright activities, and in future research one might consider imputing missing values from home visits as upright activity.

The imputation of missing values may represent a bias. The rules for imputation were conservative, increasing the risk of underestimating upright activity. However, out of 21615 observations, only 614 observations were imputed, representing 2.8 % of all observations, and the influence on the final results probably is very small if any.

Another limitation was the lack of observation of patients from 5 pm to 8 am next morning. However, the time from 8 am to 5 pm is regarded as the most active time of the day with the highest number of nurses and therapists present at the ward.

However, the strength of the observation method of Behavioural Mapping to measure the amount of motor activity is that it is a well-documented method, which has shown good correlation with accelerometer devices (Kramer et al., 2013). However, a body-worn sensor system might be an alternative method to investigate how physical activity changes across multiple days during hospital stay in future research.

Confounding factors

Confounding factors are a challenge in observational studies and may obscure the association between exposure and outcome. A confounder is a variable that has an association with both exposure and outcome (Jager et al., 2008).

Known cofounding factors in stroke research are age, sex, stroke severity and also pre-stroke function (Bhalla et al., 2013; Lai et al., 2005) . However, a limitation may be that important confounding variables in addition to those listed above may be missing from the regression models such as cognitive function, medications and sleep disorders (Kluger et al., 2013).

In **Paper I** we adjusted for possible confounding factors in activity levels including hospital ID, patient ID, age and stroke severity, in a mixed logistic regression model. In this model sex and pre-stroke function were not adjusted for because they had no additional effect in the model when age and stroke severity were added.

In **Paper II** and **Paper III** the evaluation of outcome was done 3 months later and may represent a bias because of unknown confounders such as stroke complications, rehabilitation training, exposure to diseases and natural history of recovery that may differ between individuals.

Comorbidity might also represent a confounding factor. However, a recent validation of the Charlson Comorbidity Index (which includes a number of common diseases like heart disease, diabetes mellitus, COPD and cancer) as a predictor for short-term outcome (1 month poststroke) found that the index did not give any additional prediction of outcome when adjusted for stroke severity at baseline, and functional disability pre-stroke (Denti et al., 2015). The analyses in paper II and III were adjusted for these variables.

In conclusion, this is an observational study and the internal validity might be lower than for a randomized trial; however, the study is well designed with many patients who are representative for the stroke patients admitted to Norwegian hospitals. The observational method is also well documented and we generally judge the study to have high internal validity.

5.2.1.2 The HUNT3 survey cohort

Selection

The final cohort from the HUNT3 study was age- and gender-matched to the stroke patients. The nonparticipants in the HUNT3 survey generally had lower socioeconomic status, higher mortality and higher prevalence of several chronic diseases, whilst opposite patterns were found for common problems such as musculoskeletal pain, urinary incontinence and headache. This may represent a bias to frequencies of fatigue and other comorbidities extracted in our analyses (Langhammer et al., 2012) .

5.2.2. Reliability and validity of assessment and assessment tools

Aspects of reliability and validity must be considered when choosing an appropriate questionnaire or measurement tool.

All measurement tools in clinical research should satisfy basic properties such as validity, reliability, sensitivity and responsiveness if they are to be clinically useful.

5.2.2.1 Reliability

Test-retest reliability is a measure of reliability obtained by administering the same test twice over a period of time to a group of individuals. For developing an instrument, usual stable patients are measured at different time-points. The scores from Time 1 and Time 2 can then be correlated in order to evaluate the test for stability over time. For self-assessment tools, the test-retest reliability is most important (Machin, 2007).

Inter-rater reliability is a measure of reliability used to assess the degree to which different raters agree in their assessment decisions. Inter-rater reliability is useful because human observers will not necessarily interpret answers the same way; raters may disagree as to how well certain responses or material demonstrate knowledge of the construct or skill being assessed (Mokkink et al., 2010).

5.2.2.2 Validity

Validity of measurement tools refers to whether the instrument actually measures what it is intended to measure. There are different kinds of validity. Validity for measurement tools can be subdivided into three main aspects (Mokkink et al., 2010).

(1) Content validity may be important when assessing a construct with many issues, for instance HRQoL, to ensure that it is sensible and covers the most relevant issues. *Face validity* is closely related to content validity. For instance, when fatigue is measured among stroke patients, a question such as "do you have problems with finding the right word?", which is an example of an item from the Chalder fatigue scale, probably does not measure fatigue, but mirrors problems with cognition or aphasia, which are common problems poststroke (Mokkink et al., 2010).

(2) Criterion-related validity usually includes any validity strategies that focus on the correlation of the test being validated with some well-respected outside measure(s) of the same objectives or specifications (Mokkink et al., 2010).

(3) Construct validity is one of the most important characteristics of a measurement tool. It assesses the degree to which an instrument measures the construct it was designed to measure (Mokkink et al., 2010).

5.2.2.3 Sensitivity and responsiveness

The final important property of a measurement instrument is the sensitivity to detect a change or the responsiveness when a patient's condition changes responsiveness is defined as "*the ability of an instrument to detect change over time in the construct to be measured*" (Mokkink et al., 2010). Responsiveness can be considered an aspect of validity or the validity to change in score (Guyatt et al., 1987).

5.2.3 Observer assessment

<u>Behavioural mapping:</u> The 4 observers in this study were health workers who were trained to excellent agreement by observing the same patients at the same time and discussing observation measures before performing the observation alone. The activity category we found most challenging to agree on was whether the patient was sitting with or without support out of bed; however, this problem was resolved by merging the two categories into one sitting out of bed category. This is also in agreement with how earlier mapping studies have analyzed their data. As mentioned in section 3.3, the validity of the observational

method is not examined in earlier studies of behavioural mapping, but is considered to have good face validity.

NIHSS and mRS: A similar procedure was used for the agreement on rating of NIHSS and mRS to reduce possible inter-rater bias, and we tried to make this bias as small as possible by discussing problem cases when we were uncertain. As mentioned in the method, the NIHSS (Brott et al., 1989) has been well validated and shown to be reliable both for physicians and other health workers (Goldstein & Samsa, 1997) and is commonly used in both clinical and research settings. There will always be small inter-rater disagreements, but most likely this will not represent a problem and will be offset on a group level.

mRS: was assessed by interview in person, by phone (patient or carer) or in a few circumstances using patient records. mRS is well validated against other outcome measures for stroke (Kwon et al., 2004); however, mRS is not as robust as NIHSS on inter-rater reliability, and the interpretation will of course represent a bias (Harrison et al., 2013). Even though disagreement on interpretation was discussed between the raters, there was a possibility for misclassification. When patients were able to answer, it was probably easier to classify them correctly. For those not able to answer or only using patient record, probably misclassification would cause a bias toward worse outcome. For instance, a person in a nursing home in Norway will normally need full time nursing and cannot stay alone during the daytime, and will also need to be looked after at night, and will then be classified as mRS 5. However, in a few circumstances some nursing home residents will be able to stay alone for some hours during the daytime because they are able to ring a bell, even if they are not able to answer a telephone interview, and they may then have been misclassified as an mRS 5.

The follow-up procedure where all patients were contacted in person or by phone if possible and the use of proxies ensured a high response rate, particularly for mRS.

5.2.4 Self-reported assessment questionnaires

The main outcomes in this thesis except for mRS were patient-reported outcome measures assessed in person or by telephone interviews. Some of the questionnaires such as HUNT3 fatigue questions and FSS7 were not validated for telephone interview and this might represent a bias. Patients were also able to answer the questionnaires to varying degrees due to cognitive impairment, reduced hearing ability, aphasia or other illness.

About 40% of stroke patients will experience cognitive problems including aphasia. This may influence the patients' ability to understand and answer questions and questionnaires. A review from Pendlebury et al. 2009 found that 10% of stroke patients suffered from dementia pre-stroke. Poststroke, an additional 10% suffered from dementia, and the rate was higher for recurrent strokes (Pendlebury & Rothwell, 2009).

Patients with mild aphasia and cognitive problems were possible to interview face to face, but for some of those who were not able to answer by telephone, we were not able to get patient-reported information and only information about disability was received from a carer. Aphasia patients may have problems with abstract topics, numbers and communication in general (Mazaux et al., 2013). This was also obvious for some of those with cognitive problems, and our experience was that especially questions using a Likert scale or a numeric scale were difficult when patients had lowered cognitive function and language problems.

Health-related quality of life: There are several instruments designed to measure HRQoL; some are generic and developed for use in general populations, while others are disease specific. We choose to use the EQ-5D-5L including the EQ-VAS since this is a commonly used instrument in many studies, and is also validated for use among stroke patients (Golicki, Niewada, Buczek, et al., 2015). It has shown good criterion validity and test-retest reliability (Hunger et al., 2012). It is also applicable by telephone interview (EuroQol, 2015). However, patients need to have adequate communicative skills and cognitive function for the administration of either EQ-5D-5L and EQ-VAS, as well as most other HRQoL scales. People with mild to moderate dementia have been shown to be able to rate their own HRQoL with the EQ-5D (Orgeta et al., 2015), although there are indications of a small ceiling effect, EQ-5D should be applicable also for people with mild dementia, which will affect many stroke patients (Hounsome et al., 2011). However, the VAS scale has been shown to have poor reliability also in mild dementia (Hounsome et al., 2011).

The patients in our study (**Paper II)** present their HRQoL in line with other studies in stroke populations, despite somewhat lower function measured by mRS. We also observed a ceiling effect on EQ-5D-5L, but this is also obvious for studies in the general populations and other patient populations.

EQ-5D has been shown to have a strong association with mRS, and mRS has been shown to capture more information on HRQoL than the NIHSS and Barthel Index; mRS thus provides an indicator of patients' overall HRQoL (Ali et al., 2013). However, the study showed more mismatches for good outcome and poor HRQoL than vice versa, probably meaning that the HRQoL assessments also capture aspects of stroke recovery over the information gathered by standard outcome measures.

<u>Fatigue:</u> Fatigue or perception of fatigue is a difficult construct to evaluate. Studies of post-stroke fatigue are all limited by the multidimensional nature of fatigue and the inadequacies of the fatigue scale used. Unfortunately pre-stroke fatigue was measured with a different questionnaire to post-stroke fatigue, and early post-stroke fatigue was not measured. For the

stroke cohort we applied the FSS-7 questionnaire, which has been validated in another Norwegian stroke cohort. The FSS-7 has shown even better psychometric properties in stroke patients, both for validity, reliability (test-retest) and significant changes over time, than the 9-item version. The application of a shorter form was also easier in the context of many questionnaires to answer (Lerdal & Kottorp, 2011).
The fatigue question from the HUNT3 questionnaire is unfortunately not validated. However, the face validity seems to be fairly good. The chosen cutoff on the HUNT3 fatigue question corresponded very well with the cutoff on FSS-7, which also strengthens the validity. Anyway, what the different fatigue questionnaires really measure is a subject of discussion in most studies of stroke survivors. And this is also reflected in the large variation in reported fatigue prevalence.

For the experience of pre-stroke fatigue we used a simple question and the cases were defined as fatigue if tiredness lasted more than 3 months before stroke onset (Lerdal et al., 2011). The lack of validation is also a limitation to the question of pre-stroke fatigue. However, the fact that the fatigue should have lasted for more than 3 months prestroke increases the risk of underestimating pre-stroke fatigue as compared with the FFS-7, which asks patients about their feeling of being fatigued independent of a timeframe. On the other hand, the danger of recall bias is large since the stroke survivor probably will feel worn out in the acute phase after stroke, and extrapolate it to a pre-stroke feeling.

Older people also may rate their fatigue as lower than others because they are adapted to a lower functional level and do not expect to have as much endurance as before the stroke. This also may represent the construct fatigability, and some of the older participants do not report this as fatigue, but as a natural consequence of getting older. However, it will be a problem to differentiate between these using the questionnaires, also because altered perceptions of fatigue or fatigability may arise as either a primary or a secondary manifestation of disease.

Secondary causes include medications, chronic pain, physical deconditioning, paresis, depression, and sleep disorders.

Strengths of our study of post-stroke fatigue prevalence are the largely unselected stroke sample and the appropriate and well-matched control group.

Depression: The HADS-D is a well-known and validated screening tool for depression in stroke survivors (Turner et al., 2012) A total of 249 patients completed the HADS-D questionnaire. Of those answering EQ-5D (n=262), 246 patients also answered HADS-D (i.e. only 3 patients answered the HADS-D and not the EQ-5D). HADS is slightly more time consuming than EQ-5D and also was applied after the EQ-5D-questionnaire, so that both tiredness and understanding might have influenced the ability to answer. However, reports in other patient groups indicate that patients might report more symptoms by self-administered questionnaires, so one of the reasons for our patient group referring to rather low frequencies of depression might be because the interviews were mainly conducted by phone. This is supported by the results reported by Chan et al. (Chan et al., 2004), comparing telephone versus mailed questionnaires to depressed people. Chan et al. hypothesizing that not using the extremities of answer categories is due to the non-anonymous interview. This effect could also be caused by cognitive problems, in the case it is easier for participants to remember the most recent verbal item that was presented than those presented earlier. This effect should partly be offset by the questions being applied with the rating in opposite direction for every second question.

Pain: The pain question used in **Paper 3** should be easily understandable also when it was applied by telephone interview ("Throughout life we experience pain like toothache, light headache and so on; do you experience pain other than this everyday pain? ” the response categories were yes/no, and “Is the pain experienced new after stroke onset” the response categories were yes/no). A problem with pain is the recall bias. The patients’ answer to the first question will probably be valid, since they either experience pain or they do not. Other simple and similar questionnaires are shown to be very sensitive and valid for evaluating pain versus no pain (Takekawa et al., 2015); however, question number two, asking whether the pain was new after stroke onset, may be affected by recall bias.

5.2.5 External validity of the study.

External validity refers to which extent the results for the studied population are applicable to a general population and setting (Juni et al., 2001). In this study, this means if the results are applicable for all acute, non-palliative stroke patients admitted to a stroke unit. The external validity also is dependent on the internal validity.

Stroke patients. Compared with data from the Norwegian Stroke Registry ("Årsrapport Norsk hjerneslagregister 2013/Annual Report Norwegian Stroke Registry 2013," 2014), our patient group had more severe strokes, and were slightly older. This is a result of the selection bias at inclusion where less affected patients left the hospital too early to be included in the study, while more severe strokes were included.

Since this is an observational study and the present study and earlier behavioural mapping studies in Norway showed that less affected patients were more active (Askim et al., 2014), the results probably underestimate the real sitting and upright activity levels among hospitalized patients. This also indicates that there is a real difference in activity levels between hospitals because those with less severe strokes are also those able to regulate their activity levels without support, and an enriched environment will probably enhance more out of bed activity among these patients (**Paper I**).

The findings that more upright activity in the first week after stroke onset was favorable for functional outcome 3 months later (Paper II) should be applicable to most hospitalized stroke patients, since we included patients with all stroke severities, and the sample is large. The fact that our population was a bit more severely affected should be a strength, since other studies found that those with severe strokes had worse prognosis for dependency (Langhorne et al., 2009). For the assessment of HRQoL, only 262 of the 351 stroke survivors at 3 months were able to answer. The people who answered the questionnaire were shown to have better mRS than those not able to answer. Because we know that those with worse mRS are likely to have poorer HRQoL, this is not applicable to the general stroke population, but probably represents the situation for stroke survivors who are able to answer and are mostly home dwelling (Paper II).

For Paper III the situation for those answering fatigue questionnaires is comparable with those answering the HRQoL questionnaire in Paper II, and the results are not applicable to the whole stroke population.

In conclusion, the external validity of the study is judged to be high for the activity observations where a high proportion of non-palliative eligible stroke patients were included and the results should be applicable to the hospitalized stroke population in general. The external validity of the results for the 3-month patient-reported outcome measures is lower, and the results are applicable to the less severely affected and home-dwelling stroke population.

The HUNT3 survey cohort.

In general nonparticipants in the HUNT3 survey had lower socioeconomic status, higher mortality and higher prevalence of several chronic diseases such as diabetes mellitus and myocardial infarction, and were unhealthier, whilst opposite patterns were found for common problems such as musculoskeletal pain, urinary incontinence and headache. But the rating of general health, cancer and limited daily function because of chronic disease were not different; however, rates of depression in the total population were higher, indicating that those participating were less depressed (Langhammer et al., 2012). The HUNT3 participants in the present thesis were matched by age and gender to the stroke participants, excluding those with a previous stroke. Probably the fatigue level in the cohort was slightly lower than in the average age-matched population not only because those with strokes were excluded, but also because they in fact were a bit less depressed than the average population, and depression is strongly associated with fatigue in a general population (Watt et al., 2000). Thus the external validity may be a bit weaker; nevertheless, the results should be applicable for a general healthy age-matched population.

5.3 Discussion of the main results

5.3.1 Paper I

Activity levels in patients early after stroke vary across the world. The aim of this study was to assess the variation in motor activity in patients admitted to multiple CSUs in Norway, and to explore factors associated with differences in activity levels.

The main finding from Paper I was the significant differences in activity levels between hospitals, which also have been shown by others (Bernhardt et al., 2008; Wellwood et al., 2009; West et al., 2013). Although the patients in the present study spent 44% of the daytime in bed, the activity levels are higher in Norwegian stroke units than shown in previous behavioural mapping studies worldwide (Bernhardt et al., 2008; Wellwood et al., 2009; West et al., 2013).

Time spent with a physical therapist (PT) was positively associated with upright activity. PTs promote upright activity, despite the fact that PTs only spent 42% of their therapy time targeted at walking recovery. Even in a multidisciplinary team, PTs are dedicated to participating more in mobilization and training than nurses. This will of course be reflected in the positive association between PT time and activity level. However, in a recent study, the authors found that increasing the dosage of therapy did not always translate into meaningful increases in physical activity across the day for patients undergoing rehabilitation after stroke (English et al., 2014). It may be possible to further increase patient activity through changes to current training programs that emphasize activity not just in therapy time but more broadly throughout the day, since during daytime patients are often interrupted by necessary medical assessments, while the afternoons more often are free of both therapy time and other procedures.

Time spent with nurses was negatively associated with upright activity. This finding might mirror the fact that nurses usually spend time with the patient in nursing and grooming, which obviously are necessary and important tasks. However, one of the core elements of stroke unit care is the multidisciplinary approach including joint work practice with nurses taking part in mobilization and training of independence in ADL throughout the day (Askim et al., 2012; Helsedirektoratet, 2010). Our results indicate that this part of the guidelines is not yet fully implemented.

An important finding was that serving meals in a communal area was strongly associated with more time in upright activity. This is in line with the findings from a recent study from rehabilitation centers, showing higher activity levels in the hall (Sjoholm et al., 2014). Spending time outside the bedroom might also represent an enriched environment, inducing more social activity (Janssen et al., 2014). Recent studies from inpatient-rehabilitation wards show that the ability to participate in activity outside the bedroom enhances activity and make them drive their own rehabilitation (Eng et al., 2014); however, for those with limited mobility, getting out of their rooms was a barrier because they did not want to make the staff busier (White et al., 2015).

We also have seen from our own unpublished data that the patients who suffered the mildest strokes had the greatest variation in time upright and out of bedroom, which may be explained by differences between hospitals in abilities to do other things outside the bedroom.

In all hospitals, except Hospital 2, patients spent most of the day (> 50% of daytime) alone, while nurses were the profession who were most frequently present. This is in line with previous findings from mapping studies both in hospital and rehabilitation institutions (Bernhardt et al., 2008; Skarin et al., 2013). Our results did not reveal any association between the nurse:patient ratio and activity levels. However, nurses are a key factor in increasing the activity during most of the daytime, evenings and weekends when PTs are not present, but finding ways to release time from other duties might be difficult. The increasing call for documentation is a significant barrier to such a change in working culture. On the other hand, increasing the staffing ratio for PTs, as well as requesting PTs to work out of core time could be a facilitator to induce higher activity.

Even though family spent more than 11% of the daytime with the patient, this did not have an impact on their activity levels. Family should also be regarded as a resource for activating patients; however, they may feel uncertain about how to take part in rehabilitation and stimulating the patient, and simple information might help promote their participation (van de Port et al., 2012). In addition, an enriched environment with facilities outside bedroom activity likely to promote the family's involvement should be more strongly emphasized (White et al., 2015). Since having a family carer is associated with return home, involving family in early rehabilitation might be important (Tanwir et al., 2014). Minor changes in daily routines such as facilitating patients to be more active while with nurses and family, and promoting activity in communal areas might encourage higher activity levels during hospital stay early after stroke.

5.3.2 Paper II

The main findings from Paper II were the significant association between higher amount of early upright activity and good outcome but no association between time to first mobilization and outcome three months later after adjusting for important predictors of activity and outcomes such as stroke severity, age, sex and pre-stroke function.

In the present study, patients were mobilized on average 21 hours after admission, with 76.7% of the patients mobilized within 24 hours of admission, and 44% had little or no disability (mRS 0-2) at 3 months post-stroke. Given the broad inclusion criteria for this study (all patients not receiving palliative care), this pattern of mobilization commencement probably reflects adaptations for the severely affected and unstable patients in usual care. The positive association with early upright activity has also been shown by others (Cumming et al., 2011). However, results from the recent AVERT trial indicate that caution needs to be applied in the early post-stroke period (i.e. too much training too early may be harmful) (AVERT, 2015). This new knowledge needs to be balanced against our current understanding that too much bed rest and delaying mobilization can also be harmful (Askim et al., 2014; Govan et al., 2007; Indredavik et al., 1999). It is also important to keep in mind that 50% of participants in the control group in the AVERT trial also received first mobilization within 22 hours after stroke onset, and at least 10 minutes of physiotherapy and were mobilized 3 times a day, which probably reflects that components of the intervention are already routine clinical care in most comprehensive stroke units included in the study (AVERT, 2015). It has also been shown in recent systematic reviews on rodents that reduced time to start exercise is better for a positive outcome (Austin et al., 2014; Egan et al., 2014). However, some patients might respond better to a more conservative rehabilitation protocol than applied in the AVERT trial. The patients in our study were mobilized a bit later than the control group in the AVERT trial, and the day of observation was on average 5 days after stroke onset. As proposed in earlier research, our results also suggest that a linear relationship exists between the amount of upright activity and good outcome (the more the better) at least when rehabilitation starts within the first 1 or 2 weeks after stroke onset (Kwakkel et al., 2004). However, the results from the large AVERT trial and also from the small Norwegian trial (Sundseth et al., 2012) showed that "more is better" does not apply in the very early phase after stroke. Hence, more research is needed to determine the appropriate timing and dosage of out-of-bed activity early after stroke.

The present study also showed a strong association between early activity and HRQoL, confirming the positive association between physical activity and HRQoL shown in other studies (Rand et al., 2010; Rasmussen et al., 2015). This finding was not unexpected because the EQ-5D-5L has been shown to be strongly correlated to the modified Rankin Scale (Ali et al., 2013), and type and amount of disability after stroke is also related to the EQ-5D index scores (Min & Min, 2015). The EQ-5D-5L index scores reported among the participating patients were mainly in line with previous studies assessing HRQoL in stroke survivors

(Alguren et al., 2012; Golicki, Niewada, Karlinska, et al., 2015; Janssen et al., 2013). This was evident even though our population was more dependent compared to the other studies (Alguren et al., 2012; Golicki, Niewada, Karlinska, et al., 2015). Although stroke patients rate their self-perceived health a little bit lower than the general age-matched population (Burstrom et al., 2001), their quality of life was generally good. In Norway, most hospitals offer an early supported discharge service, which has been shown to improve HRQoL in both rural and urban areas (Askim et al., 2004; Fjaertoft et al., 2004). Despite the current unknowns, this study supports previous work, including the results from the AVERT trial, showing good outcome associated with early out of bed activity in usual care (AVERT, 2015), and shows that activity applied within the first week after stroke is associated with functional independence and better HRQoL three months later.

5.3.3 Paper III

The main findings from Paper III were, firstly a higher prevalence of fatigue in stroke patients even after careful matching with a general population sample. The prevalence is lower than most previous studies where prevalence was most often reported to be in the range of 50%. There are several possible reasons for this difference. Most obviously, use of different questionnaires and different cut-offs to define fatigue will affect prevalence findings. However, a further possible explanation may be the older patient population in our study compared with other studies, since younger patients may be more aware of fatigue due to higher activity levels and increased likelihood of wanting to return to work (Dolan & Kudrna, 2015; Naess & Nyland, 2013; Wang et al., 2014) . We did not find compelling support for our hypothesis that more early motor activity would decrease the likelihood of post-stroke fatigue. Our analysis confirmed previous findings that pre-stroke fatigue, depression and pain were important predictors. Time in bed almost reached statistical significance in the model.

The stroke patients were about three times more likely to report fatigue than their community-living counterparts who had not experienced stroke. Our results also showed that the stroke patients had more than double the likelihood of having at least one other disease prior to their stroke compared to the general population, and more than double the likelihood of having 3 or more other diseases. Pre-stroke fatigue was one of the strongest independent predictors of post-stroke fatigue in our study. The percentage of stroke patients reporting pre-stroke fatigue was much higher than fatigue in the general population. This finding suggests that the higher prevalence of post-stroke fatigue may be at least in part related to the stroke population being in poorer health even before they had a stroke. The previous literature on the association between pre-stroke co-morbidities and fatigue is not clear. One study found an association between post-stroke fatigue in young patients and both diabetes mellitus and myocardial infarction (Naess et al., 2005), while two other studies found no such association (Appelros, 2006; Choi-Kwon et al., 2005). PSF is a serious problem which clearly warrants better monitoring and management. Our findings suggest that pre-stroke health is an important factor in development of PSF.

Our findings hint at the possibility that early inactivity may be associated with fatigue at three months. This may be similar to the finding that more time in bed, but not less time in higher level activities, was predictive of worse functional outcome at 3 months post stroke (Askim et al., 2014). Previous bed rest studies have shown that bed rest in general is not a benign treatment, but harmful to health (Allen et al., 1999; Thyfault & Booth, 2011). One possible mechanism by which bed rest could lead to higher levels of fatigue is the loss of cardiorespiratory fitness (CRF). CRF declines rapidly with bed rest (Coker et al., 2015). However, a recent review of cross-sectional studies found neither current physical activity levels nor CRF explained the level of fatigue experienced by people after stroke (Duncan et al., 2012). The risk of immobility-related complications increases with increased amounts of bed rest (Govan et al., 2007) suggesting that an association between fatigue and time in bed might also be explained by an increased prevalence of post-stroke complications. The reverse causal pathway is also plausible, whereby early activity is dependent on the absence of fatigue and this early fatigue persists at 3 months (van Eijsden et al., 2012). Despite our non-significant finding, we argue that further research is still needed to investigate how early fatigue and early inactivity are related to the problem of debilitating PSF.

The likelihood that the amount of bed rest is closely related to stroke severity and pre-stroke function also poses a challenge.

A recent study found that patients with stroke who had more effortful movements as determined by movement velocity during a timed hand movement task had increased likelihood of fatigue (Kuppuswamy et al., 2015). The authors proposed that the relationship could be due to either a simple effort-fatigue relationship or because both fatigue and reduced movement speed may result from an alteration in motor cortex excitability. With this finding in mind alongside our own results, post-stroke fatigue may be largely explained by a combination of poor pre-stroke health, issues secondary to stroke during the acute phase (including medications, sleep problems and complications), depression, pain, the harmful consequences of too much inactivity, and increased effort of movement related to motor impairment.

Hence our measures of activity early after stroke may not adequately represent activity or inactivity of importance in preventing the development of post-stroke fatigue.

Some previous research supports there being a difference between mental and physical fatigue, particularly after stroke. The impact of a stroke (irrespective of whether ischemic or haemorrhagic) taxes the central nervous system and increases the level of cognitive strain, which may be interpreted as fatigue.

Post-stroke fatigue presents management challenges with few options currently available with proven effectiveness (Mead et al., 2012). A combined cognitive therapy and graded exercise program has shown promise in alleviating fatigue, as well as cognitive therapy alone (Clarke et al., 2012; Zedlitz et al., 2012); however, these RCTs are small, and more research is needed on the effect of multifactorial approaches including exercise programs. It is apparent from the results of observational studies that improvement of general health and management of depression, sleep and pain should help alleviate PSF. We also suggest that determining the appropriate amount of time spent on bed rest versus out of bed activities early after stroke warrants further investigation in relation to fatigue (Duncan et al., 2015).

Although the prevalence of PSF in this relatively unselected stroke population was lower than typically reported previously, this study confirms a higher prevalence than in those without stroke and further highlights the problem of PSF. Pre-stroke health appears to be an important factor, as does post-stroke depression and pain. The role of early mobility activity in the development of fatigue following stroke remains unclear.

5.4 Clinical implications

In the present thesis, the activity levels in hospitalized stroke patients have been studied along with the associations with disability, HRQoL and fatigue 3 months later, and with factors associated with fatigue, as well as fatigue prevalence among the stroke cohort and an age- and gender-matched population not suffering from stroke.

Despite the fact that all stroke units were CSUs with a focus on early rehabilitation, there were significant differences in activity levels between the hospitals. Finding solutions to promote more activity, for instance by an enriched environment, and encouraging patients to be more active on their own or with support from family and nurses while not in therapy, may be an important approach.

Our findings that more time in upright activity was associated with better functional and HRQoL outcome supports this aspect. The weak association between the amount of time spent in bed in the early phase after stroke and increased risk of fatigue three months later indicates that prolonged bedrest should be avoided during the initial hospital stay to prevent the development of fatigue.

There is still no consensus on how to treat PSF. However, promoting activity out of bed and identifying and treating factors associated with fatigue may be an important approach. These are factors clinicians should pay attention to when following up the patient.

6 Conclusions

The conclusions of the research questions addressed in this thesis are:

- Activity levels varied significantly between patients admitted to different Norwegian stroke units.
- Differences in the amount of time spent with PTs and nurses in addition to a policy of serving meals in a communal area at the ward contributed significantly to explaining the observed differences in activity levels.
- More time spent in upright activity early after stroke was significantly associated with reduced disability (mRS) at 3-month follow-up.
- More time spent in upright activity early after stroke was significantly associated with better HRQoL (EQ-5D-5L and EQ-VAS) at 3-month follow-up, while more time in bed showed a trend toward association with more fatigue.
- There was no association between timing of mobilization and outcome.
- Prestroke fatigue, pain, and depression were all factors significantly associated with poststroke fatigue.
- Fatigue was more prevalent in the stroke cohort than in an age- and gender-matched general population without stroke.

7 Suggestions for further research

As we have pointed out in **Paper I**, environmental factors and staffs' ability to promote activity in acute stroke patients seems important. In future research, the cost-benefit of an intervention facilitating patients to more activity together with nurses and family as well as promoting activity in communal areas throughout the waking hours after the first few days of onset of stroke should be designed and tested in a randomized controlled trial.

The results from **Paper II** suggests that more upright activity early after stroke was favorable; however, the AVERT study found that too early and too much activity has the opposite effect. Future research should focus on exploring the pathophysiological mechanisms associated with early upright activity and to determine the optimal timing and dosages of activity and rest during the early phase after stroke.

Finally, regarding the results from **Paper III**, we suggest that more research must be targeted to find ways to resolve challenges both to better define fatigue and to investigate factors that can relieve fatigue perception. Our findings suggest that too much bed rest is not beneficial, but only one small trial so far has investigated and found a positive effect of physical exercise among stroke patients. Findings indicating the benefits of physical exercise in other patient groups implicate that further studies are necessary.

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Paper I

Hospital Differences in Motor Activity Early after Stroke: A Comparison of 11 Norwegian Stroke Units

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Background: Activity levels in patients early after stroke vary across the world. The primary aim of this study was to assess the variation in motor activity in patients admitted to multiple Norwegian stroke units and to identify factors which explained the variation between hospitals. *Methods:* Eligible patients were those less than 14 days after stroke, more than 18 years, not receiving palliative care. Activity levels, people present, and location were recorded by the use of a standard method of observation between 8 AM and 5 PM. Hospital policy on serving meals in communal areas was also registered. Mixed general binomial model was used to analyze, which factors explained variation in activity levels between hospitals, after adjusting for age and stroke severity. *Results:* A total of 393 patients from 11 stroke units were included. The patients spent 44.1% of the day in bed, 43.2% sitting out of bed, and 8.3% in higher motor activities (4.4% were not observed). Increased physical activity was associated with spending more time with a physical therapist, odds ratio (OR), 1.05 (95% confidence interval [CI], 1.03-1.08, $P < .001$) and admitted to a hospital serving the meals in communal areas, OR, 1.46 (95% CI, 1.09-1.95, $P = .011$). *Conclusions:* Despite variation between the hospitals, patients admitted to Norwegian stroke units spend most of the day out of bed. Time spent with a physical therapist and hospitals having a policy of serving meals in communal areas explained most of the variation in activity between hospitals. **Key Words:** Stroke—stroke units—rehabilitation—physical activity.

Stroke unit treatment is effective in reducing death and dependency after acute stroke.[1] Fast-track diagnosis and medical treatment, early mobilization out of bed, physical activity, and coordinated interdisciplinary stroke care[2,3] are identified as features of stroke unit care that are common in successful stroke units.[1] Increased amount of physical activity in the early phase after stroke appears to promote earlier discharge to home and better long-term

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outcome[4,5] and seems to be more important than simply the timing of first mobilization.[3-7] Nevertheless, previous research has shown that activity levels vary to a large extent in patients admitted to stroke units across different countries.[8-10] Understanding what drives these discrepancies could help us improve stroke care and early rehabilitation.

Common models of stroke unit care are the acute stroke unit focusing on acute medical management, and the comprehensive stroke unit (CSU) combining acute medical treatment and early rehabilitation including multidisciplinary teamwork. Observational studies show that activity levels vary to a large degree, with some studies suggesting those admitted to a CSU are more active than those admitted to an acute stroke unit.[10,11] Patients with severe stroke are shown to spend more of their daytime in bed.[5,11] But not only patient-related factors are likely to influence activity in hospital. Staff:patient ratio and mobilization policy might also influence activity levels.[11,12] There is evidence that environmental factors, like access to communal areas may help to increase activity levels in a rehabilitation setting.[13] Regardless of stroke unit model, it appears that patients spend most of their day alone.[4,14] Better understanding of the facilitators of activity could help improving stroke unit care.

The stroke units in Norway are organized as CSUs in accordance with The Norwegian National Guidelines for Stroke Treatment and Rehabilitation, published in 2010. Acute stroke patients are treated in 53 Norwegian hospitals, and out of these, 46 have well-defined stroke units. According to the Norwegian Stroke Registry, 91% of the stroke patients were treated in a CSU during their hospital stay in 2013.

The purpose of this study was to determine the amount of early motor activity in patients admitted to different Norwegian stroke units and to explore which factors explained the variation in activity between hospitals and to assess where and with whom patients spent most of their daytime.

The primary hypothesis was that patient activity levels varied across the Norwegian CSUs. The secondary hypothesis was that variation in activity between hospitals could be explained by differences in hospital characteristics and the amount of time nurses and physical therapist (PT) spent with the patients.

Material and Methods

Study Design

This was a prospective observational study including patients admitted to 11 Norwegian hospitals.

Setting

The participating hospitals were CSUs located in 3 of 4 Norwegian Health Authorities, 8 hospitals from Central Norway Health Authority, 1 hospital from Northern Norway Health Authority, and 2 hospitals from South-East Norway Health Authority. The hospitals were 2 university hospitals, 2 small (treating less than 100), and 7 middle sized (treating between 100 and 400 stroke patients per year).

Patients were eligible if they were diagnosed with a stroke within the last 14 days, age older than 18 years, Norwegian speaking, and not receiving palliative care. Patients were excluded if they were likely to be discharged from hospital with less than 5 hours of observation.

Informed consent was obtained from those able to agree. Patients who were not able to give informed consent were included if their next of kin gave oral consent to participation. This is in keeping with Norwegian consent procedures for patients unable to consent.

Also in line with the Norwegian Act on medical and health research, the Regional Committee for Medical and Health Research Ethics in Central Norway approved the study and storage of data on behalf of all participating hospitals (REC no 2011/1428).

Observational Methods

For observation, the method of behavioural mapping was used.[11,14] Observations were mainly conducted every 10 minutes from 8 AM to 5 PM. However, because of long traveling distances some of the observations were undertaken across 2 consecutive days, but covering the same period. At each time point, the observer recorded patient activity, who was attending the patient, and the patient's location. When patients were out of view (eg, in the bathroom or off ward), activity was acquired retrospectively, by questioning either the patient or the caregiver or from a separate activity form completed by the therapists (PTs and occupational therapists) during off ward treatment. However, when data could not be retrieved, they were recorded as not observed. The patients were observed for approximately 1 minute at each time point. The hospitals were contacted every second week, and observation was performed if there were 2 or more eligible patients. Four well-trained observers did all the observations. The training of the observers included assessment of agreement, and the training was not concluded until the agreement was excellent.

At each observation, 12 activities could be recorded; (1) no active motor supine; (2) no active motor on left side; (3) no active motor on right side; (4) sit support in bed; (5) sit support out of bed; (6) transfer with hoist; (7) roll and sit up; (8) sit with NO support; (9) transfer with feet on floor; (10) standing; (11) walking; and (12) stairs. We were interested in 3 main activity categories: in bed (activities 1, 2, 3, and 4), sitting out of bed (activities 5, 6, 7, and 8), and upright activity (activities 9-12).[14,15]

Five main categories of location were registered; (1) bedroom, (2) on ward communal area (hall and patient lounge), (3) therapy area, (4) bathroom, and (5) off ward (doctor's room, radiologic imaging, Doppler/echo, and other).

Five main categories of people present were registered; (1) alone, or with (2) nurse (nurse and/or nurse assistant), (3) PT, (4) family, and (5) others.

Hospital Characteristics

At each day of observation, the total number of patients admitted to the ward, the number of stroke patients, and the nurse:patient ratio (number of nurses/nurse assistants at work divided on the number of patients admitted) were recorded. We also registered whether the hospital had a policy of serving meals in communal areas.

Baseline Assessment

Demographic information including age, gender, premorbid function assessed by modified Rankin Scale (mRS),[16] stroke severity obtained by National Institutes of Health Stroke Scale,[17] stroke type (infarction or intracerebral hemorrhage),[18] and mRS at inclusion.

Data Processing and Analysis

The highest level of activity in every 10-minute interval was recorded in the database (Microsoft Access 2007). The recorded activity levels were put into 1 of the 3 predefined categories, and the proportion of time spent in each category was calculated as a percentage of the 55 observations per person.

When patients were not able to be observed for 1-2 observations because of privacy, missing activity data were imputed as "sitting out of bed." If more than 2 observations were missing, it was maintained as not observed. Missing activity data because of computed tomography/magnetic resonance scan or ultrasound were imputed as "in bed." All other occasions of "not observed" were recorded as missing.

Means and standard deviations (SDs) were used for descriptive purposes and the proportion of baseline variables, whereas the mean and 95% confidence intervals (CIs) were used to present time in each activity category.

All variables were tested for normality. The Kruskal–Wallis nonparametric test was used to compare differences in variables between hospitals.

A mixed logistic regression model was used to determine which of the independent variables were associated with activity levels. The independent variables we wanted to test were (1) nurse:patient ratio (the number of nurses divided by the total number of patients admitted at the day of observation); (2) number of stroke patients treated per year in each hospital; (3) if the meals were served in communal areas or not; and the amount of time spent with (4) a nurse/nurse assistant, (5) a PT, and (6) a family member. Because of repeated measurements for each patient and a potential cluster effect of hospital, patient id and hospital id were included as random effects in the mixed logistic regression model. Three models were tested with time spent in upright activity, sitting out of bed, and in bed as dependent variables. All analyses were adjusted for age and stroke severity.

Results

A total of 547 patients were screened for inclusion from December 2011 to June 2013. Out of these, 137 patients did not meet the inclusion criteria because of palliative treatment (n = 9), early discharge (n = 60), not Norwegian speaking (n = 3), more than 14 days since stroke onset (n = 39), and did not want to participate (n = 26), giving a total of 410 observed patients.

Furthermore, 17 patients were excluded because the final diagnostic evaluation revealed no stroke diagnosis (n = 16) or the patient withdrew from the study (n = 1). Hence, 393 patients were included in the final data analysis. All hospitals were visited from 5 to 36 times.

Patients' characteristics at baseline showed no significant differences in age, National Institutes of Health Stroke Scale, premorbid mRS, mRS at inclusion, or days since stroke onset between hospitals (Table 1).

Amount of Activity

Figure 1 shows that the mean (95% CI) proportion of daytime spent in upright activities was 8.3% (7.4-9.2) for all hospitals, varying from 4.5% (.4-8.6) to 13.4% (9.4-17.3), *P* less than .05. The proportion of daytime spent

Table 1. *Baseline patient characteristics*

Characteristics	N = 393
Age, y, mean (SD)	76.8 (11.2)
Male, n (%)	189 (48.1)
First-ever stroke, n (%)	284 (72.3)
Time since stroke, d, mean (SD)	5.2 (2.9)
NIHSS score, mean (SD)	7.9 (7.7)
Severity groups, n (%)	
Mild stroke (NIHSS $<$8)	250 (63.6)
Moderate stroke (NIHSS 8-16)	78 (19.9)
Severe stroke (NIHSS $>$16)	65 (16.5)
Stroke type, n (%)	
Infarction	338 (86.0)
Intracerebral hemorrhage	55 (14.0)
Prestroke mRS, n (%)	
0-1	204 (51.9)
2-3	150 (38.2)
4-5	39 (9.9)

Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

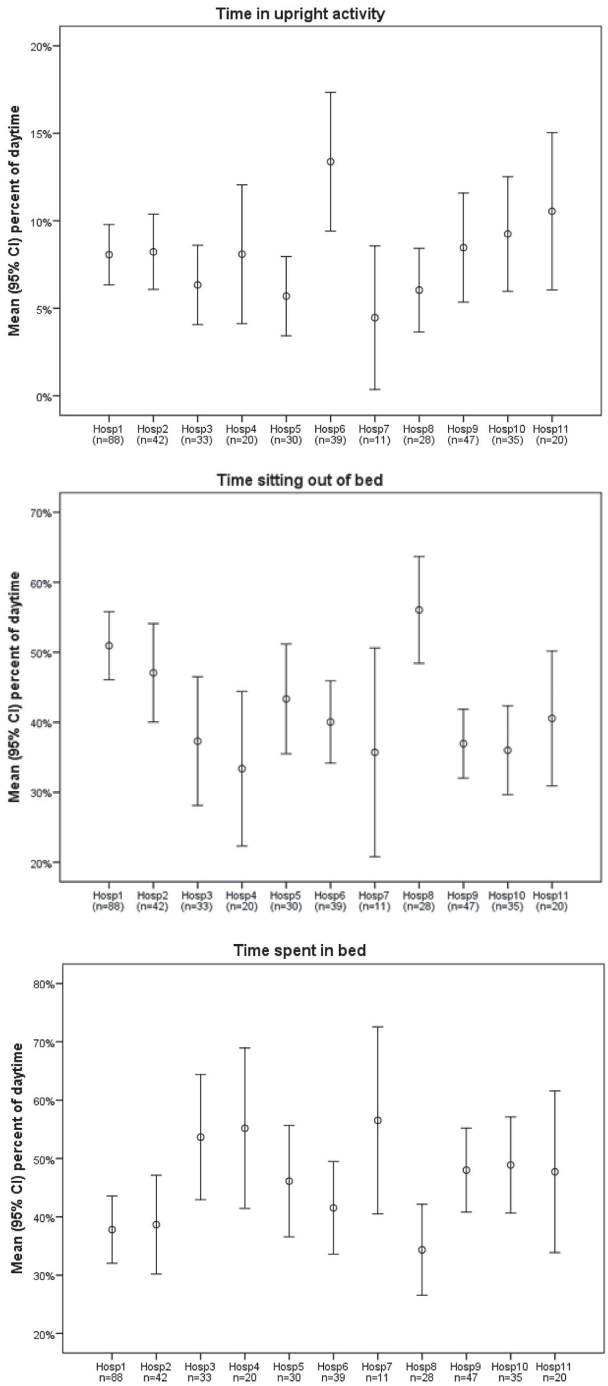

Figure 1. *Time spent in different motor activity levels. Abbreviations: CI, confidence interval; Hosp, hospital.*

Table 2. *Proportion of daytime spent in different motor activities according to stroke severity*

Activity categories	Mild stroke NIHSS <8 (n = 250)	Moderate stroke NIHSS 8-16 (n = 78)	Severe stroke NIHSS >16 (n = 65)	*P* value
Time in upright activity, mean % (95% CI)	11.8 (10.7-56.4)	3.2 (2.3-4.1)	.9 (.5-2.6)	.000
Time sitting out of bed, mean % (95% CI)	48.9 (46.5-51.4)	39.5 (34.4-44.5)	25.7 (20.9-30.6)	.000
Time in bed, mean % (95% CI)	33.9 (31.2-36.7)	53.5 (47.9-59.1)	72.0 (67.0-77.0)	.000

Abbreviations: CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale.

sitting out of bed was 43.2% (41.0-45.4), varying from 33.4% (22.3-44.4) to 56.0% (48.4-63.6), $P = .01$. While, the proportion of daytime spent in bed was 44.1% (41.5-46.8), varying from 37.8% (32.0-43.6) to 56.5% (40.5-72.6), *P* less than .001. Total time not observed was 4.4% (3.6-5.1) of the day, $P = .081$. There were significant differences in activity levels between stroke severity groups (Table 2).

People Present

Overall patients spent mean (SD) are 55.9% (18.6) of the daytime alone, 3.3% (4.1) with a PT, 14.9% (9.8) with a nurse/nurse assistant, and 11.4% (9.8) with a family member (Table 3). The remaining observations (14.5% [21.2]) were with other people (team members, patient transport, other patients, and unknown) or not observed.

The mean (SD) nurse:patient ratio at the day of observation was .56 (.15) ranging from .44 (.11) to .65 (.11). Out of all observations with PT present, the patient spent 42% of the time in upright, 42% in sitting, and 16% of the time in bed.

Patient Location

For all hospitals, patients spent mean (SD) 74.4% (22.4) of their day in the bedroom, 14.0% (17.6) of their day in communal areas on the ward, 2.7% (5.5) of their day at the therapy area, and 2.7% (3.0) in the bathroom. For location off ward, the mean time was 6.2% (8.9) of the day. Time spent in the different locations on the ward except the bathroom varied significantly between hospitals with bedroom location from 57.6% (29.3) to 88.4% (11.8), ($P < .001$), communal areas from 4.0% (5.7) to 29.4% (24.5), ($P < .001$), and time spent in therapy area varied from .0% (.0) to 5.5% (8.9), ($P < .001$), (Fig 2).

The 5 hospitals with less time spent in bedroom corresponded with those serving meals in communal areas (Fig 2 and Table 3).

Factors Associated with the Activity Levels

Patients spending more time with a PT, odds ratio (OR), 1.05 (95% CI, 1.03-1.08, $P < .001$) and patients admitted to hospitals serving the meals in communal areas, OR, 1.46 (95% CI, 1.09-1.95, $P = .011$) were more likely to have an increased activity level, whereas time spent with a nurse, OR, .98 (95% CI, .97-1.00, $P = .007$) decreased the odds for upright activity. All analyses were adjusting for age and stroke severity (Table 4).

Discussion

The present study explored factors associated with activity across a broad range of CSUs in Norway. This is the largest study of its kind. Our goal was to determine factors that may help explain interhospital variability in activity (and inactivity) in acute stroke patients.

The main findings were that the activity levels varied significantly between the hospitals and that the amount of time spent with a nurse and a PT and whether the meals were served in communal areas or not, explained most of the observed differences after adjusting for stroke severity and age. Not surprisingly, time spent with a PT and serving the meals in a dining area was positively associated with upright activity. However, time spent with a nurse was negatively associated with upright activity.

Motor Activity

Our results showed that physical therapy promotes upright activity, despite the fact that PTs only spent 42% of their therapy time targeted at walking recovery. The interpretation of our results reveals that every percent increase in time spent with a PT, that is, for every 5 minutes, the odds for being upright increased by 5%. Translated into a 20-minute additional bout of physical therapy, the odds for being upright will increase by 22% at any given time point. However, in a recent study, the authors found that increasing the dosage of therapy did not always translate into meaningful increases in physical activity across the day for patients undergoing rehabilitation after stroke.[19] So although PTs have an important role to play in promoting activity and walking recovery after stroke, they need to be mindful of the actual proportion of their treatment time devoted to these important tasks. It may be possible to further increase patient activity through changes to current training programs that emphasize activity not just in therapy time but more broadly throughout the day.

In contrast, time spent with nurses was negatively associated with upright activity. This finding might mirror the

Table 3. *Hospital characteristics and people present*

Variables	Hosp1 (n = 88)	Hosp2 (n = 42)	Hosp3 (n = 33)	Hosp4 (n = 20)	Hosp5 (n = 30)	Hosp6 (n = 39)	Hosp7 (n = 11)	Hosp8 (n = 28)	Hosp9 (n = 47)	Hosp10 (n = 35)	Hosp11 (n = 20)	Total (n = 393)
Hosp size*	536	203	112	87	137	141	65	200	301	283	285	
Communal meals	Yes	Yes	No	No	No	Yes	No	No	Yes	No	Yes	
Mean (SD), nurse: patient ratio	.65 (.11)	.54 (.12)	.51 (.21)	.48 (.12)	.64 (.14)	.44 (.11)	.56 (.19)	.54 (.08)	.55 (.17)	.62 (.22)	.59 (.09)	.56 (.15)
Mean (SD) amount of daytime												
Patient alone	52.9 (17.5)	49.6 (21.2)	66.4 (18.5)	60.3 (18.5)	52.1 (19.9)	59.9 (16.5)	60.5 (18.1)	56.4 (20.4)	51.0 (16.0)	61.0 (18.2)	58.0 (14.5)	55.9 (18.6)
With nurse	18.0 (10.4)	12.3 (7.8)	10.9 (5.9)	7.9 (4.7)	16.5 (10.1)	14.2 (13.2)	19.2 (9.2)	16.0 (8.5)	16.5 (9.5)	13.1 (9.9)	15.0 (8.9)	14.9 (9.8)
With PT	2.7 (4.6)	4.1 (4.3)	3.2 (2.7)	4.0 (3.8)	4.9 (5.7)	2.2 (3.6)	2.3 (2.5)	3.4 (3.8)	3.1 (3.9)	3.3 (4.2)	2.9 (2.5)	3.3 (4.1)
With family	15.2 (16.6)	10.5 (14.8)	11.5 (20.0)	9.8 (7.6)	10.2 (11.9)	7.8 (8.2)	9.9 (14.7)	7.9 (19.2)	13.6 (13.1)	10.1 (13.3)	8.9 (14.0)	11.4 (14.8)

Abbreviations: Hosp, hospital; PT, physical therapist; SD, standard deviation.
*Stroke patients treated annually. Data from the Norwegian Stroke Registry, average for 2012 and 2013.

fact that nurses usually spend time with the patient in nursing and grooming. However, one of the core elements of stroke unit care is the multidisciplinary approach including joint work practice with nurses taking part in mobilization and training of independence in activities of daily living throughout the day.[15,20] Our results indicate that this part of the guidelines is not yet fully implemented.

An important finding was that serving meals in a communal area was strongly associated with more time in upright activity. This is in line with the findings from a recent study from rehabilitation centers, showing higher activity levels in the hall.[21] Spending time outside the bedroom might also represent an enriched environment, inducing more social activity.[13] As shown in Table 2 and also confirmed by others,[15] patients with the most severe strokes spent most time in bed, indicating that, the need for help in mobilization probably represents a barrier to initiate transfer to the communal areas.[22]

People Present

In all hospitals, except hospital 2, patients spent most of the day (>50% of daytime) alone, while nurses were the profession who were most frequently present. This is in line with previous findings from mapping studies both in hospital and rehabilitation institutions.[11,14,23] Our results did not reveal any association between the nurse:patient ratio and activity levels. However, nurses are a key factor in increasing the activity during most of the daytime, evenings, and weekends when PTs are not present, but finding ways to release time from other duties might be difficult. The increasing call for documentation is a significant barrier to such a change in working culture. On the other hand, increasing the staffing ratio for PTs, and also request PTs to work out of core time could be a facilitator to induce higher activity.

Although family spent more than 11% of the daytime with the patient, this did not have an impact on their activity levels. Family should also be regarded as a resource for activating patients; however, they may feel uncertain about how to take part in rehabilitation and stimulate the patient, and simple information might help promote their participation.[24] Because living with a family member is associated with returning home, involving family in early rehabilitation might be important.[25]

Strengths and Limitations

A major strength of the present study was the large number of patients included from an unselected stroke population admitted to multiple Norwegian hospitals and assessment by 4 well-trained observers. However, the study has some limitations. Two of the participating hospitals were small, and the few patients included from these hospitals might represent a bias in activity data. Although the amount of missing data was very

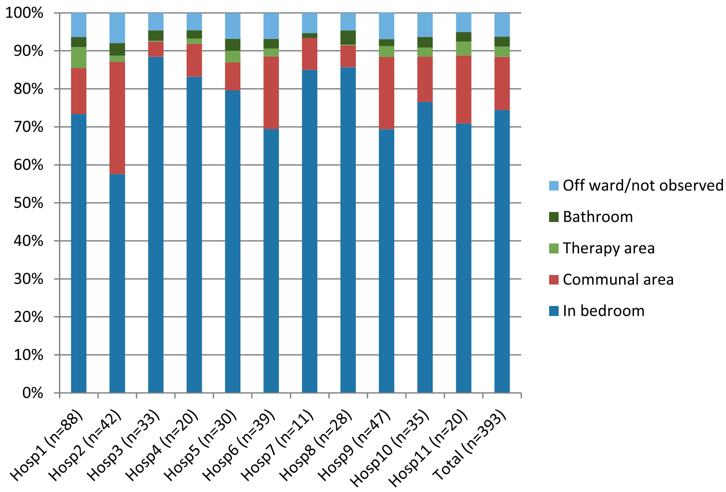

Figure 2. *Patient location during the day at different hospitals. Abbreviation: Hosp, hospital.*

small, the most common reason for missing was off-ward activity. Because off-ward activity like home visits is likely to be upright activity, this limitation represents a risk of underestimation of upright activities. Another limitation was the very short time for hospital stay in Norwegian stroke units, which might lead to a selection bias toward more severe stroke patients.

As we have pointed out in this article, environmental factors and staffs' ability to promote activity in acute stroke patients seems important. Activity levels peak in the morning and decline during the day.[26] In future research, the cost benefit of an intervention facilitating patients to more activity together with nurses and family, and promoting activity in communal areas throughout the waking hours should be designed and tested in a randomized controlled trial.

Conclusions

Despite significant differences between the hospitals, this study has shown that patients admitted to Norwegian stroke units spend most of their daytime out of bed. Differences in time spent with PT and nurses in addition to a policy of serving meals in a communal area at the ward contributed significantly to explain the observed differences in activity levels. Minor changes in daily routines such as facilitating patients to be more active while with nurses and family, and promote activity in

Table 4. *Association between independent variables and motor activity*

	Upright activity			Sitting out of bed			In bed		
Fixed effects (covariates)	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
PT with patient	1.05	1.03-1.08	.000	1.03	1.00-1.06	.021	.96	.93-.99	.006
Nurse with patient	.98	.97-1.00	.007	1.02	1.00-1.03	.018	1.00	.98-1.01	.724
Family with patient	.99	.99-1.00	.156	1.00	1.00-1.01	.536	1.00	.99-1.01	.960
Nurse:patient ratio	.89	.46-1.70	.722	1.08	.52-2.23	.845	1.01	.40-2.54	.981
Communal meals	1.46	1.09-1.95	.011	.92	.67-1.26	.610	.84	.61-1.16	.284
Hospital size	1.00	1.00-1.00	.846	1.00	1.00-1.00	.088	1.00	1.00-1.00	.102
NIHSS	.88	.86-.89	.000	.92	.91-.94	.000	1.12	1.10-1.14	.000
Age, y	.98	.98-.99	.000	1.01	1.00-1.02	.006	1.00	1.00-1.01	.681
Random effect		SD			SD			SD	
Hospital ID		0.128			0.132			0.000	
Patient ID		0.654			0.961			1.240	

Abbreviations: CI, confidence interval; NIHSS, National Institutes of Stroke Scale; OR, odds ratio; PT, physical therapist; SD, standard deviation.

communal areas might encourage higher activity levels early after stroke.

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Paper II

J Rehabil Med

ORIGINAL REPORT

UPRIGHT ACTIVITY WITHIN THE FIRST WEEK AFTER STROKE IS ASSOCIATED WITH BETTER FUNCTIONAL OUTCOME AND HEALTH-RELATED QUALITY OF LIFE: A NORWEGIAN MULTI-SITE STUDY

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Objective: **To assess the amount of early upright activity of patients managed in Norwegian stroke units and its association with functional outcome and health-related quality of life 3 months later.**
Design: **A prospective observational multi-centre study.**
Subjects: **A total of 390 acute stroke patients, mean age 76.8 years, 48.1% men, less than14 days post-stroke, recruited from 11 Norwegian stroke units.**
Methods: **Time spent in different activity categories (in bed, sitting out of bed, upright) was observed with a standard method. Outcome was assessed by modified Rankin Scale (mRS), and health-related quality of life by EuroQol-5 Dimension 5 level (EQ-5D-5L) 3 months later. Ordinal logistic and linear regression analyses were used to examine the association between activity categories and mRS and EQ-5D-5L, respectively. Age, National Institute of Health Stroke** [AQ2] **Scale (NIHSS) score, premorbid mRS, gender, and hospital-site were added as covariates.**
Results: **The odds ratio (OR) (95% confidence interval (CI)) for poorer functional outcome (higher mRS) decreased as time spent in upright activities increased (OR 0.97 (95% CI 0.94–1.00)). There was also a significant positive association between time in upright activity and higher EQ-5D-5L, Beta 0.184 (95% CI 0.001– 0.008) 3 months later.**
Conclusion: **This study confirms the beneficial effect of upright activity applied during hospital stay in Norwegian stroke units.**

Key words: stroke; rehabilitation; physical activity; outcome assessment; health-related quality of life.

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INTRODUCTION

Stroke is the second most frequent cause of death and a major [AQ3] cause of disability in adults. Up to half of stroke survivors are dependent in activities of daily living 3 months post-stroke (1, 2). Stroke patients also rate their health-related quality of life (HRQoL) lower than healthy people of the same age and people with other medical diseases (3).

Stroke unit care has shown to be the most powerful, broadly applicable treatment after acute stroke, reducing death and dependency (4). Early mobilization with out-of-bed activities, such as sitting, standing and walking, has been regarded as an important contribution to the short- and long-term effects of stroke unit care (5, 6), and is now recommended in most national guidelines for stroke care across Western Europe, Australia and North America (7). However, recently, a worldwide study of early mobilization (AVERT) demonstrated that too much out-of-bed activity within the first few days after onset of stroke may impair the recovery process (8).

Even though most guidelines recommend mobilization within 24 h, only in the Australian and Norwegian guidelines has mobilization been defined as out-of-bed activity (7, 9). Despite these recommendations, several observational studies in these countries have shown that less than 60% of patients are mobilized out of bed within 24 h after stroke onset (10, 11), indicating that guidelines alone do not change practice and that clinical practice reflects the healthcare providers' expertise, the patients' values and expectations, as well as process and pragmatic factors.

It is becoming increasingly apparent that the timing of first mobilization may be less important than the total amount and frequency of early out-of-bed activity during hospital stay (12); however, timing of first mobilization also probably acts as a proxy for the organization of post-stroke rehabilitation care in the acute setting (7). The first 2 weeks after stroke continues to be a period of great interest in recovery research, as pre-clinical studies suggest it may be a critical time-window for promoting recovery (13). Recent studies examining time spent in upright activity (defined as standing, walking, climbing stairs and all other activities, including transfer, with the feet on floor), measured on a single day within the first 2 weeks after onset of stroke have shown significant variation between hospitals (14, 15). To more fully understand the impact of this variation in clinical practice, the association between the amount of early upright activity after stroke and outcome should be more thoroughly assessed.

The overall aim of the present study was to assess the association between the timing and amount of upright activity applied in clinical practice in patients admitted to multiple Norwegian stroke units and degree of disability and HRQoL 3 months later.

We hypothesized that a higher amount of early upright activity and shorter time to first mobilization would be associated with increased probability of good functional outcome and improved HRQoL at the 3-month follow-up.

MATERIAL AND METHODS

Study design and setting

This was a prospective cohort study recruiting patients from 11 Norwegian stroke units. Motor activity was registered within the first 2 weeks of hospital stay and functional outcome was measured 3 months later.

The participating hospitals were located in Central Norway ($n=8$), in Northern Norway ($n=1$) and in South-East Norway ($n=2$). Two of the hospitals were university Hospitals, 2 were small, treating fewer than 100 patients per year, and 7 middle-sized treating between 100 and 400 stroke patients per year.

Participants

Patients were eligible if they were diagnosed with acute stroke within the previous 14 days, age >18 years, Norwegian speaking, and not receiving palliative care. Patients were excluded if they were likely to be discharged from hospital with less than 5 h of observation.

Informed consent was obtained from those who were able to agree, and for those not able to consent the next of kin gave verbal consent to participate. This is in keeping with Norwegian consent procedures for patients who are unable to consent.

The Regional Committee for Medical and Health Research Ethics in Central Norway approved the study and storage of data on behalf of all participating hospitals (REC number 2011/1428).

Observation

Every second week each hospital was visited if the hospitals had 2 or more eligible patients. Four well-trained observers travelled and performed all observations in the study. The training of the observers included assessment of agreement and the training continued until agreement was excellent.

For observation, the behavioural mapping method was used (16). Observations were conducted every 10 min from 08.00 h to 17.00 h on a single day. However, due to long travelling distances, some of the observations were undertaken across 2 consecutive days, but covering the same hours. At each time-point, the observer recorded patient activity, who was attending the patient, and the patient's location. When patients were out of view (e.g. in the bathroom or off-ward), activity was acquired retrospectively, by questioning the patient or the caregiver, or from a separate activity form completed by the physiotherapist or the occupational therapist during off-ward treatment. They were marked as not observed if it was not possible to retrieve the data. The patients were observed for approximately 1 min at each time-point.

Categories of motor activity

At each observation, 12 prescribed activities were recorded: (*i*) no active motor supine; (*ii*) no active motor on left side; (*iii*) no active motor on right side; (*iv*) sit support in bed; (*v*) sit support out of bed; (*vi*) transfer with hoist; (*vii*) roll and sit up; (*viii*) sit with NO support; (*ix*) transfer with feet on floor; (*x*) standing; (*xi*) walking; and (*xii*) stairs. For analyses, 3 main activity categories were explored: in bed (activities 1–4), sitting out of bed (activities 5–8), and all other activities with the feet on the floor were defined as upright activity (activities 9–12) (10).

Commencement of mobilization

The time to the first mobilization out of bed from hospital admission was registered prospectively.

Baseline assessment

Demographic information, including age, gender, premorbid function by modified Rankin Scale (mRS) (17), premorbid living conditions, stroke severity obtained by National Institute of Health Stroke Scale (NIHSS) (18), stroke type (infarction or haemorrhage), and mRS at inclusion were recorded.

Outcome assessment 3 months post-stroke

Degree of disability was obtained by mRS, with scores ranging from 0 (no sign or symptoms) to 6 (death). The assessment was performed as a structured interview, either face to face or by phone, with a trained assessor. Phone assessment is shown to be a reliable method to determine mRS (19, 20). For those not able to answer, healthcare providers were used as proxies or data were derived from the hospital records.

HRQoL was assessed by the European Quality of Life-5 Dimension-5 Level (EQ-5D-5L) instrument (21). EQ-5D-5L is a generic HRQoL measure consisting of 5 specific questions regarding mobility, self-care, pain/discomfort, usual activities and anxiety/depression and a visual analogue scale (EQ-VAS) where the patients demonstrate their general health state, with the worst imaginable health scored as 0 and the best imaginable health as 100. The 5 levels of answer categories, range from no problem in the given dimension (level 1: e.g. "I have no problems in walking about") to worse outcome (level 5: e.g. "I am unable to walk about"). The 5 dimensions constitute a health profile, which can be transformed into an index value, with range from –0.6 (worse health outcome) to 1.0 (best outcome). To obtain the EQ-index values we used the Danish interim EQ-5D-5L value set. EQ-5D-5L is available for telephone interview and has been shown to have better measurement properties in different chronic conditions including stroke, than the previous EQ-5D-3L (22, 23).

Data processing and analysis

The highest level of activity in every 10-min interval was recorded in the database (Microsoft Access 2007). The recorded activity levels were put into 1 of the 3 pre-defined activity categories, and the proportion of time spent in each category was calculated.

Statistical analyses were conducted using IBM SPSS version 21 and the gologit2 program in Stata version 12.

Descriptive statistics were used to report the mean and proportion of baseline variables, mean time in motor activity and the distribution of the mRS score and the EQ-5D-5L at 3 months follow-up. *t*-test statistics and Mann-Whitney *U* test were used to compare mean and median between the subgroups answering and not answering EQ-5D-5L at follow-up.

Missing activity data was imputed as sitting out of bed if 1–2 observations were missing because the patient was in the bathroom. If more than 2 observations were missing it was maintained as not observed. Missing activity data because of computed tomography (CT)/ magnetic resonance (MR) scan or ultrasound of heart and blood-vessels were also imputed as in bed activity. All other "not observed" were categorized as missing. For patients not mobilized at all, time to first mobilization was imputed as the time from admission to the time at the end of the observation.

To determine which variable was the strongest predictor for functional outcome (mRS score at 3 months) among a set of possibly correlated variables (the motor activity data) the proportional odds model, recommended by the OAST collaboration was used (24). In the proportional odds model the odds ratios (ORs) are assumed to be equivalent across all mRS-cut-points (e.g. 0 vs 1–6, then 0–1 vs 2–6, and so on). This is a straight-forward generalization of the logistic regression model. The "Brant test" was used to analyse whether this assumption was fulfilled (24).

To determine the strongest predictor for good HRQoL (EQ-5D-5L), a linear regression model was used because the standardized residuals of EQ-VAS and EQ-index were normally distributed except for a few outliers of EQ index-value.

The independent variables of interest were: (*i*) time spent in bed, (*ii*) time spent sitting out of bed, (*iii*) time spent in upright activity, and (*iv*) time from admission to first mobilization. In addition, a set of important predictors were added as covariates. Age was added because younger patients are shown to have better outcomes (25), NIHSS score was added because severe initial neurological impairment is shown to be associated with death and disability (26), pre-stroke mRS was added because pre-stroke disability is shown to be associated with poorer outcomes (1), and gender was added, even though the association with outcome is unclear (1). Finally, hospital site was added as a covariate to adjust for any possible hospital effects. The independent variables were tested in both a simple and a comprehensive multivariable model. In the simple model each independent variable was evaluated 1 at a time. In the comprehensive model time in bed and time upright were entered simultaneously and the third category (time sitting out of bed) was kept out of the analysis because it is co-dependent on the other 2 activity categories. This means that changes in 1 activity category keeping the second category constant was at the expense of sitting out of bed, which was not added to the model. Time to first mobilization was also entered in the comprehensive model.

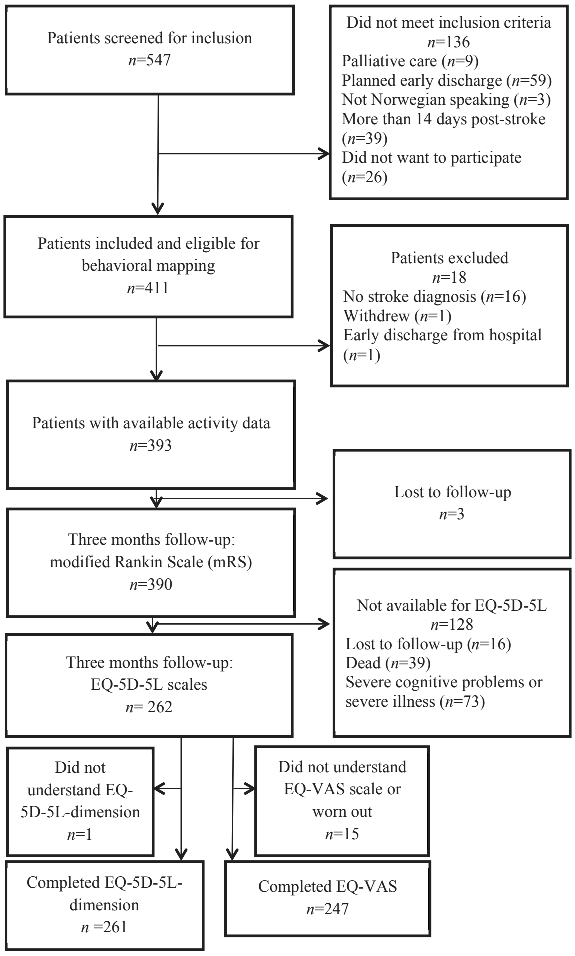

Fig. 1. Patients screened for inclusion and reason for drop out. EQ-5D-5L: European Quality of Life–5 Dimensions–5 Levels; EQ-VAS: European Quality of Life – 5 Dimensions – 5 Levels VAS scale score.

RESULTS

The study was performed between December 2011 and September 2013. A total of 547 patients were screened for inclusion. Fig. 1 shows the flow of patients through the study. A total of 390 patients were available for the analysis of mRS at 3 months, while 262 patients were available for analysis of EQ-5D-5L or EQ-VAS at 3 months. Out of these patients 261 answered the EQ-5D-5L and 247 answered the EQ-VAS. The main reasons for missing EQ-5D-5L scores were death ($n = 39$) or severe cognitive impairments or illness ($n = 73$), while 16 patients were lost to follow-up. The 14 patients who responded to the EQ-5D-5L, but not the EQ-VAS, reported problems in dealing with the VAS scale.

Seven patients were not mobilized out of bed because of severe strokes and unstable clinical condition.

The NIHSS score and, age at inclusion, in addition to median (interquartile range; IQR) mRS score at 3 months, differed significantly between those responding to the EQ-5D-5L ($n = 262$) and the stroke survivors not responding ($n = 89$). The mean (SD) differences between the 2 groups were 5.0 (5.0) points vs 12.3 (8.5) points, $p < 0.000$, on NIHSS, 74.6 (11.5) years vs 79.3 (9.0) years, $p < 0.0003$, on age and median (IQR) 3.0 (2.0–3.0) points vs 5.0 (4.0–5.0) points, $p < 0.000$, for mRS, respectively.

Table I shows the baseline characteristics of the included patients, while the mean (SD) and median (IQR) percentage of daytime spent in different motor activity levels are presented

Table I. *Baseline characteristics of patients* n = *390*

Patients' characteristics	
Age, years, mean (SD), median (range)	76.8 (11.3) 79.0 (30–100)
Male, *n* (%)	189 (48.1)
First-ever stroke, *n* (%)	284 (72.3)
Time since stroke, days, mean (SD), median (range)	5.1 (2.8) 5 (1–14)
NIHSS score, mean (SD), median (range)	7.9 (7.7) 5 (0–34)
Severity groups, *n* (%)	
Mild stroke (NIHSS < 8)	249 (63.8)
Moderate stroke (NIHSS 8–16)	76 (19.5)
Severe stroke (NIHSS > 16)	65 (16.7)
Stroke classification, *n* (%)	
Infarction	334 (85.6)
Haemorrhage	56 (14.4)4

SD: standard deviation; NIHSS: National Institute of Health Stroke Scale.

in Table II. The results showed that 266 (76.7%) of all patients were mobilized within 24 h of admission.

Fig. 2 shows that the number (%) of patients classified with mRS ≤ 2 (independent) increased from 76 (19.4%) at inclusion to 138 (35.4%) at 3 months follow-up. A total of 39 (10.0%) patients died during follow-up. Table III shows the distribution of EQ-5D-5L dimension responses at the 3-month follow-up. The number (%) of patients reporting moderate to extreme problems within the different domain was 77 (29.5%) for mobility, 50 (19.2%) for self-care, while 91 (34.9%) patients reported moderate to extreme problems within the domain of usual activities. For the domains pain/discomfort and anxiety/depression the corresponding numbers were 59 (22.6%) and 45 (17.2%), respectively, while the mean (SD) EQ-index and EQ-VAS score were 0.72 (0.25) and 60.0 (20.8), respectively.

Associations with outcome at 3-month follow-up

The partial proportional odds assumption was fulfilled for all independent variables, as the Brant's test was not significant.

Table II. *Time spent in different motor activities as a percentage of the day and time from admission to first mobilization (*n = *390)*

Motor activity category	Mean (SD)	Median (IQR)
Time spent in upright, % of day	8.3 (8.8)	5.5 (1.8–12.7)
Time spent sitting out of bed, % of day	43.3 (22.0)	44.5 (27.3–58.6)
Time spent in bed, % of day	44.1 (26.7)	41.8 (23.6–61.8)
Not observed, % of day	4.3 (7.4)	0.0 (0.0–5.5)
Time from admission to first mobilization, h	21.0 (31.9)	9.0 (2.5–22.3)

SD: standard deviation.

In the simple model, assessing one independent variable at a time adjusted for the covariates (NIHSS score, age, gender, pre-stroke mRS and hospital-site) the OR for poorer functional outcome (e.g. higher mRS score) was 0.96 (95% confidence interval (95% CI) 0.94–0.99, $p = 0.010$) as time in upright activity increased. The linear regression analysis for EQ-5D-5L showed that more time in upright activity was associated with an increase in EQ-index score, Beta 0.178 (95% CI 0.067–0.289, $p = 0.002$) and EQ-VAS score Beta 0.185 (95% CI 0.060–0.307, $p = 0.004$). Despite a significant association between increased time in bed and a decline in EQ-VAS, Beta –0.140 (95% CI –0.261 to – 0.018, $p = 0.024$), there were no other significant associations between time sitting out of bed, time in bed or time to first mobilization and outcome (Table IV).

In the comprehensive model, which included 2 activity categories and time to first mobilization at a time, adjusted [AQ4] for the covariates, the odds for poorer functional outcome decreased as time spent upright increased, OR 0.97 (95% CI: 0.94–1.00, $p = 0.048$). The comprehensive linear regression model also showed a significant positive association between time spent upright and EQ-index, Beta 0.184 (95% CI 0.055–0.312, $p = 0.005$) and EQ-VAS, Beta 0.153 (95% CI 0.008–0.296, $p = 0.038$) after adjusting for all covariates. The association between time to first mobilization and outcome

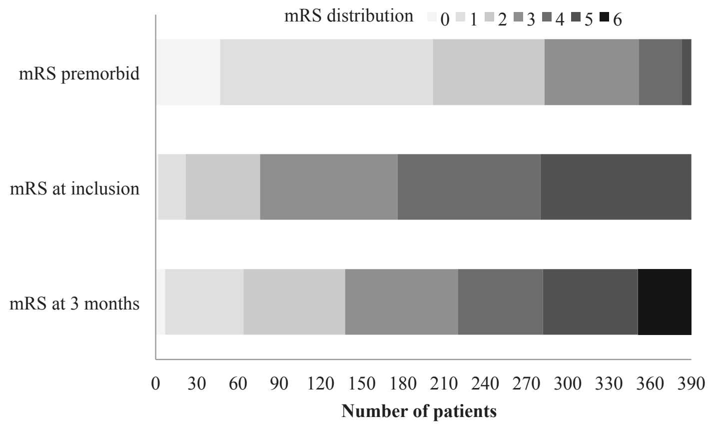

Fig. 2. Distribution of modified Rankin Scale (mRS) at different time-points.

Table III. *Distribution of EQ-5D-5L dimension responses at 3-month follow-up (*n = *261)*

Level	Mobility *n* (%)	Self-care *n* (%)	Usual activities *n* (%)	Pain/ discomfort *n* (%)	Anxiety/ depression *n* (%)
1	107 (41.0)	164 (62.8)	106 (40.6)	140 (53.6)	161 (61.7)
2	77 (29.5)	47 (18.0)	64 (24.5)	61 (23.4)	55 (21.1)
3	33 (12.6)	18 (6.9)	39 (14.9)	31 (11.9)	32 (12.3)
4	30 (11.5)	24 (9.2)	27 (10.3)	26 (10.0)	9 (3.4)
5	14 (5.4)	8 (3.1)	25 (9.6)	2 (0.8)	4 (1.5)

EQ-5D-5L: European Quality of Life–5 Dimensions–5 Levels; Level 1: indicating no problem; Level 2: indicating slight problems; Level 3: indicating moderate problems; Level 4: indicating severe problems; Level 5: indicating extreme problems.

was not significant in any analyses. The analysis included only those patients completing at 3 months (Table IV).

DISCUSSION

This multi-site study of 390 acute stroke patients admitted to 11 Norwegian stroke units is currently the largest observational study assessing the association between upright activity measured on a single day during post-stroke hospital stay and outcome 3 months later. The main finding was a significant association between higher amount of early upright activity and good outcome, but no association was found between time to first mobilization and outcome 3 months later after adjusting for important predictors of activity and outcomes such as stroke severity, age, sex and pre-stroke function.

In the present study, patients were mobilized, in mean, 21 h after admission, 76.7% of the patients were mobilized within 24 h of admission, and 44% had little or no disability (mRS 0–2) 3 months post-stroke. Given the broad inclusion criteria for this study (all patients not receiving palliative care) this pattern of mobilization commencement probably reflects adaptations for the severely affected and unstable patients in usual care.

The comprehensive multivariate model applied in this study included time to first mobilization and 2 activity categories as independent variables. Because time spent in bed, sitting out of bed and time in upright activity always add up to almost 100% (will add up to 100% if "time not observed" is included), the effect of the variable of interest, holding the second variable constant, will be at the cost of the third variable not included in the model, which was sitting out of bed. This means that for every % increase in time in upright at day-time between 08.00 h and 17.00 h (which translates into 5.4 min) we expect a 3% decrease in the risk of poorer outcome (higher mRS score), holding time in bed and time to first mobilization constant.

Our results suggest that a linear relationship exists between the amount of upright activity and good outcome (the more the better), which has also been proposed in earlier research (27). However, results from the recent AVERT trial indicate that caution needs to be applied in the early post-stroke period (i.e. too much training may be harmful) (8). This new knowledge needs to be balanced against our current understanding that too much bed rest and delaying mobilization can also be harmful (5, 6, 12). Whether the period for greatest caution is the first day or several days post-stroke is currently unknown.

The present study also showed a strong association between early activity and HRQoL, confirming the positive association between increased motor activity and HRQoL shown in other studies (28, 29). This finding was not unexpected, as the EQ-5D-5L is shown to be strongly correlated with the mRS (30). The EQ-5D-5L scores reported among the participating patients were mainly in line with previous studies assessing HRQoL in stroke survivors (31, 32). This was evident even though our population was more dependent compared with the other studies (31, 32).

Table IV. *Partial proportional odds model and linear regression analysis for the association between motor activity and outcome at 3-month follow-up*

	mRS[c]		EQ-Index[d]		EQ-VAS[d]	
Independent variables	OR (95% CI) (*n*=390)	*p*-value	Beta (95% CI) (*n*=261)	*p*-value	Beta (95% CI) (*n*=247)	*p*-value
Simple multivariate model[a]						
Time upright	0.96 (0.94 to 0.99)	0.010	0.178 (0.067 to 0.289)	0.002	0.185 (0.060 to 0.307)	0.004
Time sitting out of bed	0.99 (0.98 to 1.00)	0.221	–0.010 (–0.118 to 0.097)	0.848	0.074 (–0.047 to 0.195)	0.232
Time in bed	1.01 (1.00 to 1.02)	0.064	–0.075 (–0.183 to 0.034)	0.176	–0.140 (–0.261 to –0.018)	0.024
Time to first mobilization	1.00 (0.99 to 1.01)	0.985	–0.045 (–0.151 to 0.062)	0.411	0.006 (–0.116 to 0.128)	0.921
Complex multivariate model[b]						
Time upright	0.97 (0.94 to 1.00)	0.048	0.184 (0.055 to 0.312)	0.005	0.153 (0.008 to 0.294)	0.038
Time in bed	1.00 (0.99 to 1.01)	0.480	0.018 (–0.107 to 0.142)	0.778	–0.074 (–0.215 to 0.066)	0.299
Time to first mobilization	1.00 (0.99 to 1.01)	0.898	–0.023 (–0.130 to 0.085)	0.678	0.040 (–0.082 to 0.163)	0.516

[a]In the simple multivariable model each independent variable was evaluated 1 at a time. The analyses were adjusted for age, sex, pre-stroke function obtained by mRS, stroke severity obtained by National Institutes of Stroke Scale and hospital site.

[b]In the comprehensive multivariable model 2 independent variables were entered simultaneously. The analyses were adjusted for age, sex, pre-stroke function obtained by mRS, stroke severity obtained by National Institutes of Stroke Scale and hospital site.

[c]Partial proportional odds model.

[d]Linear regression analyses.

OR: odds ratio; mRS: modified Rankin Scale; EQ-Index: European Quality of Life – 5 Dimensions – 5 Levels index score; EQ-VAS: European Quality of Life – 5 Dimensions – 5 Levels VAS scale score.

Although stroke patients rate their self-perceived health a little lower than the general age-matched population (33), their quality of life is generally good. In Norway, most hospitals offer an early supported discharge service, which has been shown to improve HRQoL in both rural and urban areas (34, 35).

This study had a number of limitations. First, the observational design increased the risk of confounding factors associated with outcome. Secondly, there was a lack of observation of patients from 17.00 h to 08.00 h the next morning. However, the time from 08.00 h to 17.00 h is regarded as the most active time of the day, with the highest number of nurses and therapists present on the ward. A further limitation is the high proportion of patients ($n=73$) who did not respond to EQ-5D-5L because of cognitive problems or severely illness. Although proxies rate HRQoL lower than the patients themselves, a recent evaluation of EQ-5D-5L found that a proxy respondent could be used for patients not able to respond because of aphasia or dementia (23). Hence, proxies should be considered for use in future studies within this field.

The major strengths of the present study were the large sample size, including almost 400 patients from 11 Norwegian stroke units, and the naturalistic study design investigating clinical practice as usual. The study sample appears to be slightly older, with more severe strokes compared with the average Norwegian stroke population (36). The follow-up procedure, whereby all patients were contacted in person or by phone if possible, and the use of proxies ensured a high response rate, particularly for mRS. Another strength was the use of behavioural mapping to measure the amount of motor activity. This is a well-documented method, which has shown good correlation with accelerometer device (37). However, a body-worn sensor system might be an alternative method to investigate how the activity pattern changes across multiple days during hospital stay in future research.

Despite the current unknowns, this study supports previous work, including the results from the AVERT trial, showing good outcome associated with early out of bed activity in usual care (8), and shows that activity applied within the first week after stroke is associated with functional independence 3 months later. However, future research should focus on exploring the pathophysiological mechanisms associated with early upright activity and on determining the optimal dosages of activity and rest during the early phase after stroke.

In conclusion, this study confirms the beneficial effect of upright activity applied during hospital stay in Norwegian stroke units on global function and HRQoL 3 months later. There was no association between timing of mobilization and outcome. However, the optimal timing, frequency and dosage of early activity needs to be determined. There is also a need for a more thorough understanding of the pathophysiological mechanisms associated with early upright activity after stroke.

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The authors declare no conflicts of interest.

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Paper III

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Prevalence of fatigue in patients 3 months after stroke and association with early motor activity: a prospective study comparing stroke patients with a matched general population cohort

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Abstract

Background: Fatigue is a common complaint after stroke. Reasons for higher prevalence are still unclear. This study aimed to determine if fatigue prevalence in stroke patients is different to that of age and gender matched general population controls, and to explore whether early motor activity was associated with reduced likelihood of fatigue three months after stroke.

Methods: This was a prospective multicenter cohort study of stroke patients admitted to eleven regional Norwegian hospitals, within 14 days after stroke. Stroke patients ($n = 257$) were age and gender matched to participants in a general population health survey (HUNT3-survey) carried out in a regional county of central Norway. The single-item fatigue questionnaire from the HUNT3-survey was administered to both groups to compare prevalence. The association between early motor activity (*time in bed, time sitting out of bed*, and *time upright)* and fatigue at three months after stroke (Fatigue Severity Scale) was tested with logistic regression. Simple models including each activity outcome, with adjustment for stroke severity and pre-stroke function, were tested, as well as a comprehensive model that included additional independent variables of depression, pain, pre-stroke fatigue, age and gender.

Results: Prevalence was higher after stroke compared with the general population: 31.1 % versus 10.9 %. In the simple regression models, none of the early motor activity categories were associated with fatigue three months after stroke. In the comprehensive model, depression, pain and pre-stroke fatigue were significantly associated with post-stroke fatigue. Time in bed through the daytime during hospital stay approached statistical significance ($p = 0.058$) with an odds ratio for experiencing fatigue of 1.02 (95 % CI 1.00-1.04) for each additional 5.4 minutes in bed.

Conclusions: Stroke patients had higher prevalence of fatigue three months after stroke than the age and gender matched general population sample, which may be partly explained by the stroke population being in poorer health overall. The relationship between early motor activity (and inactivity) and fatigue remains unclear. Further research, which may help drive development of new treatments to target this challenging condition, is needed.

Keywords: Stroke, Fatigue, Physical activity, Early mobilization, HUNT

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Background

Fatigue is described as a "constant weariness unrelated to previous exertion levels and not usually ameliorated by rest" [1]. Perceptions of fatigue are a common complaint among older people and for those with a range of chronic diseases including stroke. The prevalence of fatigue in the general population has been variably reported from 5 to 47 %, depending on the population studied, the questionnaire used, and the threshold score used to differentiate those with fatigue from those without [2–5]. Prevalence appears to increase with the number of chronic diseases [6, 7], and is higher in women [8], but findings are inconsistent for age [3, 9].

Prevalence is elevated even further following stroke, ranging from 35 to 92 % [10], again depending on the tool used to measure fatigue, but also depending on the time since stroke and sample selection strategies [10–13]. Post-stroke fatigue (PSF) is distressing and debilitating. It is associated with higher levels of dependency [14, 15] and poorer quality of life [16]. It also independently predicts institutionalization and mortality after stroke [17, 18]. Fatigue is rarely assessed in clinical practice and poorly managed, largely because strong evidence supporting effectiveness of fatigue-reducing interventions, either for fatigue in general, or for fatigue unique to stroke patients, is lacking.

Fatigue after stroke is complex, and while fatigue can be experienced secondary to medications, sleep disorders and/or medical complications [19], it is probable that PSF also relates to the brain injury itself [14, 17, 20–22]. Ongoing fatigue may be compounded by reduced activity and subsequent deconditioning, particularly in the sub-acute phase, perhaps in combination with the increased energy cost of movement due to impairment [22–25]. Our current understanding of the biology of fatigue is limited. Understanding how PSF may differ from other fatigue is clinically important as unique management options may be required. If deconditioning and movement inefficiency play a crucial role in the experience of fatigue later after stroke, increased physical activity opportunities and movement training may be further endorsed as a treatment approach.

Several previous studies have investigated risk factors for PSF. Evidence suggests the main predictors for fatigue in the sub-acute phase are depression [11, 26], pre-stroke fatigue [26–28], and pain [29, 30]. Recent evidence suggests that activity early after stroke (step count at one month) predicts fatigue later after stroke (six and 12 months) [31]. However, knowledge is limited on the role of physical activity on fatigue levels for stroke patients, especially in the early phase after stroke.

Previous prevalence studies have often had restricted sample selection of stroke patients leading to sub-population analyses, and not controlling for age and gender in comparison populations [32–34]. The present study firstly aimed to determine the prevalence among a less selective stroke population three months after stroke, and to directly compare prevalence with an age and gender matched general population sample from a similar region. We hypothesized that the fatigue prevalence would be higher in the stroke sample. The second aim of this study was to investigate the relationship between motor activity early after stroke and PSF. Because some evidence exists supporting the positive impact of physical activity on fatigue, we hypothesized that patients engaged in more motor activity early after stroke would have reduced likelihood of fatigue at three months, after adjustment for stroke severity and pre-stroke function, and independent of depression, pain, pre-stroke fatigue, age and gender. A reversed causal pathway was also considered possible as the reduced activity early after stroke may be caused by fatigue which then persists three months after stroke [13].

Methods

Study design and settings

This was a prospective observational study including patients admitted to eleven Norwegian hospitals [35]. An age and gender matched control group was derived from a population-based study in the county of Nord-Trøndelag [36], were two of the eleven hospitals were located.

Study participants

From 1st December 2011 to 11th June 2013, all consecutive acute first ever or recurrent stroke patients (except those with subarachnoid haemorrhages) admitted to the eleven stroke units were invited to participate, provided they were over 18 years of age, understood Norwegian and were not on palliative treatment. Stroke was defined according to the World Health Organisation definition. Recruitment was within 14 days after stroke onset. In keeping with Norwegian consent procedures, for patients unable to sign informed consent, verbal consent to participate was obtained from their next of kin. Further details of the study methods can be found in a prior publication [35]. Patients alive at three months, were contacted either in person or by telephone interview for assessment of perceptions of fatigue, depression, and pain.

Community-dwelling controls came from the Nord-Trøndelag population Health Survey3 (HUNT3-survey) [36]. The HUNT3-survey is a population-based study of the Norwegian county of Nord-Trøndelag. Two of the eleven hospitals in the stroke study were located in Nord-Trøndelag. Data were collected from October 2006 to June 2008. All adult residents aged ≥ 20 years were invited to participate in the study. The HUNT3-

survey included several priority public health issues, and questionnaires included fatigue [37, 38], as outlined below. Of 93,860 eligible adults, 50,807 (54.1 %) returned the questionnaire and written consent. Participation was highest among people 60–69 years (71 %) decreasing to 18 % in the oldest age group 90–96 years. There was a selection bias toward more healthy individuals and higher socioeconomic status [39].

Ethics

The Regional Committee for Medical and Health Research Ethics in Central Norway approved the study and storage of data on behalf of all participating hospitals and also the use of data from the HUNT3-survey (REC numbers 2011/1428 and 2012/675 respectively).

Baseline assessment of stroke patients

Baseline characteristics of the stroke participants measured at inclusion included age, gender, pre-stroke function measured by modified Rankin scale (mRS) [40], stroke severity measured using National Institutes of Health Stroke Scale (NIHSS) [41], stroke type by Oxford classification [42], co-morbidities and pre-stroke fatigue. Pre-stroke fatigue was estimated from the following two items: 'Did you experience fatigue before you had your stroke' (yes/no), and, 'If yes, how long did you experience fatigue' (less than a week, less than three months, 3–6 months and more than six months). Patients who reported fatigue lasting longer than three months before the stroke were classified as having pre-stroke fatigue [11].

For the early motor activity outcomes, participants were observed every 10th minute during a working day from 8.00 am to 5.00 pm using the method of *behavioural mapping*. Motor activity was defined as the proportions of the daytime spent (i) *in bed*, (ii) *sitting out of bed* and (iii) *upright*. The procedure was reported in detail in a previous publication [43].

Data extracted from the HUNT3-survey

Age and gender were used to select the general population sample from HUNT3-survey participants and data collected from the matched participants included comorbidities and fatigue.

Outcome measures

Stroke patients were assessed three months after the stroke. Fatigue was measured in both samples (stroke and controls) using a simple fatigue questionnaire from the HUNT3-survey. This was a single question about weariness/fatigue: "Do you feel, for the most part, strong and fit or tired and worn out?". There were seven response categories which ranged from "1 = very fit and healthy" to "7 = very tired and worn out", with the middle option as neutral. Fatigue was defined as a score ≥ 5. In the stroke group, a second fatigue questionnaire, the Fatigue Severity Scale (FSS) was also administered. The 9-item FSS is the most commonly used scale to measure fatigue in stroke patients [16, 28, 44]. The shorter 7-item version of the FSS, FSS-7, was shown to have better psychometric properties in patients with stroke than the original 9-item version [2]. The FSS-7 was therefore chosen for this study.

Pain was assessed by a simple question 'Did you experience new pain after stroke? (yes/no)'. Depression was assessed by Hospital Anxiety and Depression Scale (HADS) [45]. HADS is a self-report questionnaire which comprises two subscales HADS-anxiety and HADS-depression (HADS-D), each with seven items scored from zero to three. The scores are summed to give a total score for each subscale ranging from 0 to 21.

Data management and analysis

Stroke patients were matched by age (up to a maximum of 2 years difference) and gender to respondents from the HUNT3-survey [36] who had all the outcome measures of interest to this study and no history of previous stroke. The HUNT participant of the same gender with the closest age (in 0.1 year increments) to each stroke participant was selected, with the matching procedure carried out blinded to any other outcome measure. The number of participants with available data determined the sample size for the study.

FSS scores from the 7-point Likert scale response options were averaged to yield a score from 1.0 to 7.0. Higher scores indicate higher fatigue levels. Most studies recommend a cut-off score of ≥ 4.0 as indicative of fatigue [33, 46]. The FSS-7 and HADS-D questionnaires were excluded if less than four items were answered. Up to three missing items were imputed with the average of the answered items.

Fatigue prevalence was examined in both groups using the HUNT3-survey questionnaire. The proportion of participants from each group reporting fatigue ≥ 5 on this questionnaire was compared using the chi-square test. Fatigue prevalence among the stroke patients was also reported using the FSS-7 with cut off of ≥ 4.0.

The association between early motor activity and PSF was tested using logistic regression models with fatigue dichotomised using FSS-7 score ≥ 4.0. Proportion of daytime *in bed*, *sitting out of bed* and *upright* were each tested in separate simple models. Stroke severity (NIHSS score) and pre-stroke function (mRS) were included as covariates. A single comprehensive multivariable logistic regression model also including HADS-D score, pain, pre-stroke fatigue, age and gender as additional independent variables was also examined. In this model both *time in bed* and *time upright* were included but *time sitting out of bed* was excluded as it is co-dependent on the other two activity categories. This model was designed to determine whether early motor activity or inactivity were independently associated with fatigue at 3 months.

Results

Two hundred and fifty-seven stroke participants were age and gender matched to HUNT3-survey participants for the prevalence study, and 199 stroke participants had the outcome measures needed for inclusion in the regression models (Fig. 1). Four patients had missing items on the FSS-7 questionnaire (one had three items missing and three had one item missing) and had the missing data imputed. There was a mean of 4.2 (SD 2.8) days from admission to the stroke unit to the day of inclusion in the study and behavioural mapping. Table 1 shows the descriptive data and fatigue prevalence for the age-gender-matched cohort. Data were available in both groups for several comorbid diseases. These were hypertension, heart failure, myocardial infarct, lung disease (including asthma and COPD), kidney disease, diabetes mellitus, cancer and connective tissue disease (including rheumatoid arthritis and spondylitis). Thirty-four percent of the HUNT3-survey cohort had none of these diseases, while only 16 % of the stroke patients had none. Twenty-five percent of the stroke patients had three or more of the diseases, compared with only 11 % in the general population. Most patients were classified as PACI (40 %) according to the Oxford Classification, with only 7 % as TACI. Prevalence of fatigue ranged from 24 to 41 % across the different classification groups using the HUNT3 survey fatigue question, and ranged from 35 to 44 % using FSS-7.

Chi-square test indicated a significant difference in fatigue prevalence between the groups (31.1 % among stroke versus 10.9 % among healthy controls, $p < 0.001$). Odds of a stroke patient experiencing fatigue three months after stroke were 3.7 times the odds for the general population. The prevalence of fatigue was broadly similar if using the FSS-7 scale with a cut off of ≥ 4.0 for

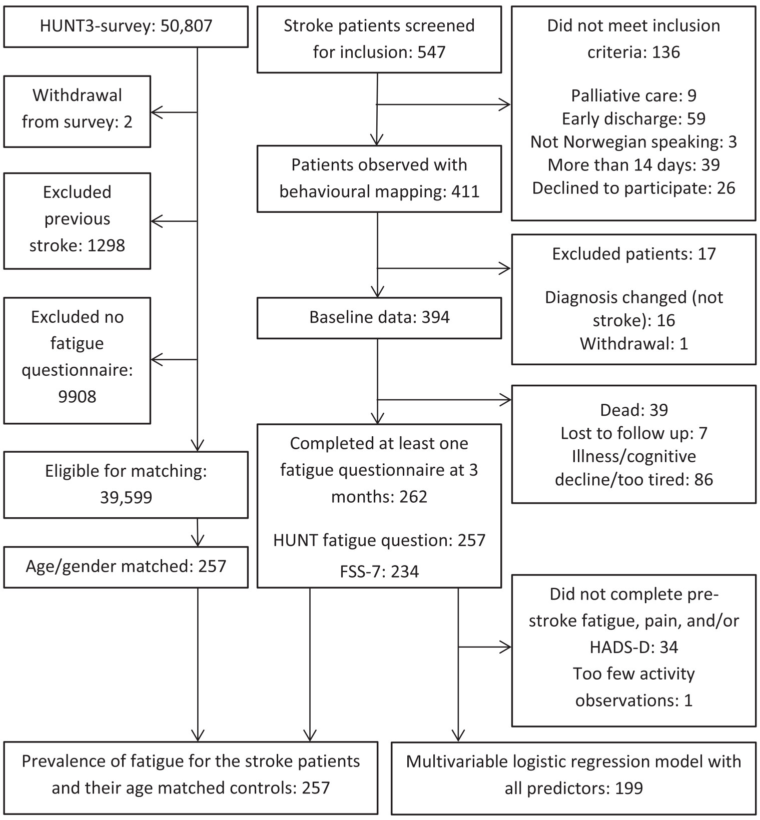

Fig. 1 Flow of participants through the study

Table 1 Descriptive data and prevalence

			Stroke	HUNT3-survey
Gender, % female			46.3 %	46.3 %
Age, mean (SD, range)			74.8 (11.4, 30.7–91.7)	74.8 (11.5, 30.7–92.5)
HUNT3 fatigue question (Do you feel, for the most part, strong and fit or tired and worn out?), n (%)	1. Very strong and fit		6 (2.3 %)	11 (4.3 %)
	2. Strong and fit		29 (11.3 %)	42 (16.3 %)
	3. Somewhat strong and fit		60 (23.3 %)	88 (34.2 %)
	4. Somewhat in between		82 (31.9 %)	88 (34.2 %)
	5. Somewhat tired and worn out		42 (16.3 %)	21 (8.2 %)
	6. Tired and worn out		20 (7.8 %)	6 (2.3 %)
	7. Very tired and worn out		18 (7.0 %)	1 (0.4 %)
Fatigue (HUNT3), % score ≥ 5			31.1 %	10.9 %
Fatigue (FSS-7), % score ≥ 4.0			34.6 %	-
Early motor activity, mean (SD)	% of day in bed		36.6 (23.4)	-
	% of day sitting out of bed		47.4 (19.9)	-
	% of day upright		10.9 (9.2)	-
	% of day not observed		5.1 (7.9)	-
Stroke severity (NIHSS), mean (SD)			5.0 (5.0)	
Function at inclusion (mRS), median, mean (SD)			3, 3.2 (1.1)	-
Function at 3 months (mRS), median, mean (SD)			2, 2.5 (1.2)	-
		n (% of cohort)	% reporting fatigue with HUNT3, FSS-7	
Oxford stroke classification groups	TACI	17 (7 %)	41 %, 38 %	-
	PACI	103 (40 %)	34 %, 40 %	-
	LACI	58 (23 %)	24 %, 35 %	-
	POCI	47 (18 %)	30 %, 44 %	-
	Haemorrhagic	32 (13 %)	31 %, 35 %	-
Co-morbidities, % of cohort	Hypertension		68 %	48 %
	Heart failure		10 %	7 %
	Myocardial infarct		19 %	14 %
	Lung disease (including asthma and COPD)		12 %	14 %
	Kidney disease		3 %	2 %
	Diabetes mellitus		15 %	11 %
	Cancer		18 %	9 %
	Connective tissue disease (including rheumatoid arthritis and spondylitis		8 %	8 %

Descriptive data, prevalence of fatigue and early motor activity data are provided for the stroke patients ($n = 257$) and their age/gender-matched counterparts ($n = 257$) from HUNT3-Survey

FSS-7 7-item Fatigue Severity Scale, *mRS* modified Rankin Scale (range of scores 0–5), *NIHSS* National Institutes of Health Stroke Scale (range of scores 0–42), *COPD* chronic obstructive pulmonary disease

fatigue or using the HUNT3-survey fatigue question with cut off of ≥ 5 (34.6 and 31.1 % respectively).

The simple regression models testing the association of each of the early motor activity variables with fatigue (controlling for pre-stroke function and stroke severity) showed no association: proportion of *time in bed* OR 95 % CI 0.99–1.02 ($p = 0.14$), *time sitting out of bed* OR 95 % CI 0.98–1.01 ($p = 0.21$), and *time upright* OR 95 % CI 0.96–1.03 ($p = 0.58$). In the comprehensive model, which included the independent variables in the simple models plus age, gender, pre-stroke fatigue, depression, and pain, only pre-stroke fatigue, depression and pain were significantly associated with fatigue at three months (Table 2). Proportion of *time in bed* approached significance ($p = 0.058$). If the point estimate for *time in*

Table 2 Descriptive data and results of comprehensive multiple variable regression model

Independent variables		B	OR (95 % CI)
Gender, n (%) female	91 (45.7 %)	−0.58	0.56 (0.26–1.21)
Age, mean (SD, range)	73.8 (11.7, 30.7–91.3)	−0.002	1.00 (0.97–1.03)
Pre-stroke fatigue, n (%) yes	53 (26.6 %)	1.30*	3.67 (1.62–8.31)
Depression (HADS-D), mean (SD)	3.8 (3.8)	0.27*	1.31 (1.17–1.47)
Pain (new since stroke), n (%) yes	38 (19.1 %)	1.51*	4.55 (1.82–11.34)
Pre-stroke function (mRS), mean (SD)	1.4 (1.1)	0.04	1.04 (0.70–1.54)
Stroke severity (NIHSS), mean (SD)	4.0 (3.7)	0.07	1.08 (0.97–1.19)
Early motor activity:			
% of day in bed, mean (SD)	35.0 (22.8)	0.02*	1.02 (1.00–1.04)
% of day upright, mean (SD)	11.8 (9.3)	0.03	1.03 (0.98–1.07)

N = 199, dependent variable fatigue (FSS-7 score ≥ 4.0), *significant at $p < 0.05$, *significant at $p < 0.10$ (trend). 77 participants (38.7 %) had fatigue
HADS-D Hospital Anxiety & Depression Scale – Depression subscale (range of scores 0–21), *mRS* modified Rankin Scale (range of scores 0–5), *NIHSS* National Institutes of Health Stroke Scale (range of scores 0–42)

bed of B = 0.02 was correct, then for every additional 1 % of the daytime (approximately 5.4 min) spent in bed, there was 2 % greater odds of experiencing fatigue at three months, holding all other variables constant.

Pre-stroke fatigue was one of the strongest independent predictors of PSF in our model (OR 3.7, 95 % CI 1.6–8.3, $p = 0.002$). The percentage of stroke patients that reported pre-stroke fatigue (had experienced fatigue prior to their stroke lasting at least three months) was 27 %, which was much higher than fatigue in the general population (11 %), although different measurement questionnaires were used. Of the 53 stroke participants reporting pre-stroke fatigue, 30 (57 %), reported fatigue at three months. However, about a third (32 %) of the 146 without pre-stroke fatigue reported fatigue three months after stroke.

Discussion

The main finding from the study was, a higher prevalence of fatigue in stroke patients even after careful matching with a general population sample. Prevalence of fatigue three months after stroke was around one third, using either FSS-7 with a cut off ≥ 4.0, or using the HUNT3-survey questionnaire with a cut off ≥ 5. The prevalence is lower than most previous studies where prevalence was most often reported in the range of 50 %. There are several possible reasons for this difference. Most obviously, use of different questionnaires and different cut-offs to define fatigue will affect prevalence findings. However, a further possible explanation may be the older patient population in our study compared with other studies. Younger patients may be more aware of fatigue due to increased likelihood of wanting to return to work, more social activities, and higher activity levels [9, 12, 47]. We did not find compelling support for our hypothesis that more early motor activity would be associated with decreased likelihood of PSF. Our analysis confirms previous findings that prestoke fatigue, depression and pain are important predictors. *Time in bed* almost reached statistical significance in the model, with 95 % CI for OR ranging from 1.00 (no association) to 1.04 (4 % greater odds of having fatigue for every 5.4 min of extra bed rest).

The stroke patients were about three times more likely to report fatigue than their community-living counterparts who had not experienced stroke. Our results also showed that the stroke patients had more than double the likelihood of having at least one other disease prior to their stroke compared to the general population, and more than double the likelihood of having three or more other diseases. This finding suggests that the higher prevalence of PSF may be at least in part related to the stroke population being in poorer health even before they had a stroke. The previous literature on the association between pre-stroke co-morbidities and fatigue is not clear. A study in young patients found an association between PSF and both diabetes mellitus and myocardial infarction [32], while two other studies found no such association [14, 15]. PSF is a serious problem which clearly warrants better monitoring and management. Our findings suggest that pre-stroke health is an important factor in development of PSF.

Our findings hint at the possibility that early inactivity may be associated with fatigue at three months. This may be similar to the finding that more time in bed, but not less time in higher level activities, was predictive of worse functional outcome three months after stroke [48]. Previous bed rest studies have shown bed rest in general is not a benign treatment, but harmful to health [49, 50]. One possible mechanism by which bed rest could lead to higher levels of fatigue is the loss of cardiorespiratory fitness (CRF). CRF declines rapidly with bed rest [51], and is related to fatigue scores [52]. However, a recent review of cross-sectional studies found neither current physical activity levels nor CRF explained the level of fatigue experienced by people after stroke [53]. The risk of immobility-related complications increases with increased amounts of bed rest [54] suggesting that an association between fatigue and time in bed might also be explained by an increased prevalence of poststroke complications. The reverse causal pathway is also plausible, whereby early activity is dependent on the absence of fatigue. Despite our non-significant finding, we argue that further research is still needed to investigate how early fatigue and early inactivity are related to the problem of debilitating PSF.

A recent study found that patients with stroke, who had more effortful movement as determined by movement velocity during a timed hand movement task, were found to have increased likelihood of fatigue [22]. The authors proposed that the relationship could be due to either a simple effort-fatigue relationship or because both fatigue and reduced movement speed may result from an alteration in motor cortex excitability. With this finding in mind alongside our own results, PSF may be largely explained by a combination of poor pre-stroke health, effects of the brain injury (including early inflammatory effects), issues secondary to stroke during the acute phase (including medications, sleep problems and complications), depression, pain, the harmful consequences of too much inactivity, and increased effort of movement related to motor impairment.

Strengths of our study of PSF prevalence are the largely unselected stroke sample and the appropriate and well-matched control group. The main limitations of our study are that important confounding variables may be missing from the regression models such as cognitive function, medications and sleep disorders [19]. However, all models were adjusted for the most common and significant predicting variables after stroke. Secondly, there may be bias introduced because participants excluded due to lost to follow-up ($n = 7$), illness/cognitive decline/too tired ($n = 86$), or failure to complete pre-stroke fatigue, pain or depression questionnaires ($n = 34$) was potentially non-random. This group was likely to include the least healthy among the cohort. Thirdly, our measures of activity early after stroke may not adequately represent activity, or inactivity, of importance in preventing the development of PSF. All studies of PSF are limited by the multidimensional nature of fatigue and the inadequacies of the fatigue measurement tools used. Pre-stroke fatigue was measured with a different questionnaire to PSF, which may compromise our study, and early PSF was not measured. Finally, as the stroke units were all in Norway where national guidelines strongly recommend promotion of early out of bed activity, there may not have been sufficient between-individual spread of inactivity/activity levels for the role of early motor activity in predicting PSF to be revealed. The likelihood that the amount of bedrest is closely related to stroke severity and pre-stroke function also poses a challenge in this and future studies. Carefully controlling for these confounders as in the present study, using pre-stroke mRS and NIHSS in the models, is helpful but may still be inadequate. These limitations may have resulted in the lack of support for our second hypothesis.

Some previous research supports there being a difference between mental and physical fatigue, particularly after stroke. The impact of a stroke (irrespective of whether ischemic or haemorrhagic) taxes the central nervous system and increases the level of cognitive strain, which may be interpreted as fatigue. Stroke patients may be physically capable of participating in rehabilitation exercises or physical activity, but feel unable to engage in the activity due a depletion of cognitive reserves or higher vascular burden. Global increases in allostatic load coupled with negative affect may further compound this problem. Drawing a distinction between mental and physical fatigue is currently difficult and controversial and was not attempted in our study. However, we suggest further research along these lines may yield important knowledge and facilitate management of the problem of PSF in the future.

PSF presents management challenges with few options currently available with proven effectiveness [55]. A combined cognitive therapy and graded exercise program has shown promise in alleviating fatigue, as well as cognitive therapy alone [56, 57]. However these trials are small and more research is needed on the effect of multifactorial approaches including exercise programs. It is apparent from the results of observational studies that improvement of general health and management of depression, sleep and pain should all help alleviate PSF. We also suggest that determining the appropriate amount of time spent on bed-rest versus out of bed activities early after stroke warrants urgent further investigation in relation to fatigue [31].

Conclusions

Despite the lower prevalence of PSF in this relatively unselected stroke population than typically previously reported, this study confirms a higher prevalence than in those without stroke and further highlights the problem of PSF. Pre-stroke health appears to be an important factor, as does post-stroke depression and pain. The role of early motor activity in the development of fatigue following stroke remains unclear.

Abbreviations

NIHSS: National Institutes of Health Stroke Scale; mRS: Modified Rankin Scale; FSS-7: Seven-item Fatigue Severity Scale; HADS-D: Hospital Anxiety & Depression Scale – Depression subscale; OR: Odds ratio; CI: Confidence interval.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

BI and TA conceived the study. TE, AH, JB and TA designed the study and were involved in interpretation of the data. TE analysed the data and drafted the manuscript. AH participated in acquisition of data and data management. BI, JB, AH, and TA were involved in critically revising the manuscript. All authors read and approved the final manuscript.

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Appendix

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