Delirium in hip fracture patients: consequences, prevention strategies and pathophysiological mechanisms

Thesis by
Leiv Otto Watne
2014

Department of Geriatric Medicine
Oslo University Hospital
Oslo, Norway

Institute of Clinical Medicine
Faculty of Medicine
University of Oslo

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 1874

ISBN 978-82-8264-905-6

Cover: Hanne Baadsgaard Utigard.
Printed in Norway: AIT Oslo AS.

Produced in co-operation with Akademika Publishing.
The thesis is produced by Akademika Publishing merely in connection with the thesis defence. Kindly direct all inquiries regarding the thesis to the copyright holder or the unit which grants the doctorate.

Table of Contents

Acknowledgements

The work presented in this thesis was carried out at Oslo University Hospital from September 2009 to June 2014. My fellowship was funded by the Research Council of Norway.

I would like to thank the patients and their care takers participating in the study and the staff at the Department of Orthopedic Surgery and the Department of Geriatrics at Oslo University Hospital, Ullevaal.

I would especially express my gratitude to:

Torgeir B. Wyller: My main supervisor, for recruiting me to this project. You have given me valuable advices in all steps of the project. Your enthusiasm is inspiring!

Ingvild Saltvedt/Frede Frihagen: My co-supervisors for all your advices in planning the study and help in drafting the manuscripts. A special thanks to Frede for introducing me to your orthopedic colleagues and reminding them to include patients in the study.

Radojka Koristovic: My main clinical supervisor for teaching me how orthogeriatric care should be done in real life.

Anne Torbergsen: For assisting me in collecting data. And not the least for being a good companion in many (sometimes quite boring) sessions with the SPSS database.

Espen Molden: For doing the measurements of anticholinergic activity and helping with drafting my first scientific paper.

Knut Engedal: For sharing all your expertise and knowledge in the planning of the study and analysis of the results.

Ane Victoria Idland: Thank you for making our two-person open plan office tidier! I am very impressed that you also managed cognitively test and collect CSF from 155 healthy elderly persons!

Oslo Delirium Research Group: I am very grateful to be part one of the few groups in the World dedicated to delirium research! We have several exciting ongoing projects and many more are planned.

Vibeke Juliebø: My project was in some way a continuation of your PhD project. Thank you for sharing all your experience in how data collection is done!

Johan Ræder: For helping me to organize the collection of CSF from the hip fracture patients and for your competent advice in analysing the results and drafting of manuscripts.

Eva Skovlund: For answering all my questions regarding the statistics, planning of the analyses and writing the statistical analysis plan.

Anne Garmark, Anne Lise Eriksen and other colleagues at Loftet: The standard at our offices at Loftet must be the worst at the entire Oslo University Hospital, but the atmosphere must be the best! I really appreciate working with you!

Research nurses Elisabeth Fragaat, Camilla Marie Andersen, Tone Fredriksen, Linda Feldt, Julie Ask Ottesen: You were all carefully selected, and you all met our high expectations! I am very grateful that you did the data collection with such a degree of thoroughness, enthusiasm, empathy and humour. It has been great working with you!

Roanna Hall/Alasdair MacLullich: For being so kind to me at the EDA meeting in Amsterdam; I knew absolutely no one at my first scientific meeting. I think we already have accomplished a lot, and I am looking forward to continue the collaboration in the future.

Bjørnar Hassel: For doing so many interesting and advanced analyses of the CSF and serum samples and for explaining me what the results mean. I hope we get the chance to continue the collaboration in the future.

Family: To Oda, my wife, and our three wonderful children; Sjur, Ragni and Asta. Since I started to work with this project, our family has more than doubled in size. You know how much I love to be with my family, but nevertheless I predict that the children/scientific paper ratio will decrease from now.

Summary in English

Background

A hip fracture is a dramatic event with serious consequences. Many patients do not survive the first year after the fracture, and those who survive will often experience loss of function and increased need of assistance. Patients suffering a hip fracture are often elderly and frail, and many suffer from several medical conditions in addition to the fracture. The patients often use several medications, have malnutrition and poor social support. Dementia is very common. All these conditions are often seen among patients treated by geriatricians, and it has therefore been argued that a hip fracture is a geriatric, rather than an orthopedic disease. In many countries geriatricians have been involved in the care of such patients. A structured collaboration between orthopedic surgeons and geriatricians is labeled an orthogeriatric service. There exists a wide range of models of orthogeriatric care, and despite a lot of research, it is still not concluded which orthogeriatric model is most effective. Due to demographic changes, an increase in the number of hip fractures can be expected in the future. With limited resources it is therefore interesting to know which orthogeriatric model is best.

Delirium, an acute change in cognition and alertness, is a common complication in hip fracture patients and is associated with poor outcome, including a dramatically increased risk of dementia. There is little knowledge concerning what happens in the brain during delirium, and no effective drug treatment exists. Delirium can in many cases be prevented through optimizing the quality of medical care. Multidisciplinary geriatric intervention has been shown to be particularly effective in preventing delirium in hip fracture patients.

When this study first was planned, the main objective was to evaluate the orthogeriatric service in use at Oslo University Hospital - Ullevaal from June 2008 to January 2012. We hypothesised that the intervention could be effective in reducing delirium and thus prevent long term cognitive decline. During the work, some further aims have emerged, including studying the long-term consequences of delirium and its pathophysiology.

Methods

From September 2009 to January 2012, 329 patients acutely admitted with a hip fracture were included in this study. All patients were included in the Emergency Room (ER) at Oslo University Hospital, Ullevaal. In the ER, the patients were randomized to stay in either the acute geriatric ward or the orthopedic ward. The patients were sent directly from the ER to the allocated ward, and had their whole hospital stay in the same ward, except for surgery and a few hours in the post operative care unit.

While the patients were admitted in the hospital they were closely monitored for complications, especially delirium. The care givers were interviewed for pre-fracture cognitive function and function in activities of daily living (ADL).

Since the hip fracture patients often are elderly and frail, we believed that they could benefit of the expertise and routines established in the acute geriatric ward. We hypothesised that this intervention could be effective in reducing delirium and thus prevent long term cognitive decline. To explore this hypothesis, the patients were assessed with cognitive tests four and twelve months after surgery. In addition to evaluate the effect of the orthogeriatric model, we could use these data to explore the effect delirium had on cognition in the long run.

In relation to the surgery, cerebrospinal fluid (CSF) and blood samples were collected. These samples have been analyzed in order to explore possible pathogenic mechanisms in delirium. In these analyses we have also included samples collected from hip fracture patients in Edinburgh, and elderly patients undergoing other elective surgery in Oslo.

Results

We found no evidence that cognitive function four months after surgery was improved in patients treated pre- and postoperatively in an acute geriatric ward, compared to usual care in an orthopaedic ward. The intervention had, however, a positive effect on mobility in patients not admitted from nursing homes.

Delirium was an important predictor of accelerated cognitive decline in patients that had dementia before the fracture.

Anticholinergic activity was not higher in CSF or serum in patients with delirium compared to those that did not have delirium. In those patients that developed delirium, and did not have dementia before the fracture, AA was associated with delirium severity.

Neopterin (a marker of inflammation) was higher in CSF and serum in patients with delirium. This supports a theory of inflammation being important in the pathogenesis of delirium.

Conclusion

The orthogeriatric model tested in this study was not effective in reducing delirium or long term cognitive decline. There was, however, a trend that the intervention had a positive effect on mobility in patients not admitted from nursing homes.

Delirium is very common among hip fracture patients, and in our study 50 % of the patients were affected. We found that delirium was associated with acceleration of cognitive decline in patients that had dementia before the fracture.

Analyses of CSF and blood taken from the hip fracture patients in our study have given important new knowledge regarding the pathophysiology in delirium. Yet, much more research is needed to increase our understanding of this common, dramatic and serious condition.

Norsk samandrag

Bakgrunn

Eit hoftebrot er ei dramatisk hending, som har alvorlege konsekvenser for dei som vert råka. Mange vil ikkje overleve det første året, og av dei som overlever er det mange som vil få funksjonsnedsetting og auka trong til hjelp. Pasientar med hoftebrot er ofte gamle og skrøpelege og dei har ofte mange sjukdomar i tillegg til brotet. Det er vanleg at dei brukar mange medisinar, dei er ofte underernærte og mange lever isolert. Demens er vanleg. Dette er tilstandar som er vanlege hos pasientar som vert handsama av geriatarar, og ein har difor argumentert med at eit hoftebrot like mykje er ei utfordring for geriatarar som for ortopedar. I fleire land har det difor vorte stadig meir vanleg at geriatarar har involvert seg i handsaminga av pasientar med hoftebrot. Eit slikt strukturert samarbeid mellom ortopedar og geriatarar kallast «ortogeriatri». Det finnast ei mengd ulike modellar, og til tross for mykje forsking, har ein ikkje klart å konkludere med kva som er den mest effektive modellen. På grunn av demografiske endringar kan ein vente at det blir fleire pasientar med hoftebrot i tida framover, og sidan helsevesenet har avgrensa med ressursar, er det viktig å finne ut meir om korleis ein mest effektivt kan organisere handsaminga av slike pasientar.

Delirium er ein tilstand med ein akutt endring i kognisjon og merksemd, og er spesielt vanleg hos pasientar med hoftebrot. Tilstanden er knytta til dårleg prognose, inkludert ei dramatisk auke i risiko for demens. Vi veit veldig lite om kva som skjer i hjernen ved delirium, og det finnast ingen effektive medisinar. Delirium kan i mange tilfelle forebyggast gjennom god medisinsk handsaming. Tverrfagleg geriatrisk intervensjon har vist seg spesielt effektivt i å forebygge delirium hos pasientar med hoftebrot.

Då denne studien først vart planlagt, var det viktigaste målet å evaluere den ortogeriatriske modellen som var i bruk på Oslo Universitetssykehus - Ullevål frå juni 2008 til januar 2012. Vår hypotese var at intervensjonen ville vere effektiv i å redusere forekomsten av delirium og gjennom dette forebygge kognitiv forverring på sikt. I løpet av prosjektperioden har også andre målsettingar dukka opp, inkludert å studere korleis delirium virkar inn på kognisjonen på sikt. Vi har også studert kva som skjer i hjernen ved eit delirium.

Metode

Frå september 2009 til januar 2012 vart 329 pasientar med hoftebrot inkludert i denne studien. Alle desse var akutt innlagt på Oslo Universitetssykehus - Ullevål og dei vart inkludert i akuttmottaket. Der vart dei randomisert til eit opphald i akuttgeriatrisk avdeling eller i ortopedisk avdeling. Pasientane vart sendt direkte frå akuttmottaket til den avdelinga som dei vart randomisert til og hadde heile opphaldet i same avdeling med unntak av operasjonen og nokre få timar i postoperativ avdeling.

Medan pasientane var innlagt i sjukehuset vart dei nøye overvåka for komplikasjonar. Vi var spesielt nøye med å registere om pasientane fekk delirium. Pårørande vart intervjua slik at vi kunne skape oss eit bilete av korleis pasientane fungerte kognitivt og i det daglege før brotet.

Sidan pasientar med hoftebrot ofte er gamle og skrøpelige trudde vi at dei ville ha nytte av å bli handsama i akutt geriatrisk avdeling sidan ein der har mykje erfaring eldre pasienter. Vår hypotese var at vi skulle klare å forbygge delirium, og gjennom dette betre den kognitive funksjonen på sikt. For å teste denne hypotesa, undersøkte vi pasientane med kognitive testar fire og tolv månadar etter operasjonen. I tillegg til å kunne evaluere effekten av vår ortogeriatriske modell, kunne vi bruke resultatet av desse testane til å seie noko om korleis delirium hadde påvirka den kognitive funksjonen på sikt.

I samband med operasjonen for hoftebrotet samla vi spinalvæske og blodprøver frå pasientane. Vi har analysert desse prøvene for å lære meir om patofysiologiske samanhengar ved delirium. Då vi gjorde desse analysene inkluderte vi også prøver som vart samla inn frå pasientar med hoftebrot i Edinburgh, og prøver tekne i Oslo frå eldre pasientar som vart operert for andre tilstander enn hoftebrot.

Resultat

Vi fann ingenting som tyda på at den kognitive funksjonen fire og tolv månadar etter operasjonen var betre hos pasientar som vart handsama i akuttgeriatrisk avdeling. Det såg imidlertid ut til at gangfunksjonen var forbetra hjå dei pasientane som ikkje budde på sjukeheim før brotet.

Vi fann at delirium var ein viktig prediktor for akselerert kognitiv svikt hos pasientar som hadde demens allereie før brotet.

Antikolinerg aktivitet (AA) var ikkje høgare i spinalvæske eller blod hos pasientar med delirium samanlikna med dei som ikkje hadde delirium. Hjå pasientar som fekk delirium, men som ikkje hadde demens før brotet, såg det imidlertid ut til at alvorsgraden av delirium hadde ein samanheng med nivået av AA.

Neopterin (ein markør på inflammasjon) var høgare i spinalvæske og blod hos pasientar med delirium. Dette funnet støttar ein hypotese om at inflammasjon er viktig for utvikling av delirium.

Konklusjon

Den ortogeriatriske modellen som vart testa i denne studien var ikkje effektiv i å redusere forekomsten av delirium eller forebygge kognitiv svikt på sikt. Modellen virka imidlertid å ha ein gunstig effekt på mobiliteten hjå pasientar som ikkje budde på sjukeheim før hoftebrotet.

Delirium er særs vanleg hjå pasientar med hoftebrot, og i vår studie vart halvparten av pasientane råka. Vi fann at delirium var assosiert med ei forverring av den kognitive svikta hjå pasientar som hadde demens allereie før brotet.

Analyse av spinalvæske og blod tatt frå pasientane i vår studie har gjeve oss viktig ny kunnskap om patofysiologien ved delirium. Same kva krevast det mykje meir forsking for å betre vår forståing av denne vanlege, dramatiske og alvorlege tilstanden.

Abbreviations

5-HIAA - 5-hydroxyindoleacetic

AchE - acetylcholinesterase

AA - Anticholinergic Activity

ACB - Anticholinergic Cognitive Burden

AD - Alzheimer's disease

ADL - Activities of Daily Living

APACHE II - Acute Physiology and Chronic Health Evalutation II

ASA score - American Society of Anesthesiologists score

CAM - Confusion Assessment Method

CDR - Clinical Dementia Rating

CERAD - the Consortium Establish a Registry for Alzheimer's disease

CGA - Comprensice Geriatric Assessment

CNS - Central Nervous System

CRP - C-reactive protein

CSDD - Cornell Scale for Depression in Dementia

CSF - Cerebrospinal fluid

DRS-R-98 - Delirium Rating Scale Revised-98

DSM - Diagnostic and Statistical Manual for Mental Disorders

ELISA - Enzyme-linked immunosorbent assay

ER - Emergency Room

HVA - Homovanillic Acid

ICD -10 International Classification of Diseases 10^{th} edition

ICU - Intensive Care Unit

IL - interleukin

IQCODE - the Informant Questionnaire on Cognitive Decline in the Elderly

LPS - Lipopolysaccharide

MHPG - 3-Methoxy-4-hydroxyphenylglycol

MDAS - Memorial Delirium Assessment Scale

MMSE - Mini Mental State Examination

PTSD - Postraumatic stress disorder

RASS - Richmond Agitation Sedation Scale

REK - Regional Committee for Ethics in Medical Research in Norway

RCT - Randomized Controlled Trials

SAP - Stastical Analysis Plan

TNF - Tumor Necrosis Factor

UTI - Urinary Tract Infection

List of papers

I. **Delirium is a risk factor for further cognitive decline in cognitively impaired hip fracture patients** Krogseth M, Watne LO, Wyller TB, Skovlund E, Engedal K, Juliebo V. Manuscript

II. **The effect of a pre- and postoperative orthogeriatric service on cognitive function in patients with hip fracture: randomized controlled trial (Oslo Orthogeriatric Trial)** Watne LO, Torbergsen AC, Conroy S, Engedal K, Frihagen F, Hjorthaug GA, Juliebo V, Raeder J, Saltvedt I, Skovlund E, Wyller TB. BMC Med. 2014 Apr 15;12(1):63.

III. **Anticholinergic activity in cerebrospinal fluid and serum in individuals with hip fracture with and without delirium** Watne LO, Hall RJ, Molden E, Raeder J, Frihagen F, Maclullich AM, Juliebo V, Nyman A, Meagher D, Wyller TB. J Am Geriatr Soc. 2014 Jan 2.

IV. **Cerebrospinal fluid levels of neopterin are elevated in delirium after hip fracture. A role for cellular immunity or oxidative stress?** Hall R*, Watne LO*, Idland AV, Raeder J, Frihagen F, MacLullich AMJ, Wyller TB, Fekkes D. Manuscript

*Joint first author

1 Introduction

A hip fracture is a dramatic event with serious consequences. Since the patients often are elderly and frail, orthogeriatric co-management has become increasingly common. Due to demographic changes an increase in the number of hip fractures can be expected in the future.

Delirium, an acute change in cognition and alertness, is a common complication in hip fracture patients and is associated with poor outcome, including a dramatically increased risk of incident dementia. No effective drug treatment exists, but delirium can in many cases be prevented through optimizing the quality of medical care. Multidisciplinary geriatric intervention has been shown to be particularly effective in preventing delirium in hip fracture patients.

When this study first was planned, the main objective was to evaluate the orthogeriatric service in use at Oslo University Hospital - Ullevaal from June 2008 to January 2012. We hypothesised that the intervention could be effective in reducing delirium and thus prevent long term cognitive decline. During the work, some further aims have emerged.

1.1 **Delirium**

1.1.1 **Definition**

Delirium is a syndrome of acute change in cognition and alertness, and altered, often psychotic behaviour. Synonyms include “confusion”, “acute confusional state” and “acute brain failure”. According to DSM-5, diagnostic criteria for delirium comprise a disturbance in attention and awareness, change in cognition, rapid onset, and the disturbance has to be a direct physiologic consequence of a general medical condition(Association, 2013). The DSM-5 was published in May 2013, and was the update of DSM IV-TR published in 2000(Association, 2000). The main difference between DSM-5 and DSM IV-TR is that in DSM-5 “disturbance in attention” has replaced “disturbance in consciousness” as a core feature for delirium. The DSM-5 also emphasizes that in order to fulfil the criteria for delirium, the cognitive disturbances can not be explained with another “pre-existing, established or evolving neurocognitive disorder” and in particular not coma. ICD-10 has a more restrictive definition of delirium compared to DSM-5(Organization, 2008). Delirium prevalence is naturally dependent on which diagnostic criteria are used (Laurila et al., 2003, Cole et al., 2003, Neufeld and Thomas, 2013, Rooney et al., 2014). Most delirium studies published the last decade have used the CAM and/or the DSM IV-TR criteria for diagnosing delirium.

Regardless of the definition used, the diagnosis of delirium is clinical. No laboratory or imaging test can diagnose delirium.

Table 1. DSM-IV-TR Criteria for Delirium
A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.
B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia.
C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequense of a general medical condition.

Table 2. DSM-5 Criteria for Delirium
A. A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of the day.
C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
D. The disturbances in Criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

Table 3. ICD-10 Criteria for Delirium
A. Clouding of consciousness i.e. reduced clarity of awareness of the environment, with reduced ability to focus, sustain, or shift attention.
B. Disturbance of cognition, manifested by both: (1) impairment of immediate recall and recent memory, with relative intact remote memory; (2) disorientation in time, place or person.
C. At least one of the following psychomotor disturbances: (1) rapid, unpredictable shifts from hypo-activity to hyper-activity; (2) increased reaction time; (3) increased or decreased flow of speech; (4) enhanced startle reaction
D. Disturbance of sleep or the sleep-wake cycle, manifest by at least one of the following: (1) insomnia, which in severe cases may involve total sleep loss, with or without daytime drowsiness, or reversal of the sleep-wake cycle; (2) nocturnal worsening of symptoms; (3) disturbing dreams and nightmares which may continue as hallucinations or illusions after awakening.
E. Rapid onset and fluctuations of the symptoms over the course of the day.
F. Objective evidence from history, physical and neurological examination or laboratory tests of an underlying cerebral or systemic disease (other than psychoactive substance-related) that can be presumed to be responsible for the clinical manifestations in A-D.

1.1.2 **Prevalence**

Delirium is one of the most common acute medical conditions, and the point prevalence in a typical university hospital has been estimated to 20 %(Ryan et al., 2013). This implies that at Oslo University hospital - Ullevaal with 800 beds, 160 patients will have delirium at any given time.

Delirium is the consequence of a complex interrelationship of predisposing factors ("vulnerability") and precipitating factors (Inouye, 1999). Dementia and older age are among the most important predisposing factors, but even the most robust patient can develop delirium if exposed to sufficient stress. The interplay between predisposing and precipitating factors are reflected in the fact that two of the wards with highest prevalence of delirium in a hospital is the acute geriatric ward (high vulnerability) and the ICUs (severe precipitating factors) with reported occurrence rates of up to 50 % in the acute geriatric wards and 80 % in ICUs(Siddiqi et al., 2006, Jones and Pisani, 2012, Inouye et al., 2013). In the course of an

admission for a hip fracture, 40 - 50 % of the patients will experience delirium (Bruce et al., 2007).

1.1.3 **Detection, prevention and treatment of delirium**

Despite the fact that delirium is prevalent, possible preventable, and has negative impact on prognosis, it is often unrecognized by hospital staff, both by nurses and physicians (Laurila et al., 2003, Ryan et al., 2013, Rooney et al., 2014). Since the diagnosis relies solely on clinical observation, detection rates are sensitive to the skills, awareness and experience of the healthcare personnel. This is illustrated by the wide range of prevalences and incidences reported in different studies; the reported prevalence for delirium in hip fracture patients varies from 4 to 53 %(Bruce et al., 2007). Several screening and diagnostic tools have been developed to improve detection rates and the diagnostic precision(Hall et al., 2012). Two recently published reviews conclude that the Confusion Assessment Method (CAM)(Inouye et al., 1990), Memorial Delirium Assessment Scale (MDAS)(Breitbart et al., 1997) and Delirium Rating Scale Revised-98 (DRS - R98)(Trzepacz et al., 2001) are reliable and validated instruments that can be recommended(Wong et al., 2010, Adamis et al., 2010).

The most used diagnostic tool is the CAM, a four-step algorithm originally validated against the DSM-III criteria for delirium. It was developed by Sharon Inouye at Yale University, USA, and the original publication claims that the CAM can be completed in less than five minutes with sensitivity 94-100 % and a specificity of 90-95 %(Inouye et al., 1990). Other studies have, however, reported both sensitivity and specificity to be much lower(Laurila et al., 2002) and without proper training of the evaluators, the sensitivity has been reported as low as 13 %(Rolfson et al., 1999). Most clinicians find that it takes more than five minutes to complete the CAM since it is highly recommended that an objective cognitive test is used to inform the CAM (MMSE was used in the original publication). It has also has been argued that to perceive delirium as a binary phenomenon is an oversimplification and since delirium in reality represent a continuum, it should better be reported on a ordinal scale(Radtke et al., 2010). This criticism is relevant, but the introduction of CAM has undoubtedly been important for progress in delirium research since its widespread use have made it easier to compare studies.

Delirium can to some extent be predicted clinically(Guenther et al., 2013, Menzies et al., 2012, Inouye, 1999, Kennedy et al., 2014). It has also been suggested that as many of 30 - 40 % delirium cases are preventable through optimizing the quality of medical care(Inouye et al., 2013). Multidisciplinary geriatric intervention seems to be particularly effective in preventing delirium in hip fracture patients(Marcantonio et al., 2001, Deschodt et al., 2012, Milisen et al., 2001, Lundstrom et al., 2007, Lundstrom et al., 1999, Gustafson et al., 1991, Wong Tin Niam et al., 2005). There is no effective pharmacologic treatment once delirium has developed(Inouye et al., 2013), but haloperidol is often used to reduce symptoms, also in Norway.

Figure 1. The Confusion Assessment Method(Inouye et al., 1990).

CONFUSION ASSESSMENT METHOD (CAM) SHORTENED VERSION WORKSHEET

EVALUATOR: DATE:

I. ACUTE ONSET AND FLUCTUATING COURSE

BOX 1

a) Is there evidence of an acute change in mental status from the patient's baseline? No ____ Yes _____

b) Did the (abnormal) behavior fluctuate during the day, that is tend to come and go or increase and decrease in severity? No _____ Yes _____

II. INATTENTION

Did the patient have difficulty focusing attention, for example, being easily distractible or having difficulty keeping track of what was being said? No _____ Yes _____

III. DISORGANIZED THINKING

BOX 2

Was the patient 's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject? No _____ Yes _____

IV. ALTERED LEVEL OF CONSCIOUSNESS

Overall, how would you rate the patient's level of consciousness?

-- Alert (normal)

-- Vigilant (hyperalert)
-- Lethargic (drowsy, easily aroused)
-- Stupor (difficult to arouse)
-- Coma (unarousable)

Do any checks appear in this box? No _____ Yes _____

If all items in Box 1 are checked and at least one item in Box 2 is checked a diagnosis of delirium is suggested.

1.1.4 **Outcomes after delirium**

Delirium can be an immensely stressful experience for patients and their relatives(MacLullich and Hall, 2011). When assessing patients in the outpatient clinic after a hospital admission, it is a common experience that one of the issues patients often need to discuss is the "confusion" they experienced while admitted. Patients are often embarrassed after a delirious episode because they have a notion that they acted strangely and uncivil(Schofield, 1997). The hallucinations that often occurs in delirium can be extremely frightening, and delirium can induce PTSD(Davydow et al., 2008).

Delirium has been considered a transient condition, and for most patients it resolves within some days, although in some patients the symptoms lasts for several weeks(Meagher et al., 2012). During the last decade, accumulating evidence indicate, however, that delirium is an independent risk factor for poor outcome. In a meta analysis published in JAMA in 2010, delirium was associated with an increased risk for death (HR 1.95), institutionalization (OR 2.41) and a dramatically increased risk of dementia (OR 12.51)(Witlox et al., 2010), see section 2.1.6 for details.

1.1.5 **Pathophysiology**

Given the magnitude of the problem, delirium has been greatly understudied. It is illustrative that both European Delirium Association and the American Delirium Society both were founded less than ten years ago. In overviews over biomarkers and treatment trials, the most striking finding is the low number of patients included in studies(Khan et al., 2011, Hall et al., 2011, Inouye et al., 2013).

The interest in delirium from researchers is increasing, but the current knowledge regarding the pathophysiologic mechanisms is still scarce. As a useful theoretical model, a basic classification of etiological factors has been proposed: (a) direct brain insults and (b) aberrant stress responses (MacLullich et al., 2008). Insults that directly affect the brain can reasonably induce delirium. Examples are hypoxia(Schoen et al., 2011), hypercapnia(Scala, 2011), cerebral hypoperfusion(Yokota et al., 2003) and drugs(Gaudreau and Gagnon, 2005). It is harder to understand how a diverse array of extra cerebral events like UTI, pulmonary infection, myocardial infarction, urine retention, and hip fracture, all can cause the same CNS symptoms. It is proposed that delirium in such cases is triggered by aberrant stress responses,

mediated through the hypothalamic-pituitary-adrenal (HPA) axis, the autonomous nervous system and the inflammatory system(MacLullich et al., 2008, Cerejeira et al., 2014, Cunningham and MacLullich, 2012). Additional hypothesis of delirium pathophysiology include diurnal dysregulation(Fitzgerald et al., 2013, de Rooij et al., 2014), network disconnectivity(Sanders, 2011), genetic factors(van Munster et al., 2009), neurotransmitter dysregulation (Hshieh et al., 2008, Trzepacz, 2000)neuronal aging(Norden and Godbout, 2013, Cunningham, 2013), and oxidative stress(Maldonado, 2013, Hughes et al., 2012). Variable amounts of data exits to support these different theories. The two most studied is "the neurotransmitter hypothesis" and "the neuroinflammation hypothesis". The following sections will give an overview of these two.

The neurotransmitter hypothesis

Regardless of which other factors might be involved, neurotransmitters are likely to play a role in delirium pathogenesis. Acetylcholine and the monoamines (adrenalin, noradrenalin, dopamine, serotonin) are the neurotransmitters most studied delirium. In general, delirium has been associated with acetylcholine deficiency, noradrenalin and dopamine excess, and an increase as well as a decrease in serotonin(Maldonado, 2013). The theory that cholinergic depletion can be a mechanism in the pathogenesis of delirium has as a basis that acetylcholine plays an important role in many of the domains affected in delirium, e.g. attention, perception and arousal(Trzepacz, 2000, Hshieh et al., 2008). The theory is supported by the fact that substances with strong anticholinergic activities (AA) can induce delirium, with atropine as the classic example. It has also been a clinical experience that medications with high anticholinergic activity can induce delirium(Han et al., 2001). Several studies have found an association between high serum AA and delirium(Campbell et al., 2009, Carnahan et al., 2002). A positive association between serum AA and delirium severity has also been reported(Flacker et al., 1998). But there are also studies reporting no association between serum AA and delirium, and the only study that measured serum AA in hip fracture patients found no association(van Munster et al., 2007). Cholinergic dysfunction was once proposed as a possible "final common pathway" in delirium(Trzepacz, 2000), but reports from the last decade suggest that it might not be that simple. It must also be mentioned that treatment/prevention trials with cholinesterase inhibitors have not been successful(van Eijk et al., 2010, Liptzin et al., 2005, Gamberini et al., 2009).

GABA is the main inhibitory and glutamate the main excitatory neurotransmitter, and disturbances in these systems are believed to play a role in dementia(Danysz and Parsons, 2012, Huang and Mucke, 2012). Their role in the pathophysiology of delirium has been explored to a much lesser degree and data are limited to case reports (Inouye et al., 2013). Clinically, the importance of GABA is suggested by the observation that benzodiazepines may precipitate or worsen delirium(Pisani et al., 2009, Kudoh et al., 2004).

Direct CNS measurement of neurotransmitter concentrations in patients is extremely difficult, so one must rely on measurements of precursors and/or metabolites. Amino acids are the precursors for the monoamines dopamine, noradrenalin and serotonin, and are accordingly of interest in delirium research. Phenylalanine and tyrosine (dopamine and noradrenalin precursors) has been found to be elevated in patients with delirium, supportive of a theory of higher monoaminergic tone(Flacker and Lipsitz, 2000, van der Mast et al., 2000, Pandharipande et al., 2009). For tryptophan (precursor of serotonin) the literature is more complicated since both increased and decreased levels have been associated with delirium. Lower levels of tryptophan have been found to be associated with postoperative delirium in abdominal and thoracic surgery(van der Mast et al., 1991, van der Mast and Fekkes, 2000, Robinson et al., 2008, Osse et al., 2012). Higher (and lower) levels were associated with delirium in patients in an intensive care unit(Pandharipande et al., 2009) and in a study that included patients admitted to a geriatric medical unit no difference in any amino acids was found between delirious patients and age matched controls(van der Cammen et al., 2006). In a study of hip fracture patients there was no difference in tryptophan between patients with and without delirium(de Jonghe et al., 2012). A possible explanation for these somewhat contradictive results is the difference in patient populations.

Monoamine metabolites (HVA: dopamine, 5-HIAA: serotonin, MHPG: noradrenaline) have also been measured in delirium. HVA has been found to be elevated in serum in both surgical (Osse et al., 2012) and medical (van der Cammen et al., 2006) patients. The latter study also found elevated 5-HIAA in delirium. In a Japanese study of 66 patients with delirium and 16 healthy controls, both HVA and MHPG were higher in patients with delirium. Interestingly, both HVA and MHPG levels decreased in relation to resolution of the delirious episode (Nakamura et al., 1997). HVA have also been found to be elevated in CSF in delirious patients, but this difference was significant only for those patients with hallucinations(Ramirez-Bermudez et al., 2008). CSF levels of 5-HIAA has been measured in

one study, and compared to controls had patients with delirium and no prior CNS disease elevated levels of 5-HIAA(Koponen et al., 1994).

The neuroinflammation hypothesis

Since delirium often occurs in relation to acute illness, the assumption that delirium is associated with inflammation can be traced back for centuries(Cerejeira et al., 2014). A commonly used marker of inflammation is the C-reactive protein (CRP), and several (but not all(de Rooij et al., 2007, Adamis et al., 2007)) studies have found an association with high CRP and delirium, both in medical (Macdonald et al., 2007, Ritchie et al., 2014, White et al., 2005) and surgical patients(Burkhart et al., 2010) and in patients in ICU units(Zhang et al., 2014).

Cytokines are small proteins important in cell signaling, especially in the immune system. Cytokines from the periphery can enter the brain via different routes, and activated microglia in the brain can produce cytokines(Westhoff et al., 2013, de Rooij et al., 2007). Cytokines are therefore believed to play a central role in delirium pathogenesis(van Gool et al., 2010). The two first studies (both in medical patients) that assessed the association between peripheral cytokines (measured in serum) and delirium were a Dutch study of 165 patients(de Rooij et al., 2007) and a study from the UK with 164 patients (cytokines measured in only 60) (Adamis et al., 2007). The Dutch study found that more patients with delirium had detectable levels of the pro-inflammatory cytokines IL-6 and IL-8. This was in contrast to the UK study that found no difference in IL-6 (IL-8 not measured) between patients with and without delirium. A possible explanation for this discrepancy is that the Dutch study used a multiplex immunoassay for analysis, whereas the UK study used the more sensitive ELISA method. Many of the measured cytokines in the Dutch study never reached the detection limit, but no such problem was reported in the UK study. When comparing levels of cytokines above the detection limit, there was no difference in levels between patients with and without delirium in the Dutch study. A similar methodological problem was seen in a study from Portugal where five cytokines (IL-8, IL-1ß, IL-6, IL-10 and TNFα) were measured in plasma pre- and postoperatively in 101 patients undergoing elective hip arthroplasty. Only IL-10 were detectable in all samples, and of the other cytokines were up to 44 % (TNFα postoperatively) not detectable. This study found no difference in any of the measured cytokines, but patients with delirium had a greater pro/anti inflammatory ratio after surgery, suggesting that delirium

is associated to an unbalanced inflammatory response(Cerejeira et al., 2012). A study of 100 ICU patients (50 with delirium) found that the pro-inflammatory cytokines IL-6 and IL-8, but also the anti-inflammatory cytokines IL1-RA and IL-10, were higher in those with delirium(van den Boogaard et al., 2011). Another recently published study also investigated inflammatory markers in ICU patients. This study included 78 patients (31 with delirium) admitted to a mixed ICU in a hospital in Brazil. Blood samples were collected within 12 hours of enrollment. Patients with delirium had higher levels of the inflammatory markers soluble TNF Receptor (STNFR) 1 and 2, adiponectin and IL-1β, also when adjusting for sepsis and sedation. There was however no significant difference in TNFα, IL6 or IL10(Ritter et al., 2014).

CSF levels of cytokines have been measured in two studies in delirium. In a study of 36 patients with hip fracture, CSF was sampled at the onset of spinal anesthesia. Fifteen of the patients developed delirium (nine before surgery). Six cytokines were measured with an immunoassay, but only IL-8 (33/36 samples) and IL-6 (3/36 samples) were above the detection limit. IL-8 was higher in patients with delirium(MacLullich et al., 2011). A larger study from the Netherlands also sampled CSF from hip fracture patients at the time of spinal anesthesia. This study comprised 61 patients that all were free from delirium at the time of CSF sampling, and 23 of these developed delirium after surgery. Forty-one different cytokines and chemokines were measured using an immunoassay, but only 16 of those were detectable in more than 50 % of the patients. None of the measured compounds were higher in patients with delirium, but fms-like tyrosine kinase-3 (Flt-3L), IL-1RA and IL-6 were significantly lower in patients with delirium. Flt-3L is believed to play a role in chronic inflammatory states and IL-1RA is an inhibitor of the pro-inflammatory cytokines IL-1α and IL-1ß. It is harder to understand that IL-6 was lower in patients with delirium since IL-6 is considered to be a pro-inflammatory cytokine. The authors suggest that the findings could be interpreted that delirium is the result of a dysfunctional inflammatory state, where reduced anti-inflammatory mediators play a more important role than an increased pro-inflammatory activity (Westhoff et al., 2013).

In a postmortem study brain autopsies were performed within 24 hours after death in nine patients with delirium and six age-matched controls. In patients with delirium markers of microglial activity (HLA-DR and CD 68), astrocyte activity (GFAP) and IL-6 were increased.

These findings are in support of increased inflammatory activity in the brain in delirium(Munster et al., 2011).

Another marker of pro-inflammatory status is neopterin, a pteridine produced by activated monocytes and macrophages(Murr et al., 2002). A study of 125 patients undergoing elective cardiac surgery found increased plasma levels of neopterin in patients with delirium both pre- and postoperatively(Osse et al., 2012).

A role of inflammation is also supported by animal studies. In an animal model of prion disease it was showed that aged animals and those with chronic neurodegeneration showed a more profound CNS inflammation (IL-1ß expression and neutrophil infiltration) to a relatively minor systemic inflammation. The exaggerated immune response could be explained by the primary neurodegeneration that had led to a priming of microglia making them more responsive to subsequent inflammatory stimuli(Cunningham et al., 2005). The same research group also showed that that a challenge with LPS (that initiate an immune response) induced acute and transient cognitive deficits (mimicking delirium) only in animals with chronic cognitive impairment(Murray et al., 2012) The "microglial priming hypothesis" can in some part explain why a minor insult like a UTI can produce delirium in a patient with dementia, but not in more robust individuals(Cunningham and MacLullich, 2012, van Gool et al., 2010).

Delirium pathophysiology - conclusion

Both the neurotransmitter hypothesis and the neuroinflammation hypothesis are supported by data. Of the neurotransmitters, acetylcholine deficiency seems to be theoretically best founded, but has only moderate support by data. The data is more convincing regarding a higher monoaminergic activity associated with delirium, since elevated levels of both monoamine precursors and metabolites have been demonstrated in delirium. It is, however, important to realize that (with exception on HVA and 5-HIAA) all the monoamine precursors and metabolites have only been measured in the periphery (blood) and this does not necessarily mirror CNS levels. Most persuasive is the evidence for the neuroinflammation hypothesis since this is supported by several studies in both serum and CSF and also by animal models.

Since delirium is the result of a complex interrelationship of predisposing and precipitating factors (that both directly and indirectly can influence brain functions), it seems unlikely that there should be a "final common pathway" in the pathogenesis. This is also the conclusion in the most recent reviews(Inouye et al., 2013, Maldonado, 2013, MacLullich et al., 2008). Different pathways are likely to be intertwined; e.g. is the cholinergic system balanced with monoamine activity(Hshieh et al., 2008) and there has also been described interactions between the cholinergic and the inflammatory system in delirium(Cerejeira et al., 2012).

1.1.6 **Delirium and dementia**

Dementia is an important and well known risk factor for delirium (Fick et al., 2002). More than 50 % of patients with dementia will experience delirium in the course of an admission to a medical ward(Inouye et al., 2013) with even higher figures for demented patients admitted for acute surgical conditions(Juliebo et al., 2009, Stenvall et al., 2012). There is accumulating evidence that delirium also constitutes an independent risk factor for dementia. Since delirium often occurs in relation to acute illness, it is a challenge to design studies that can explore whether delirium lies on the causal pathway to dementia, but during the last decade an increasing amount of evidence have suggested that this is the case. A meta analysis published in 2010 focused on the associations between delirium and long term outcomes (mortality, institutionalization, dementia), and found an 12-fold increase in risk of dementia in patients that had experienced delirium(Witlox et al., 2010). Only two studies (241 patients in total) were included in the analysis on dementia in this meta analysis, but several studies have been published afterwards supporting the conclusion.

In a study of 225 patients scheduled for coronary-artery bypass grafting, a lower percentage of patients with delirium than of those without had returned to their preoperative cognitive level six months after surgery (24 % vs 40%, p=0.01)(Saczynski et al., 2012). The serious consequence of delirium on long term cognition also in people without dementia was clearly demonstrated in a newly published study of patients treated in intensive care units (median age 61). Only 6 % of the patients had cognitive impairment at baseline, but three months after discharge 40 % had global cognition scores 1.5 SD below the population means and 26 % had scores 2 SD below population means (similar to scores for patients with mild Alzheimer's disease)(Pandharipande et al., 2013). Similar findings were reported from a study where hip fracture patients free from dementia were cognitively tested six months after surgery. After

adjusting for other risk factors, delirium in the acute phase emerged as the strongest predictor for incident dementia (OR 10.5)(Krogseth et al., 2011).

Delirium is also shown to be a risk factor for accelerated cognitive decline in patients with an already established diagnosis of dementia. In a study from 2009, 408 patients with Alzheimer's disease were followed at six months intervals to determine cognitive trajectories. Those patients that experienced delirium during the follow-up period (n=72) had a significant acceleration of the cognitive decline(Fong et al., 2009). The follow up period in this study was six months, so it was impossible to conclude whether a delirious episode had resulted in a permanent deterioration of cognitive trajectories. The same research group have, however, more recently published a separate report of the same patients showing that the cognitive deterioration lasted for up to five years(Gross et al., 2012). In the same cohort delirium was also associated with increased risk of mortality and institutionalization(Fong et al., 2012).

To summarize; delirium seems to be able to precipitate dementia in patients that are cognitively intact, and to induce a more rapid pace of deterioration in those already demented.

From delirium to dementia and vice versa: pathophysiological mechanisms.

Since the conditions are clinically linked, the pathophysiologic mechanisms are also likely to be linked(Eikelenboom and Hoogendijk, 1999). Different pathophysiological theories exist for the increased risk of delirium in patients with dementia. Normal aging is associated with a shift in the inflammatory profile towards a more pro-inflammatory state (Ferrucci et al., 2004). Age and chronic cognitive impairment are also associated with microglial priming(Cunningham et al., 2005) and an increased blood brain barrier permeability(Zlokovic, 2011), factors that both can contribute to an exaggerated inflammatory activity in the brain in response to a minor insult in the periphery (e.g. an UTI).

Since the understanding of even the basic elements in the pathophysiology of delirium is moderate, the pathophysiologic mechanisms linking delirium to dementia is almost absent. The link between delirium and dementia has only been demonstrated in epidemiological studies, all published during the last 5 - 10 years. But one intriguing study exists that has explored pathophysiological mechanisms from delirium to dementia. In that study, 553 individuals above 85 years were continuously monitored for delirium and followed with cognitive tests at baseline, 3, 5, 8 and 10 years. After adjusting for other risk factors, an

episode of delirium dramatically increased the risk of incident dementia (OR 8.7). Delirium was also associated with deterioration of preexisting dementia (OR 3.1). Brain autopsy was performed in 52 %. In patients with dementia precipitated by an episode of delirium, the typical neuropathological markers of dementia were not found. In patients with dementia and no history of delirium, all pathologies were in accordance with those described as typical for dementia. This finding suggests that the effect of delirium upon permanent cognitive decline may not be mediated by classical neuropathologies associated with dementia(Davis et al., 2012).

For many patients, a delirious episode is the direct precipitating factor for incident dementia, and to study the pathophysiological mechanisms in delirium might therefore represent an alternative angle to study dementia pathophysiology.

1.2 Orthogeriatrics

1.2.1 Definition and historical background

Hip fracture patients are among the frailest patients in a hospital. Median age is more than 80 years and many suffer from co-morbidities, polypharmacy, poor social support and malnutrition(Gjertsen et al., 2008, Ranhoff et al., 2010). Dementia is common, and 40 - 50 % will experience delirium perioperatively(Juliebo et al., 2009, Bruce et al., 2007). It has been argued that a hip fracture represents a geriatric, rather than an orthopedic disease(Adunsky et al., 2005), and for several decades different models of orthopedic-geriatric co-management of these patients have been developed. Such a structured collaboration between orthopedic surgeons and geriatricians is labeled an orthogeriatric service.

The first orthogeriatric services was developed in the UK more than 50 years ago(Hempsall et al., 1990, Devas, 1974) and the first RCT on orthogeriatric care was performed almost 30 years ago (Gilchrist et al., 1988). Since then, orthogeriatric services have been established in many countries(Pioli et al., 2014). UK is still the country leading the way where early involvement of geriatricians has been considered a Golden standard and those hospitals not living up to this standard experience economical penalties(Association, 2007).

1.2.2 Different orthogeriatric models

Every model where some sort of structured geriatric input is included in treatment of elderly patients with fractures can fit under the label “orthogeriatric care”. As expected, a wide range of orthogeriatric models exists; from simple models were the geriatric input is limited to a liaison service to integrated orthogeriatric units(Kates et al., 2010a).

Some of these models have been scientifically evaluated. The studies show a considerable heterogeneity in design, patient selection, outcome measures and organization of follow up assessments. It has thus been difficult to draw conclusions regarding the superiority of one particular model.

Since 2010, four reviews have been published where the authors have tried to summarize the current knowledge (Kammerlander et al., 2010, Giusti et al., 2011, De Rui et al., 2012, Grigoryan et al., 2014). The authors have categorized the individual studies into main groups

and have to some extent pooled data to evaluate what models is most efficient. The authors have grouped the orthogeriatric models somewhat different. *Kammerlander (adopted by De Rui)* uses four different categories: 1) orthopedic ward and geriatric consultant service, 2) orthopedic ward and daily consultative service, 3) geriatric and rehabilitation ward and orthopedic consultant service and 4) orthopedic ward and integrated care. *Giusti* uses five categories: 1) traditional model - orthopedic ward, 2) consultant team - orthopedic ward, 3) interdisciplinary care/clinical pathway - orthopedic ward, 4) Geriatric-Led Fracture Service - Geriatric/Rehabilitative Ward, 5) Geriatric Co-management Care - OrthoGeriatric Unit. *Grigoryan* uses only three categories: 1) Routine Geriatric Consultation, 2) Geriatric Ward, 3) Shared Care. The different reviews have classified some of the included studies differently (e.g. is the study from Taiwan(Shyu et al., 2005) considered "integrated care" by Kammerlander, but "routine geriatric consultation" by Grigoryan).

This chapter will give a brief overview of studies where orthogeriatric care is compared to usual care. I have adopted the classification from Kammerlander to group studies. Some studies are not mentioned in Kammerlander (some are published after the review), and those are marked. Some studies are also grouped differently from Kammerlander when this seemed more accurate from the original publication(Gilchrist et al., 1988, Shyu et al., 2005, Vidan et al., 2005). From some of the orthogeriatric models several reports are published, and those are commented together. Models that only are compared to national averages or figures reported in the literature are not included.

Orthopedic ward and geriatric consultant service (Kammerlander 1)

This is the simplest model. The patients are treated in an orthopedic ward, and the geriatric input is limited to a liaison service, often provided by a geriatric team, sometimes labeled inpatient geriatric consultant team (IGCT). Eleven studies (reporting from six models) exist in this category.

Gilchrist WJ, 1988(Gilchrist et al., 1988) (Categorized this as "*Geriatric and rehabilitation ward and orthopedic consultant service" in Kammerlander 2010):* This is the worlds first RCT on orthogeriatic care including patients from October 1984 to July 1986. In February 1983 was an orthogeriatric model introduced at an orthopedic ward at this hospital in

Glasgow, Scotland. In this ward, the orthopedic surgeons were responsible for the overall care of the patients, but a weekly combined round was performed by a geriatrician and orthopedic surgeon, followed by an interdisciplinary meeting involving all team members. As control group served patients treated in regular orthopedic wards without any orthogeriatric input. Patients (only women above 65) were randomized to intervention (n=97) or control (n=125) after surgery, and the mean length of stay before randomization was 10 days in both groups. There was no significant difference in mortality, LOS or discharge destination. More medical conditions were recognized in those randomized to orthogeriatric care.

My comment: The orthogeriatric input is limited. Start of the intervention was on average 10 days after surgery, and these two factors can probably explain the lack of effect.

Kennie DC, 1988(Kennie et al., 1988). This was a prospective randomized study conducted in the UK were 108 women (54 randomized to intervention) above 65 years with hip fracture were included. The intervention was postoperative, and when patients were judged to be fit enough for transfer, those randomized to intervention were moved to a rehabilitation ward (5 km in ambulance) in a "predetermined random sequence". Those randomized to intervention had their daily medical attention provided by a general practitioner. A geriatrician was attending the ward twice weekly. Patients treated in the intervention group had significantly better physical independence. Length of stay was also shorter in the intervention group (24 v 41 days).

My comment: Selected patients. The intervention had effect, but LOS was so long that it is not comparable to today's standards.

Gustafson, 1991(Gustafson et al., 1991): Based upon experiences from earlier studies on delirium in hip fracture patients(Gustafson et al., 1988), an orthogeriatric model was established at this hospital in Umea, Sweden. The new model focused on short waiting time to surgery, thrombosis prophylaxis, oxygen therapy and anesthesiologic techniques. A geriatrician assessed the patients pre- and postoperatively. To evaluate the effect of the new model were 103 hip fracture patients prospectively included from December 1986 to January 1988. The primary focus of the study was delirium prevention, and outcomes were compared to those in the control study with 111 patients included at the same hospital between March 1983 and June 1984(Gustafson et al., 1988). Fewer patients in the intervention study developed delirium (47.6 vs 61.3 %, $p<0.05$). The intervention also had a positive impact on

delirium severity and duration. LOS was reduced after implementation of the new model (11.6 vs 17.4, p<0.001), and fewer patients developed postoperative complications.

My comment: the orthogeriatric service was effective, and the intervention started pre-operatively. The delirium rates were high also after implementation of the intervention. The non-randomized design is acknowledged by the authors as a problem.

Naglie G, 2002(Naglie et al., 2002): In a prospective randomized study from Canada, 279 hip fracture patients above 70 years were included from June 1993 through March 1997. The intervention was interdisciplinary care provided in an orthopedic ward. Patients randomized to intervention (n=141) were treated in a different ward with separate staff. The intervention was use of protocols and standardized orders, early mobilization (twice daily physiotherapy Monday – Friday), early participation in self-care and individualized discharge planning. Twice weekly there was an interdisciplinary meeting. The intervention showed no effect on outcomes three and six months after surgery (mobility, mortality, place of residence). The initial LOS was longer in the intervention group (29 v 21 days, $p < 0.001$), but the mean number of days spent in an institution over the first six months after surgery was similar.

My comment: Nice design, but only postoperative intervention. Selected patients (only 280/689 eligible patients were included). 56 patients could not be included because no bed was available on the interdisciplinary care unit.

Shuy 2005, 2008, 2010 (Shyu et al., 2005, Shyu et al., 2008, Shyu et al., 2010)(Categorized as "orthopedic ward and integrated care" in Kammerlander 2010): This was a single-blinded prospective randomized study from Taiwan that recruited 162 patients above 60 years from September 2001 to November 2003. All patients were treated in the orthopedic ward. The intervention was a geriatric consultation service, a rehabilitation program, and a discharge planning service. The rehabilitation continued after discharge from hospital. Significantly more patients randomized to intervention had recovered their previous walking ability after one (55 vs 37 %, p=0.004) and three months (78 vs 51 %, p=0.001)(Shyu et al., 2005). The beneficial effect lasted one(Shyu et al., 2008) and two years(Shyu et al., 2010) after inclusion. In addition to better mobility, patients randomized to intervention had significantly fewer depressive symptoms at the follow up controls.

My comment: Of 935 patients admitted with hip fracture in the inclusion period, only 162 (17 %) were included in the study. The most important reason was that the patients were either too physically or cognitively impaired to meet inclusion criteria. This sample is thus representing the fittest fraction of the hip fracture patients. Usual care in the study seems also to be limited. The intervention continued after discharge. It also needs to be mentioned that at the follow up controls the participants were blinded to allocation, but not the evaluators.

Ho, 2009, Leung 2011(Ho et al., 2009, Leung et al., 2011) (not in Kammerlander 2010): Two different reports from an orthogeriatric model established at Prince of Wales Hospital in Hong Kong in August 2005. After the introduction of the program, a geriatrician and a geriatric nurse carried out the medical management in the orthopedic ward three times a week. Patients treated the first year after implementation of the program (n=278) were compared to those treated the year before implementation (n=277). The intervention had impressive results with shorter LOS (9.7 v 8.3 days, p=0.001), lower in hospital mortality (4 v 1 %, p=0.02) and 1-year mortality (20 v 11 %, p=0.005), and a shorter waiting time for surgery (median 2 v 1 day, p<0.001) (Ho et al., 2009). Patients in the intervention group was also more likely to be independent in ADL after 3 (29.5 vs 27.8 %, p=0.003) and 12 months (24.5 vs 23.7 %, p=0.02). In the article from Leung(Leung et al., 2011), reporting from same patients, the authors speculate that the positive effect seen by introduction of the program, by large can be explained by the reduction in waiting time for surgery (mean 55 v 45 hours, p=0.02).

My comment: Historical controls. Usual care seems not so good. Long waiting time for surgery, but the huge difference in median (Ho) and mean (Leung) is confusing.

Deschodt, 2011, 2012. Milisen 2001.(Deschodt et al., 2011, Deschodt et al., 2012, Milisen et al., 2001) (not in Kammerlander 2010): These studies were conducted the University Hospital in Leuven, Belgium. The orthogeriatric model in use is orthogeriatric care provided by a geriatric team. The two most recent reports are from a patient material collected from February to December 2007. 177 hip fracture patients above 65 years were included. The patients were included in the emergency room, and allocated to one of two trauma wards (one intervention and one control) based upon availability of beds. The intervention was assessments and advice by the inpatient geriatric consultation team (IGCT). The intervention was not effective in any of the reported outcomes in the first report from this study (functional status, length of stay, mortality, new nursing home admissions and readmissions 6 weeks, 4 months and 12 months after surgery (Deschodt et al., 2011). The intervention was, however,

effective in reducing post operative delirium (53 v 37 %, p=0.04) as described in a separate report(Deschodt et al., 2012). There was no difference in delirium duration or severity. A study from 2001 evaluated a similar orthogeriatric model in the same hospital in a before-after design. In this study was delirium duration and severity reduced in patients treated after implementation of the intervention (Milisen et al., 2001).

My comment: In the study from 2011 was the allocation to intervention done in a non-randomized way and the outcome assessments were not done blinded. Very short delirium duration (1 day) raises the suspicion that delirium monitoring has not been optimal. The study from 2001 was a before-after study.

Table 4. Overview of studies evaluating an orthogeriatric model in accordance with Kammerlander model 1

Study	Number of patients	Study design	Timing and organization of follow up controls	Evaluation	Conclusion
Gilchrist, 1988. UK	N=222	Prospective randomized	No follow up. Mortality registered at 3 and 6 months.	LOS, mortality, medical conditions.	There was no significant difference in mortality, LOS or discharge destination. More medical conditions were recognized in those randomized to orthogeriatric care.
Kennie, 1988. UK	N=108	Prospective randomized	No follow up	LOS, Physical independence at discharge, Discharge destination	More patients treated in the intervention group was physical independent at discharge. Length of stay was also shorter in the intervention group (24 vs 41 days).
Gustafson, 1991. Sweden	N=214	Prospective with retrospective controls	No follow up	Delirium. Delirium severity and duration. LOS. Complications	Fewer patients in the intervention study developed delirium (47.6 vs 61.3 %, $p<0.05$). The intervention had also a positive impact on delirium severity and duration. LOS was reduced after implementation of the new model (11.6 vs 17.4, $p<0.001$), and fewer patients developed postoperative complications.
Naglie, 2002. Canada	N=279	Prospective randomized	3 and 6 months. Interviews with patients and caretakers.	Mobility, mortality, place of recidence	No effect on outcomes 3 and 6 months after surgery. The initial LOS was longer in the intervention group (29 v 21 days, $p < 0.001$), but the mean number of days spent in an institution over the first six months after surgery was similar.
Shuy 2005, 2008, 2010. Taiwan	N=162	Prospective randomized (using flip of a coin).	1,3,12 and 24 months. Face-to-face evaluation with a combination of performance based and self reported measures. Assessors not blinded.	Physical function, mobility, pain, depression	Significantly more patients randomized to intervention had recovered their previous walking ability. The effect lasted for 12 and 24 months. In addition the intervention group significantly fewer depressive symptoms.
Ho 2009, Leung 2011. Hong Kong	N=565	Retrospective before and after chart review	3 and 12 months. Data collected from regular out-patients visits.	LOS, waiting time for surgery, mortality,	The intervention had impressive results with shorter LOS (9.7 v 8.3 days, $p=0.001$), lower in hospital (4 v 1 %, $p=0.02$) and 1-year mortality (20 v 11 %, $p=0.005$). More patients were independent in ADL after 3 and 12 months. The authors suggest the beneficial effect in large part could be explained by the reduction in waiting time for surgery (mean 55 v 45 hours, $p=0.02$).
Deschodt 2011, 2012. Milisen 2001. Belgium	N=177 (Deschodt) N=120 (Milisen)	Deschodt: Prospective controlled study. Milisen: before/after	6 weeks, 4 and 12 months. Telephone interview with patients or relatives.	Functional status, LOS, mortality, new nursing home admissions. Delirium.	The intervention was only effective in reducing post operative delirium (53 v 37 %, $p=0.04$).

Orthopedic ward and daily consultative service (Kammerlander 2)

This is a variant of model 1. The difference is that there is a daily geriatric service. In the evenings and weekends is it usually no geriatric service available. 14 studies exist in this category.

Zuckerman JD, 1992(Zuckerman et al., 1992) In august 1985, the Geriatric Hip Fracture Program (GHFP) was introduced at an orthopedic ward at The Hospital for Joint Disease, New York. The GHFP used a multidisciplinary team (geriatrician, nurse, physiotherapist, occupational therapist, nutritionist) with weekly meetings. 431 patients included in the program were compared to 60 patients treated before the introduction of the program. There were significantly fewer patients with postoperative complications (38 vs 65 %, $p<0.001$) after the introduction of the program and more were able to ambulate independently at discharge (56 vs 18 %, $p<0.001$).

My comment: Beneficial effect of the model, but before - after design. LOS was approx. 25 days, so not comparable to today's standards.

Anotelli Incalzi R, 1993(Antonelli Incalzi et al., 1993) In the Catholic University of the Sacred Heart, a geriatrician was assigned to provide the daily medical care for geriatric patients in the orthopedic ward. 287 patients were prospectively included in 1989-1990 (after the implementation of the new model) and outcomes were compared to 474 patients treated in 1985-1988 (before implementation). All patients above 70 years could be included, not only hip fracture patients. Mortality dropped from 18 % to 8.4 % ($p<0.001$) after the implementation of the new model. LOS was significantly lower for hip fracture patients (29 vs 38 days, $p<0.003$).

My comment: The intervention was limited, but had huge impact on mortality and LOS. Both are, however, much higher than todays standards, also after the implementation of the orthogeriatric model.

Swanson CE, 1998(Swanson et al., 1998): This prospective randomized controlled study from Brisbane, Australia, enrolled 71 patients from October 1994 to July 1995. For those randomized to intervention (N=38), a multidisciplinary team provided early intervention comprising early surgery, early mobilization, daily assessments, weekly multidisciplinary meetings, planned discharge and home assessment visits before discharge. Mean LOS was

shorter in the intervention group (33 v 21 days, p<0.01). There was no difference in mortality, ADL, mobility or complications.

My comment: the study aimed to include 120, but the effect on LOS (primary endpoint) was much larger than expected so the difference was statistically significant even with less patients included than planned. Demented patients and patients from nursing homes were excluded.

Marcantonio 2001 (Marcantonio et al., 2001)(not in Kammerlander 2010): This RCT included 126 patients with hip fracture. Those randomized to intervention (n=62) received geriatric consultation preoperatively or within 24 hours of surgery. The geriatrician performed daily visits for the patients randomized to intervention and made recommendations based on a structured protocol. The primary outcome was delirium, and fewer patients randomized to intervention had delirium (50 v 32 %, p=0.04). The intervention seemed to be most effective in those patients free from prefracture dementia, but this was not statistically significant, probably because of small numbers. The intervention had no effect on delirium duration or LOS.

My comment: well designed study. The intervention was effective, but was aimed at one particular condition (delirium). There is no information about outcomes after discharge.

Khan R, 2002(Khan et al., 2002): In this study, data was collected prospectively from 745 patients admitted from January 1992 through December 1996 to three different orthopedic wards at Mayday University Hospital, Surrey, UK. In December 1994 a geriatrician was hired, and from then orthogeriatric care was introduced in one of the wards. The geriatrician saw the patients twice a week, and once a week there was a multidisciplinary meeting. The introduction of the program had no effect on LOS (26 days in both groups) or mortality. Neither was there any difference in percentage of patients discharged to "pre-admission place of residence".

My comment: Only historical controls. Details are lacking regarding the intervention, but it seems very limited. Nothing is mentioned regarding the multidisciplinary team.

Koval KJ, 2004(Koval et al., 2004): A new report from the same hospital as in Zuckerman 1992 (Zuckerman is among the co-authors). In 1990 the orthogeriatric model was further developed (Zuckerman described that GHFP was introduced in 1985) and a clinical pathway

was introduced for hip fracture patients. In this new model, the multidisciplinary approach was further developed and structured, and included also pre-operative elements ("appropriate multidisciplinary consultation, as dictated by the patient's comorbid conditions"). Outcomes for 318 patients treated earlier (July 1987 - December 1989) was compared to those of 747 patients treated after the implementation of the program (January 1990 - December 2001). The LOS was significantly reduced after the introduction of the new program (22 v 14 days, $p < 0.001$). In-hospital mortality (5 v 2 %, $p < 0.001$) and 1-year mortality (14 v 9 %, $p < 0.01$) was also reduced.

My comment: only historical controls. The intervention is well described, and includes both pre- and postoperative elements. No follow up controls with objective assessments.

Roberts HC, 2004(Roberts et al., 2004): This study evaluated the effect of the implementation of "ICP - integrated care pathway" in 2000. From November 1998 to October 1999, 395 patients were prospectively included in the study. The inclusion was put on hold for seven months in order to implement the program, before 369 patients were included from June 2000 to May 2001. The intervention was provided by a multi-disciplinary team. The primary outcome was LOS in the orthopedic unit, and this increased after the implementation of ICP (23 v 16 days, $p<0.0005$). Significantly more patients treated in ICP could walk independently at discharge (73 v 63 %, $p=0.033$). There was also a significant reduction in pressure sores and UTIs in the ICP. On the other hand, more cardiac complications were registered in the ICP group.

My comment: the intervention is not well described. No follow up controls.

Vidán M, 2005(Vidan et al., 2005) (Categorized as « Orthopedic ward and integrated care" in Kammerlander 2010): In this study from Madrid, Spain, 321 hip fracture patients were included between February and December 1997. All patients shared the same orthopedic wards, but those randomized to intervention (n=157) were assessed daily by a geriatric team, and the geriatrician had the daily medical responsibility for the patients. The patients were randomized after an initial screening performed within the first 48 hours after admission. The patients underwent clinical assessments 3, 6, and 12 months after discharge. LOS (the primary outcome) was two days shorter in the intervention group (18 vs 16 days, $p=0.06$). There was no difference in waiting time for surgery (76 vs 79 hours, $p=0.25$). There was a significant reduction in in hospital mortality (5.5 vs 0.6 %, $p=0.03$), and major medical complications (61

vs 45 %, p=0.003). There was also a trend towards better ADL recovery in the intervention group at the 3 months follow up control (53 vs 43 %, p=0.10).

My comment: one of the few RCTs. Overall is the impression that patients randomized to orthogeriatric care had favorable outcomes, although LOS was the primary outcome. Since the patients were assessed up to 48 hours after admission, many patients did probably not have any pre-operative intervention. Very long waiting time for surgery. There is limited information regarding usual care.

Niam D, 2005(Wong Tin Niam et al., 2005) (not in Kammerlander 2010): A new clinical pathway was introduced in 2001 at this hospital in Fremantle, Austrialia. In this new model was a geriatrician assessing hip fracture patients in the orthopedic ward and recommendations were given. Patients were included in the study from August to December 2001, 28 patients before the implementation of the program (controls) and 71 after the implementation (cases). Delirium was the primary endpoint, and this was daily assessed with the CAM (completed by the geriatrician). After the intervention delirium was reduced (12.7 vs 37.5 %, p=0.012). There was also a non significant reduction in delirium duration (3 vs 5 days, p=0.43). LOS was the same (12.1 vs 11.8 days).

My comment: The intervention had huge impact on delirium rates. There are however several methodological weaknesses in addition to the before-after design. The most notable is that delirium (the primary endpoint) was assessed by the same geriatrician who did the intervention.

Barone 2006(Barone et al., 2006). Italy(not in Kammerlander 2010): In 2001, an orthogeriatric service was established at this hospital in Genoa, Italy. The service provided multidisciplinary evaluation of hip fracture patients in the orthopedic unit. A geriatrician was responsible for medical care. Rehabilitation continued after discharge. The service ended after one year, and to evaluate its efficacy, one compared outcomes for 252 patients treated in the unit to 272 patients admitted in the year before the unit was established (control group 1) and 295 patients admitted the year after the unit was closed (control group 2). Telephone interview was conducted 1 year after discharge. Significantly more patients were alive after 1 year of those treated in the orthogeriatric unit (75%), compared to control group 1 (65%) and control group 2 (67%).

My comment: This is only a letter to editor, so limited information is given.

Fisher AA, 2006(Fisher et al., 2006). This is a study from Canberra, Australia that evaluated the effect of introduction of a model (GM - geriatric medicine) were a geriatrician from 1998 began overseeing daily medical care for hip fracture patients. Data were collected prospectively from introduction of the program and until 2002 (447 patients) and outcomes were compared to those of 504 patients treated before the introduction of GM (1995 - 1997). The geriatrician worked daytime (0800 - 1700) in weekdays, and in weekends and at night care was provided by geriatricians on call. In-hospital mortality was reduced after the introduction of GM (4.7 v 7.7 %, $p<0.01$). Postoperative complications were also significantly reduced. Readmissions to medical wards the first six months after discharge were reduced from 28 % to 7.6 %, $p<0.001$. There was no effect on LOS (median 11 in both groups).

My comment: only the role of the geriatrician is described, nothing about the rest of the multidisciplinary team (the paper refers to the GM-team but it is not further described). The intervention started preoperatively. Retrospective controls is not optimal, as noted by Koval in a comment after the article. Data collected from charts and registers, no objective testing of patients.

Cogan L, 2010(Cogan et al., 2010): In this study from Dublin, Ireland, the aim was "to show that introduction of orthogeriatric services improved care and better patients outcomes". Sometime between 2001 and 2006 (the paper those not describe the exact timing), orthogeriatric care was implemented at the hospital. Data was collected from the charts of 103 patients admitted prior to the introduction of the program (before May 2001), and outcomes were compared to 98 patients admitted after January 2006. After the introduction of the program, a geriatrician attended hip fracture patients in weekdays and the staff had weekly interdisciplinary meetings. The use of protocols was introduced and rehabilitation was emphasized. The introduction of the program had no effect on waiting time to surgery (1.9 days in both groups). LOS increased from 23 to 30 days. In-hospital mortality (20 v 8 %) and 1-year mortality (45 v 34 %) was reduced.

My comment: The article lack details regarding the orthogeriatric program and the timing of the introduction. The waiting time for surgery is long in both groups, as well as LOS. The differences seems not be tested for significance.

Gregersen, 2012 (Gregersen et al., 2012)(not in Kammerlander 2010): This retrospective before-after study from Aarhus, Denmark evaluated the effect of the implementation of a geriatric team (geriatrician, physiotherapist and nurse) in 2003. During daytime in the weekdays, the team provided full time geriatric and orthopedic care for hip fracture patients in the orthopedic ward, but in the weekends and in the nights the team was not available. 262 patients treated in 2000 (before the implementation) were compared to 233 patients included after the implementation of the program in 2003. LOS was reduced from 15 to 13 days after the implementation of the program, but there was no effect on re-admissions or mortality. As the data was collected by retrospective chart reviews, no objective measures regarding physical or cognitive function was available.

My comment: Not optimal design. Some relevant data is missing (type of fracture, type of surgery, co-morbidities).

Wagner, 2012(Wagner et al., 2012) (not in Kammerlander 2010): This study is from the Catholic University in Santiago, Chile, where an orthogeriatric service was established in July 2009. From the description of the models it seems like the hip fracture patients were treated in the orthopedic ward, but were daily assessed by the geriatric team. After surgery, the geriatric team had the primary medical responsibility for the patients, but also gave advice preoperatively. To evaluate the new service, patients were prospectively included from July 2009 to May 2011 (n=92) and outcomes were compared for those admitted between January 2007 and June 2009 (before the service was established, n=183). There was no difference in LOS after implementation of the new model (9 vs 8 days, p=0.51), and also no difference in in-hospital mortality (2.2 % vs 1.1 %, p=0.46) or 1 year survival (87 % in both groups). More post-operative complications were registered after the introduction of the orthogeriatric service, most notably delirium (60 vs 19 %, p<0.001). This difference was by the authors interpreted to be explained by higher awareness of the condition.

My comment: The geriatric intervention is not well described, and even less is explained about usual care.

Bhattacharyya, 2013(Bhattacharyya et al., 2013) (not in Kammerlander 2010): In August 2010, an orthogeriatric service was established at this hospital in Glasgow, UK. The orthogeriatric team worked on a liaison basis preoperatively and until 48 hours after surgery. After that, the orthogeriatric team had the primary responsibility for the patients. Outcomes

were compared for 274 patients treated in the old model (admitted between January 2010 and July 2010) with those of 249 patients treated in the new model (August 2010 and February 2011). LOS was reduced in the new model (19.5 vs 25, p=0.22), and a higher percentage of the intervention patients returned to pre fracture residence (73 vs 57 %, p<0.001).

My comment: The primary focus in this study was satisfaction among health care workers, not patient outcomes. The majority of staff believed that quality of care had improved.

Table 5. Overview of studies evaluating an orthogeriatric model in accordance with Kammerlander model 2

Study	Number of patients	Study design	Timing and organization of follow up controls	Evaluation	Conclusion
Zuckerman, 1992. USA	N=491	Prospective with retrospective controls	No follow up	LOS, post operative complication, mortality. mobility	There were significantly fewer patients with postoperative complications (38 vs 65 %, p<0.001) after the introduction of the program and more were able to ambulate independently at discharge (56 vs 18 %, p<0.001).
Antonelli Incalzi, 1993. Italy	N=761	Prospective with retrospective controls	No follow-up	LOS, mortality, operation rate	Mortality dropped from 18 % to 8.4 % (p<0.001) after the implementation of the new model. LOS was significantly lower for hip fracture patients (29 vs 38 days, p<0.003).
Swanson, 1998. Australia.	N=71	Prospective randomized	1 and 6 months. Data collected either at the 6 months out patient control or by telephone interviews.	LOS, mortality, ADL	Mean LOS was shorter in the intervention group (33 v 21 days, p<0.01). There was no difference in mortality, ADL, mobility, complications.
Marcantoni o, 2001. USA	N=126	Prospective randomized	No follow up	Delirium, LOS. Delirium assessments were done by a rater blinded to allocation.	Fewer patients with delirium in those randomized to intervention (50 v 32 %, p=0.04). No effect on delirium duration or LOS.
Khan, 2002. UK	N=745	Prospective with retrospective controls. No randomization.	No follow up	LOS, mortality, rate of discharges to «pre-admissions place of residence.	The introduction of the program had no effect on LOS (26 days in both groups) or the other outcomes.
Koval, 2004. USA.	N=1065	Prospective with retrospective controls	3,6,12 months and then every 6 months until death. Interviews with patients or family member.	LOS, mortality, mobility.	The LOS was significantly reduced after the introduction of the new program (22 v 14 days, p < 0.001). In-hospital mortality (5 v 2 %, p < 0.001) and 1-year mortality (14 v 9 %, p < 0.01) was also reduced. No effect of ambulation.
Roberts, 2004. UK.	N=395	Prospective before and after	No follow up. Mortality and re-admissions after 1 month registered.	LOS, mortality, complications, readmissions, mobility	LOS increased after the implementation of ICP (23 v 16 days, p<0.0005). Significantly more patients treated in ICP could walk independently at discharge (73 v 63 %, p=0.033). There was also a significant reduction in pressure sores

					and UTI in ICP. On the other hand was more cardiac complications were registered in the ICP group.
Vidán, 2005. Spain	N=321	Prospective randomized controlled trial	3,6,12 months. Interviews with patients and relatives.	LOS, complications, mortality, ADL recovery	LOS (the primary outcome) was two days shorter in the intervention group (16 vs 18 days, p=0.06). There was a significant reduction in in hospital mortality (0.6 vs 5.5 %, p=0.03), and major medical complications (45 vs 61 %, p=0.003). There was also a trend towards better ADL recovery in the intervention group at the 3 months follow up control (53 vs 43 %, p=0.10).
Niam, 2005. Australia	N=99	Prospective before -after	No follow up	Delirium, LOS	After the intervention delirium was reduced (12.7 vs 37.5 %, p=0.012). There was also a non significant reduction in delirium duration (3 vs 5 days, p=0.43). LOS was the same (12.1 vs 11.8 days).
Barone 2006. Italy	N=819	Retrospective before and after	12 months. Telephone interview were conducted.	LOS. Mortality	Significantly more patients were alive after 1 year of those treated in the orthogeriatric unit (75%), compared to those admitted before (65%) and after (67%) the unit was closed.
Fisher, 2006. Australia.	N=951	Prospective with retrospective controls	No follow up. 6 months re-admissions registered.	LOS, mortality, complications	In hospital mortality was reduced after the introduction of GM (4.7 v 7.7 %, p<0.01). Postoperative complications were also significantly reduced. Readmissions to medical wards the first six months after discharge were reduced from 28 % to 7.6 %, p<0.001. There was no effect on LOS (median 11 in both groups).
Cogan, 2010	N=201	Retrospective chart review before and after	No follow up. 12 months mortality registered.	LOS, mortality, waiting time for surgery	The introduction of the program had no effect on reduction of waiting time to surgery (1.9 days in both groups). LOS increased from 23 to 30 days. In hospital mortality (20 v 8 %) and 1-year mortality (45 v 34 %) was reduced.
Gregersen, 2012. Denmark	N=495	Retrospective chart review before and after	No follow up. Re-admissions and mortality registered at 3,6 and 24 months	LOS, mortality, re-admissions	LOS reduced from 15 to 13 days after implementation of the program. No effect on re-admissions or mortality
Wagner, 2012. Chile	N=275	Prospective with retrospective controls	No follow up. Mortality and re-admissions registered for up to 48 months.	LOS, mortality, complications	There was no difference in LOS after implementation of the new model (9 vs 8 days, p=0.51), and also no difference in in-hospital mortality (2.2 % vs 1.1 %, p=0.46) or 1 year survival (87 % in both groups). More post-operative complications was registered after the introduction of the orthogeriatric service, most notably delirium (60 vs 19 %, p<0.001).
Bhattachary ya, 2013. UK	N=523	Retrospective chart review before and after	No follow up	LOS, mortality, discharge destination	LOS was reduced in the new model (19.5 vs 25, p=0.22), and more returned to pre fracture residence (73 vs 57 %, p<0.001).

Geriatric and rehabilitation ward and orthopedic consultant service (Kammerlander 3)

In this model the patients are treated in a geriatric ward, and the geriatricians have the primary responsibility for the patients. The orthopedic surgeon is consultative. 12 studies (reporting from 6 models) exist in this category.

Boyd RV, 1983(Boyd et al., 1983): In 1978, a new orthogeriatric unit opened at this hospital in Nottingham, UK. The medical staffing was geriatricians with a consultant orthopedic surgeon and the ward had also a multidisciplinary team. The orthogeriatric ward received patients from eight different orthopedic surgeons in orthopedic wards. Mostly, but not exclusively, hip fracture patients were admitted to the ward. To evaluate this unit the researchers compared LOS, waiting time for surgery, in hospital mortality and discharge destination for the female hip fracture patients admitted to the unit in 1977 (before the unit opened, n=289) to those treated in 1979 (after the unit had opened, n=482). LOS was reduced from 66 to 48 days and waiting time for surgery from 3 to 2.6 days. In-hospital mortality was also reduced (22 vs 17 %). There were only minor changes in discharge destination.

My comment: Before and after study. Only postoperative intervention. LOS, waiting time for surgery and in-hospital mortality is much higher than today. No significance testing of differences. Kammerlander have extracted other numbers regarding participants (I think he is wrong).

Adunsky A, 2003, 2005, 2011. Ginsberg 2013(Adunsky et al., 2003, Adunsky et al., 2005, Adunsky et al., 2011, Ginsberg et al., 2013): In 1999, an orthogeriatric service was established at Sheba hospital in Tel Aviv, Israel(Adunsky et al., 2002). In this model, the patients are treated in a geriatric ward based upon the concept that "a hip fracture is a geriatric, rather than an orthopedic disease". In this model is the patients were transferred directly from the ER to the orthogeriatric ward, and returned to the ward after surgery. There are several reports from the "Sheba-model". In the study from 2003, patients were included in the emergency room and allocated directly to the orthogeriatric ward (n=116) or to orthopedic ward (n=204). The allocation was based on availability of beds. The patients allocated to intervention had shorter LOS (32 vs 27 days, $p<0.01$) and an almost two-fold chance of successful rehabilitation as defined as more than 50 % increase in "relative functional gain". The effect on waiting time for surgery is not reported in the 2003 article, but in the article published in 2005 that included 592 patients treated in the Sheba model, the mean waiting

time for surgery was 3.6 ± 3.4 days. Compared to historical controls this model also reduced 1 year mortality (17.3 vs 14.8 %, p=0.016) (Adunsky 2011) and using register data the model was also shown to be cost-effective (Ginsberg 2013).

My comment: The model is advanced, and seems to be the one that most closely resembles the model used at Ullevaal 2008 - 2012. The studies reports beneficial effects, but only the study from 2003 had an experimental design (quasi-randomization based on availability of beds). In that study also patients randomized to usual care were admitted to the orthogeriatric unit postoperatively, so the study mainly assessed the effect of preoperative orthogeriatric intervention. The waiting time for surgery was extremely long, also after implementation of the orthogeriatic model.

Stenvall M, 2007, 2012. Lundstrom 2007(Stenvall et al., 2007, Lundstrom et al., 2007, Stenvall et al., 2012): In this study from Umea in Sweden were 199 patients included between May 2000 and December 2002. This model is a further development of the orthogeriatric service at this hospital, as described in earlier reports(Gustafson et al., 1991). The patients were randomized to postoperative care in a geriatric ward or usual care in the orthopedic ward. In addition to the intervention during the hospital stay, those randomized to intervention were assessed four months after surgery to detect and treat any complications. LOS was significantly reduced (40 vs 30 days, p=0.028). Ssignificantly more patients allocated to intervention had regained independence in personal ADL four (OR 2.5) and 12 months (OR 3.5) after surgery. There was no difference in re-admissions or mortality. The model was also effective in preventing postoperative delirium (75 vs 55 %, p=0.003) and reducing delirium duration (10 vs 5 days, p=0.009) (Lundstrom et al., 2007). The intervention was particularly effective for patients with dementia, with significant reduction in postoperative delirium (97 vs 68 %, p=0.002), UTI (64 vs 21 %, p=0.001) and falls (34 vs 1, p=0.006) during the hospital stay and with improved outcomes at the follow up controls (Stenvall et al., 2012).

My comment: Well designed study. Only postoperative intervention, but there was also intervention after discharge from hospital. Assessors were not blinded. High delirium rates may be indicative of poor quality of the usual care.

Miura, 2009(Miura et al., 2009) (not in Kammerlander 2010): The Hip Fracture Service (HFS) was introduced at this hospital in Oregon, USA, in 2001. This was an interdisciplinary geriatrician led program, and was developed in collaboration between geriatricians and

orthopedic surgeons. The orthogeriatric ward was located in the orthopedic ward, but a geriatrician had the primary responsibility for the patients. New practices were initiated in the HFS, protocols, preprinted orders and standardized assessments were used. To evaluate the HFS were 91 patients prospectively included between 2001 and 2002. Outcomes were compared to 72 patients admitted in 2000 (before the program). LOS was reduced after the introduction of HFS (6.1 vs 4.6, $p<0.001$). More patients in HFS were operated before 24 hours (50.5 vs 22.2 %, $p<0.001$). HFS was also cost effective. Re-admission the first 30 days after surgery was 11 % in the HFS group, but this data was not collected for the control group.

My comment: Seems like a good design, but only historical controls. No clinical endpoints are reported. No follow up.

Mazzola, 2010(Mazzola et al., 2011) (not in Kammerlander 2010): This study from Monza, Italy compared two different orthogeriatric care (OC) programs. In OC-1, patients were admitted directly to the orthogeriatric ward from the ER, whereas in OC-2 the patients were admitted first to the orthopedic ward and then to the orthogeriatric ward postoperatively. Patients were prospectively included in the study from March 2007 to June 2009. Patients were included in OC-1 (n=174) when a bed was available, otherwise to OC-2 (n=87). There was no significant differences between patients treated in OC-1 and OC-2 with regard to waiting time for surgery (mean 2.8 days in both groups) or LOS (13 days in both groups), but patients treated in OC-1 had shorter mobilization time (2.9 vs 3.6 days, $p=0.01$).

My comment: Only pre-operative intervention differed between groups, and in contrast to Adunsky, the effect was limited. Only mobilization time was different, but it is unclear from the paper what the authors mean by this variable. Since this is most likely to be a variable measured postoperatively, one would expect that this difference emerged by chance since the intervention seemed to be identical in both groups postoperatively. Waiting time for surgery is long in both groups.

Sletvold, 2011. Saltvedt, 2012(Sletvold et al., 2011, Saltvedt et al., 2012) (not in Kammerlander 2010): Only the protocol and details regarding the intervention have been published (Saltvedt et al., 2012, Sletvold et al., 2011) from this RCT of 397 hip fracture patients included at St Olav hospital, Trondheim, Norway from April 2008 to December 2010. The patients were included in the ER and randomized to usual care in the orthopedic ward or to an orthogeriatric service provided in the acute geriatric ward. The patients were

transferred directly from the ER to the allocated unit. The intervention used CGA as a basis for planning of care. The intervention emphasized adequate nutrition, early mobilisation and early discharge planning. The primary endpoint was mobility, assessed with SPPB. The main results from this RCT have not been published yet, but preliminary results have been presented at conferences (Nordic Congress of Gerontology, Copenhagen June 2012), and patients randomized to intervention had significantly better SPPB four months after surgery.

My comment: This is a large RCT with impressive design. Only preliminary data are reported.

Table 6. Overview of studies evaluating an orthogeriatric model in accordance with Kammerlander model 3

Study	Number of patients	Study design	Timing and organization of follow up controls	Evaluation	Conclusion
Boyd, 1983. UK	N=771	Retrospective before and after	No follow up.	LOS, mortality, waiting time for surgery, discharge destination	LOS was reduced from 66 to 48 days and waiting time for surgery from 3 to 2.6 days. In hospital mortality was also reduced (22 vs 17 %). There were only minor changes in discharge destination.
Adunsky, 2003, 2005, 2011. Gingsberg 2013. Israel	N=330	Prospective quasi-randomised controlled	No follow up controls, but mortality data is registered up to 12 months after surgery.	LOS, mortality, functional function at discharge	Those allocated to intervention had shorter LOS (32 vs 27 days, $p<0.01$) and almost two-fold chance of successful rehabilitation as defined as more than 50 % increase in "relative functional gain".
Stenvall 2007, 2012. Lundstrom 2007. Sweden.	N=199	Prospective randomized controlled	Home visits 4 and 12 months performed by research nurses.	LOS, mortality, postoperative complications, delirium, ADL functions	Significantly more patients allocated to intervention had regained independence in personal ADL performance f (OR 2.5) and 12 months (OR 3.5) after surgery. There was no difference in re-admissions or mortality. The model was also effective in preventing postoperative delirium (75 vs 55 %, $p=0.003$) and reducing delirium duration (10 vs 5 days, $p=0.009$). The intervention was particular effective for patients with dementia, with significant reduction in postoperative delirium (97 vs 68 %, $p=0.002$), UTI (64 vs 21 %, $p=0.001$) and falls (34 vs 1, $p=0.006$) during the hospital stay.
Miura, 2009. USA	N=161	Prospective with retrospective controls	No follow up.	LOS, mortality, cost	LOS was reduced after the introduction of HFS (6.1 vs 4.6, $p<0.001$). More patients in HFS was operated before 24 hours (50.5 vs 22.2 %, $p<0.001$). HFS was also cost effective.
Mazzola, 2010. Italy	N=261	Prospective quasi-randomized controlled (by availability of beds)	No follow up	LOS, waiting time for surgery, mobilization time	There was no significant differences between patients treated in OC-1 and OC-2 in regard to waiting time for surgery (mean 2.8 days in both groups), LOS (13 days in both groups), but patients treated in OC-1 had shorter mobilization time (2.9 vs 3.6 days, $p=0.01$).
Sletvold, 2011. Saltvedt 2012. Norway	N=397 (only pre-liminary data presented)	Prospective randomized controlled trial.	The patients were assessed in the outpatient clinic 1,4,12 months by research assistants blinded to allocation.	Mobility, LOS, mortality, health economics, place of residence, ADL	The main results from this RCT have not been published yet, but preliminary results have been presented at conferences (Nordic Congress of Gerontology, Copenhagen June 2012), and patients randomized to intervention had significantly better mobility four months after surgery

Orthopedic ward and integrated care (Kammerlander 4)

This is the most advanced model were the orthopedic surgeons and geriatricians co-manage the patients on a daily basis. Eight studies (reporting from five models) exist in this category.

Lundström M, 1999(Lundstrom et al., 1999) (not in Kammerlander 2010): From January to December 1993 were 49 patients (mean age 79.7 year, 17 men) with femoral neck fractures included in this study from Piteå, Sweden. The patients were treated at the Department of Rehabilitation where the orthopedic surgeons and the geriatricians co-managed the patients. The patients were admitted directly from the ER. The intervention included education of the staff, prevention and treatment of delirium, individual planning of care and rehabilitation, daily involvement of physiotherapists and occupational therapists, and focus on nutrition. The model was compared to historical cohorts of hip fracture patients in the same and other hospitals. Compared to 35 patients included in a study conducted at the same hospital from April 1983 to May 1984(Brannstrom et al., 1991, Brannstrom et al., 1989), more patients returned to independent living on discharge (93 vs 33%, p=0.02), and more could walk independently with walking aids at discharge (89 v 60 %, p=0.003) after implementation of the new model. There was also a non-significant reduction of postoperative delirium (27 % vs 43 %, p=0.13). There was no difference in patients living independently 6 months after surgery (80 vs 85 %, p=0.62). The LOS was 13 days in both groups.

My comment: The orthogeriatric model is advanced and well described. The intervention started pre-operatively and was very effective. There are however methodological problems with the study (small sample size, use of historical controls).

Khasraghi FA, 2005(Khasraghi et al., 2005): In April 1998 a Hip Fracture Service (HFS) was established at Johns Hopkins medical center in Baltimore, USA. This was a cooperation between the Department of Orthopedic surgery and the Division of Geriatric Medicine, and geriatricians and orthopedic surgeons co-manage the patients. To evaluate this new service, patient charts and the hospital discharge database were reviewed for 510 patients (273 in HFS group) admitted with hip fracture between January 1995 and December 2000. Postoperative complications were significantly reduced after the introduction of HFS (51 vs 36 %,). Waiting time for surgery (46 vs 26 hours) and LOS (8.1 vs 5.7 days) were also significantly reduced, and significantly fewer were discharged to nursing homes (23 vs 13 %).

My comment: Only historical data. No objective measurements and no follow up controls. Also no information regarding re-admissions and mortality.

Friedman S, 2008, 2009. Kates 2010, 2011(Friedman et al., 2008, Friedman SM, 2009, Kates et al., 2010b, Kates et al., 2011): A Geriatric Fracture Center (GFC) was developed at the Mayo clinic in Rochester, USA in 2004. This model ("The Rochester Model) is an advanced orthogeriatric service were the patients on a daily basis are co-managed by geriatricians and orthopedic surgeons(Kates et al., 2010a). There are several reports from this model. In the study from 2009, outcomes from 193 hip fracture patients admitted to GFC between May 2005 to April 2006 were compared to outcomes from 121 hip fracture patients admitted to a nearby hospital (without orthogeriatric service) in the same period. Those treated in GFC had shorter waiting time for surgery (24 vs 37 hours, $p=0.007$), shorter LOS (4.6 vs 8.3 days, $p<0.001$) and fewer complications 31 vs 46 %, $p=0.005$). There was no difference in hospital mortality or re-admissions the first 30 days after surgery(Friedman SM, 2009). The Rochester model is also cost effective compared to historical data (Kates et al., 2011) and to a national average (Kates et al., 2010b).

My comment: The Rochester model is very impressive and is considered the reference model for orthogeriatric collaboration based on co-management of elderly patients with hip fractures(Pioli et al., 2014). The outcomes are however only compared to historical controls, other hospitals, or national averages.

González-Montalvo JI, 2010(Gonzalez-Montalvo et al., 2010)(not in Kammerlander 2010): This study was conducted at La Paz University Hospital in Madrid and compared two different orthogeriatric models. Model 1 was established in 1995 in the form of geriatric liaison service for patients in the orthopedic ward. In February 2007 was a new service (Model 2) established were geriatricians and orthopedic surgeons co-managed the patients on a daily basis. To compare these two models, patients were included in the study between February and August 2007. The patients were allocated between model 1 (n=123) and model 2 (101) in a quasi-randomized way (alternate days and depending on bed availability). Waiting time for surgery (5 vs 6 days, $p<0.001$) and LOS (12 vs 18 days, $p<0.001$) was shorter in Model 2. There was no difference in in-hospital mortality, discharge destinations or mobility at discharge.

My comment: The waiting time for surgery was extremely long in both groups. Given the negative effect waiting time for surgery has on outcome(Pioli et al., 2012a), one would expect that any intervention would have only minor effect in this study.

Dy 2011(Dy et al., 2012)(not in Kammerlander 2010): At this hospital in New York, USA, an orthogeriatric model (MOTS - Medical Orthopedic Trauma Service) was introduced in March 2008. In this model, elderly hip fracture patients were on a daily basis co-managed by physicians from Dept. of Internal Medicine and Orthopedic Surgery. To evaluate this model, data were collected retrospectively from chart reviews from May to December 2007 (pre-MOTS, n=144) and May to December 2008 (MOTS, n=162). Fewer patients had complications after introduction of MOTS (56 vs 72 %, p=0.002. There was a trend of higher 1-year mortality after the introduction of MOTS (33 vs 18 %, p=0.16). There was no difference in waiting time for surgery (1.4 vs 1.5 days, p=0.62) or LOS (7 vs 8.4, p=0.50).

My comment: It is not clear whether the medical input was given by geriatricians, although the authors describe a multidisciplinary approach to the patients.

Table 7. Overview of studies evaluating an orthogeriatric model in accordance with Kammerlander model 4					
Study	Number of patients	Study design	Timing and organization of follow up controls	Evaluation	Conclusion
Lundström, 1999. Sweden	N=49	Prospective with retrospective controls	6 months. Interviews with patients and caregivers.	Delirium, LOS, mobility	Compared to 35 patients included in a study conducted at the same hospital from April 1983 to May 1984, did more patients return to independent living on discharge (93 vs 33%, p=0.02), and more could walk independently with walking aids at discharge (89 v 60 %, p=0.003) after implementation of the new model. There was also a non-significant reduction of postoperative delirium (27 % vs 43 %, p=0.13). There was no difference in patients living independently 6 months after surgery (80 vs 85 %, p=0.62). The LOS was 13 days in both groups.
Khasraghi, 2005. USA	N=510	Retrospective before and after chart review	No follow up	LOS, waiting time for surgery, complications, discharge destinations	Postoperative complications were significantly reduced after the introduction of HFS (51 vs 36 %,). Waiting time for surgery (46 vs 26 hours) and LOS (8.1 vs 5.7 days) were also significantly reduced and significantly fewer were discharged to nursing homes (23 vs 13 %).
Friedman 2008, 2009. Kates 2010, 2011. USA	N=314	Retrospective chart review. Data compared to other hospitals, historical data and national average.	No follow up. 30 days re-admissions registered.	LOS, waiting time for surgery, mortality, re admissions	Those treated in GFC had shorter waiting time for surgery (24 vs 37 hours, p=0.007), shorter LOS (4.6 vs 8.3 days, p<0.001) and fewer complications 31 vs 46 %, p=0.005) compared to patients treated at a nearby hospital without orthogeriatric service. There was no difference in in hospital mortality or re-admissions the first 30 days after surgery.
González-Montalvo, 2010	N=224	Prospective quasi-randomization (alternate days an bed-availability)	No follow up.	LOS, waiting time for surgery, mobility at discharge, discharge destination.	Waiting time for surgery (5 vs 6 days, p<0.001) and LOS (12 vs 18 days, p<0.001) was shorter in Model 2. There was no difference in in-hospital mortality, discharge destinations or mobility at discharge.
Dy, 2012. USA.	N=306.	Retrospective chart review before after	No follow up. Readmissions and mortality 3 and 12 months after surgery is reported.	LOS, waiting time for surgery, mortality, complications	Fewer patients had complications after introduction of MOTS (56 vs 72 %, p=0.002. There was a trend of higher 1-year mortality after the introduction of MOTS (33 vs 18 %, p=0.16). There was no difference in waiting time for surgery (1.4 vs 1.5 days, p=0.62) or LOS (7 vs 8.4, p=0.50).

1.2.3 **Which orthogeriatric model is most effective?**

There are considerable methodological problems with most of the published studies. The most serious is the use of historical controls. Such design has been criticized because medical and surgical improvements can impact results, and it is therefore impossible to judge how much of the improvements can be explained by the orthogeriatric service(Koval, 2006).

Another problem is that most studies evaluate the effect of the orthogeriatric model only by register data; LOS, waiting time for surgery and mortality is the most used indicators. Although important, these do not necessarily catch the potential benefits (or harms) of an orthogeriatric approach. Most studies have no follow up visits, so it is not possible to say if the effect of the intervention lasted (or first appeared) after discharge. Of all the studies identified in the previous chapter, outcomes after follow up (other than re-admission and mortality) was only reported in 11 (Leung et al., 2011, Deschodt et al., 2011, Shyu et al., 2010, Naglie et al., 2002, Koval et al., 2004, Vidan et al., 2005, Barone et al., 2006, Stenvall et al., 2007, Swanson et al., 1998, Lundstrom et al., 1999, Sletvold et al., 2011). Of these, two studies use data from regular outpatient visits(Swanson et al., 1998, Leung et al., 2011). In five other studies, follow up data were collected by (telephone) interview with patients and/or careers (Barone et al., 2006, Deschodt et al., 2011, Koval et al., 2004, Naglie et al., 2002, Lundstrom et al., 1999). Only four studies describe a face-to-face evaluation of the patients(Shyu et al., 2010, Stenvall et al., 2007, Vidan et al., 2005, Sletvold et al., 2011).

A third important point is that in most studies, the intervention started postoperatively; a paradox since geriatric input might be especially beneficial in the vulnerable period from fracture to surgery. A recently published metaanalysis focusing on early orthogeriatric treatment(Buecking et al., 2013) identified only five RCTs of orthogeriatric care were there was any form of preoperatively intervention(Naglie et al., 2002, Stenvall et al., 2007, Shyu et al., 2010, Vidan et al., 2005, Uy et al., 2008). The metaanalysis concluded that there was a trend towards improved outcomes in early orthogeriatric intervention programs, but the small number of included patients (n=970 in total), did not allow this benefit to be demonstrated with certainty. It has to be mentioned that among the studies included in the meta analysis is no preoperative intervention described in the study from Canada(Naglie et al., 2002). In the Swedish study was the randomization procedure carried out preoperatively, but the intervention started after surgery(Stenvall et al., 2007). Also in the Spanish study (Vidan et

al., 2005), it is likely that many patients had already undergone surgery before inclusion, since the patients were included and randomized after an initial screening that was performed within 48 hours of admission. Lastly it must be noticed that inclusion in the Australian trial (Uy et al., 2008) was terminated after inclusion of only 11 patients due to changes in Australian health care politics creating financial incentives to have only immobile patients to nursing homes, making it impossible to recruit patients (for this reason it is not discussed in the previous chapter). So studies where there is any substantial preoperative input is even scarcer than indicated by the metaanalysis.

Patients with dementia are often excluded from hip fracture trails(Hebert-Davies et al., 2012), but such patients constitute a huge part of the hip fracture population. One can speculate if these particular frail patients would benefit most from geriatric interventions, but even in studies of orthogeriatric care such patients are sometimes excluded (Shyu et al., 2010, Koval et al., 2004, Swanson et al., 1998).

Even with all these limitations, the overall conclusion from the literature is that elderly patients with hip fractures benefit from orthogeriatric care. This is also supported by a Cochrane review on “Multidisciplinary rehabilitation for older people with hip fractures”, where there was a trend of lower risk of poor outcome for patients treated with multidisciplinary rehabilitation compared to usual care poor outcome (risk ratio 0.89; 95% confidence interval 0.78 to 1.01)(Handoll et al., 2009).

It is, however, difficult to draw firm conclusions regarding the superiority of one particular model due to heterogeneity of the organization of care in the different models as well as in the research design. Only in one of the reviews of orthogeriatric care (Grigoryan et al., 2014) did the authors pool data, and the conclusion was that co-managed care in an integrated model seemed to give best results. This was also the conclusion in the other three reviews. To facilitate the comparison of different models in the future, an expert panel have recently published an article where a set of outcome indicators are identified to be included in the evaluation of orthogeriatric models(Liem et al., 2013).

1.2.4 Orthogeriatric models at Oslo University hospital - Ullevaal

The last two decades have different models of orthogeriatric care been in use at Oslo University Hospital - Ullevaal.

1997 - 2002 HOBRUS: postoperative rehabilitation in the geriatric ward

This was the first model where the Department of Orthopedic Surgery and Department of Geriatric Medicine started to collaborate in the treatment of hip fracture patients. From the autumn 1997 was a model implemented where patients were transferred to the geriatric ward five days after surgery. A nurse was assigned to assess which patients were most likely to profit from such rehabilitation. This model was not scientifically evaluated, but in a report written for the hospital administration it is concluded that this model functioned satisfactory and that the quality of care had been improved. Total LOS in the hospital was reduced by 25 % after implementation of the model.

March 2004 - December 2006: "Eldre med brudd" (Kammerlander model 2)

"Eldre med brudd" ("Elderly with fractures") was a project carried out in collaboration between Department of Orthopedic Surgery and Department of Geriatric Medicine. In this model, 10 beds in the orthopedic ward were reserved for elderly patients with fractures (not only hip fractures). A geriatric team (geriatrician, nurse and physiotherapist) assessed the patients daily, and had the day to day responsibility for the patients. The team was not available in the evenings or in the weekends. This is in line with a Kammerlander model 2.

This model was also not scientifically tested, but the conclusion from the health care personnel involved was that this model improved quality of care. It was, however, acknowledged as a problem that there was a geriatric service only at daytime. In the termination of the project the plan was to make a joint effort to establish a separate orthogeriatric unit with shared care (in line with Kammerlander model 4). Due to administrative challenges regarding financing, this was never achieved.

June 2008 - January 2012: Hip fracture patients in the acute geriatric ward (Kammerlander model 3)

In connection with a re-organization of the acute geriatric ward in 2008, it was decided that four beds should be reserved for hip fracture patients. The patients were admitted to the ward directly from the ER and the geriatricians had the primary medical responsibility for the patients the entire stay. This is in line with Kammerlander model 3. The allocation to the acute geriatric ward was based primarily on availability of beds. The new service had capacity to serve approximately half of the hip fractures admitted to the hospital, and it was thus decided to randomly allocate patients to the acute geriatric ward and the orthopedic ward in order to evaluate the new service in an RCT. The first patient was included in the RCT in September 2009, and this serve as the foundation for this PhD.

2 Aims of the study

Based on the knowledge gaps regarding delirium prognosis, delirium pathophysiology and the impact on delirium by different models of care, three main aims emerged for this thesis:

I. To investigate the effect of delirium on cognitive trajectories (paper I)

II. To evaluate the effect of the orthogeriatric model (Kammerlander model 3) in use at Oslo University hospital - Ullevaal from June 2008 to January 2012 (paper II)

III. To explore pathophysiological mechanisms in delirium (paper III and IV)

3 Patients and methods

3.1 **Participants**

The patients came from four different patient samples (flowchart). For patients included in the RCT (paper II, sample 1), I had the daily responsibility for running the study and collecting data. I was also involved in planning and organization of the inclusion and data collection in sample 4. I have not been involved in collection or planning of sample 2 and sample 3. This chapter will describe the different patient samples. Most details will be given for sample 1.

Sample 1(Watne): 329 hip fracture patients were included between September 2009 and January 2012 at Oslo University Hospital, Ullevaal. Inclusion and randomisation took place in the ER by the orthopaedic surgeon on call. Patients were randomised to treatment and care in an acute geriatric ward or standard orthopaedic ward. The patients had their entire hospital stay in the same ward except for surgery and a few hours in the postoperative care unit. The patients were assessed four and twelve months after surgery by research nurses blinded to allocation. The main objective of the study was to evaluate the orthogeriatric service in use at the hospital from June 2008 to January 2012. CSF was collected from 143 patients at the onset of anesthesia, and has been analyzed in order to investigate pathophysiological mechanisms in delirium.

Sample 2 (Juliebø/Krogseth): 364 hip fracture patients were included between September 2005 and December 2006 at Oslo University Hospital, Ullevaal and Diakonhjemmet Hospital in Oslo. A research team of two researchers and three study nurses performed daily reviews of the patient registries to identify patients with hip fracture. Eligible patients were included within 48 hours of admission. The main objective was to prospectively investigate the prevalence of pre- and postoperative delirium, and to identify important risk factors(Juliebo et al., 2009). One-hundred-seventy-four of the included patients were assessed six months after surgery by a physician (Maria Krogseth) blinded to delirium status, in order to explore the effect of delirium in patients with (paper I) and without prefracture cognitive impairment(Krogseth et al., 2011).

Sample 3 (Hall): 108 hip fracture patients were included at the Royal Infirmary, Edinburgh, Scotland from September 9, 2009 to April 27, 2011. The patients were included in the

Orthopedic Unit by a geriatrician (Roanna Hall). The patients were closely monitored for delirium during a two-week perioperative period, and assessed 3, 6 and 12 months after surgery. CSF was collected at the onset of anesthesia, and the main objective was to assess the role of cortisol and inflammation in delirium. The study design was similar to the RCT (Sample 1), with the same measurements of prefracture cognitive status (IQCODE) and delirium (CAM). Data from Oslo and Edinburgh could therefore be pooled (paper III and IV).

Sample 4 (Idland): 155 Patients above 65 years of age scheduled for elective orthopedic, gynecologic or urologic surgery in spinal anesthesia were recruited at three different hospitals in Oslo between February 2012 and June 2013 (Oslo University Hospital - Aker, Oslo University Hospital - Ullevaal, Diakonhjemmet hospital). The patients were thoroughly cognitively tested some days before surgery and CSF was collected at the onset of spinal anesthesia. The patients will be followed up with cognitive tests once a year for five years. The main objective with this study was to collect serum and CSF from cognitively healthy elderly patients that can serve as a reference material for studies on delirium and dementia pathology.

The selection of patients in the different studies was as follow:

Paper I: This study included hip fracture patients from sample 1 and sample 2. Only patients with a prefracture IQCODE ≥ 3.44 were included, n=287.

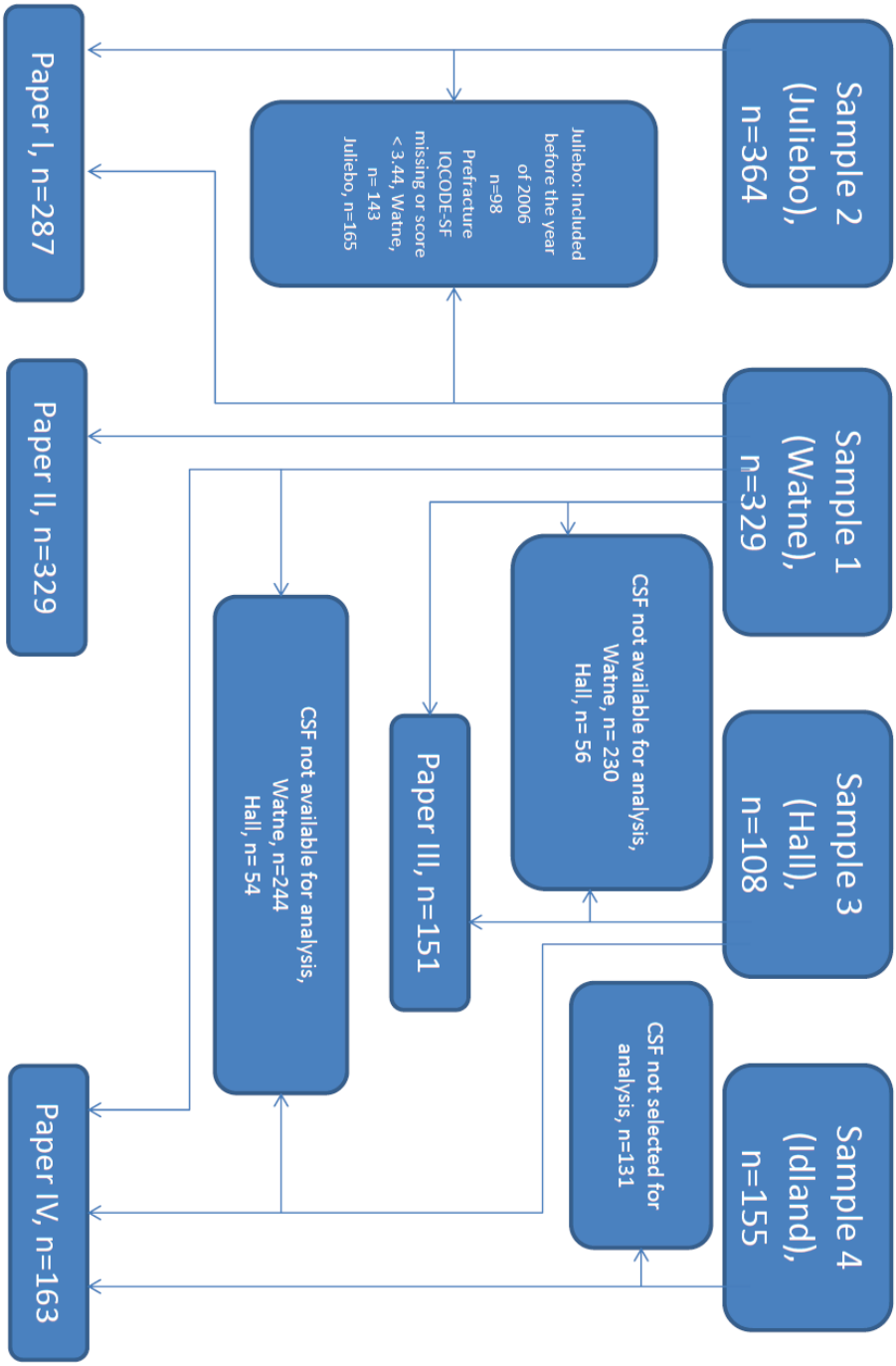
Paper II: This study included all patients in the RCT (sample 1), n=329

Paper III: This study included hip fracture patients from Oslo (sample 1, n=99) and Edinburgh (sample 3, n=52) with an available CSF and serum sample by May 2011.

Paper IV: This study included hip fracture patients from Oslo (sample 1, n=85) and Edinburgh (sample 3, n=54) with CSF and preoperative serum samples available. CSF samples from 24 randomly selected healthy controls (sample 4) were also included.

See figure 2 for details regarding selection of patients in the different papers.

Figure 2. Selection of patients in the different papers.



3.2 Assessments

Table 8 gives an overview of assessments and timing of assessments in the different patient samples. The following sections will give a detailed description of those used in sample 1.

3.2.1 Assessment methods

Screening for delirium: All patients were screened once daily for delirium with the CAM(Inouye et al., 1990) preoperatively and until the fifth postoperative day (all) or until discharge (delirious patients). The study physician or a study nurse (Elisabeth Fragaat (EF) from Sept 2009 to May 2010, Tone Fredriksen (TF) from May 2010 to January 2012) did all the assessments. The inter-rater agreement between the geriatrician and each of the two study nurses was assessed in 13 (LOW and EF) and 23 (LOW and TF) patients, respectively, showing excellent agreement in distinguishing delirious from non-delirious patients (both showing kappa = 1), and good agreement in distinguishing subsyndromal delirium from patients with no signs of delirium (kappa = 0.65 for LOW and EF and kappa = 0.79 for LOW and TF). If the nurse was unsure about the diagnosis, the study physician was consulted. The CAM score was based on information from nurses, close relatives and hospital records reporting symptoms the last 24 hours, in combination with a 10 - 30 minutes interview with the patients. Tests of cognition, attention and alertness in the delirium assessments were: Digit span forward and backward and orientation and delayed recall from the Memorial Delirium Assessment Scale (MDAS) (Breitbart et al., 1997). Delirium severity was measured with MDAS. Patients were regularly assessed on weekdays only, but staff members that had been working during weekends were interviewed every Monday and the case notes scrutinised in order to reveal potential episodes of delirium. The mean number of delirium assessments during the stay was 5.7 (SD 2.7).

Biomedical factors: Diagnosis was collected from previous medical records, and the Charlson Comorbidity Index(Charlson et al., 1987) was calculated. The American Society of Anesthesiologists (ASA) score was collected from the anesthesiology records, and type of fracture and surgery was collected from the surgery records. Height was calculated using knee-heel length (Chumlea et al., 1998) and the patients were weighed by a chair scale. BMI was calculated. At the follow up controls, height was measured in those able to stand, and

knee-heel length in all. Weight at follow-up controls was assessed by a standing scale that was calibrated to the chair scale used during hospital stay.

Process of care: Waiting time for surgery was calculated as time from admission in the ER to start of anesthesia. Mobilization after surgery was used as a process measure. This was registered the second day after surgery based on case notes and observations. From September 2011, mobilization and walking was also recorded with the activPAL™ body-worn sensor system(Grant et al., 2006). The sensor was attached on the anterior aspect of the non-affected thigh as soon as possible after surgery and was worn until discharge.

Clinical findings: Blood pressure (BP), temperature, oxygen saturation and ECG at admission and postoperatively was collected from hospital records. The Acute Physiology and Chronic Health Evaluation II (APACHE II)(Knaus et al., 1985) score on admission to hospital was calculated as a measure of physiological disturbance, though without information on arterial blood gases and hematocrit. Length of anesthesia and surgery and the lowest BP during surgery was registered.

Medications: Medications the patients used at admission, discharge and the follow up controls were registered. During the hospital stay the daily use of medications in addition to the regular was registered. Medications given in the operating theater were also registered. The anticholinergic drug burden of regular medications registered on admission was calculated using the Anticholinergic Cognitive Burden (ACB) scale (Boustani et al., 2008).

Cognitive status: Prefracture cognitive status was estimated with the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). 3.44 was used as a cutoff for probable cognitive impairment(Jorm, 2004, Jorm, 1994).

At the follow up controls, cognitive function was assessed with several measures. The two included in the primary endpoint in the RCT were the 10 words test from Consortium to Establish a Registry for Alzheimer's disease battery (CERAD)(Welsh et al., 1994) and The Clinical Dementia Rating scale (CDR)(Hughes et al., 1982). CERAD is a memory test in which patients are asked to recall 10 words after having them presented orally or visually. We used the immediate and delayed recall tasks of the test. This test is shown to be sensitive for memory changes in persons with good cognitive functioning(Karrasch et al., 2005). CDR is based on information from the best available sources as a combination of patient and proxy

information and is sensitive for cognitive changes in patients with dementia. We used the "sum of boxes" scoring adding up to a sum score ranging from zero (no dementia symptoms) to 18 (severe dementia). The sum score is in most studies shown to correlate highly with the original categorical score of zero to three(Barca et al., 2010).

Other tests of cognition at follow up were the MMSE(Folstein et al., 1975), clock drawing test(Shulman, 2000), and the IQCODE. At the four months control we used a modified version of the IQCODE where the relatives were asked for changes since just before the fracture. At the 12 months control we used the regular version of IQCODE.

One specialist in geriatric medicine (Professor Torgeir Wyller) and one specialist in old age psychiatry (Professor Knut Engedal) assessed whether the patients fulfilled the ICD-10 criteria for dementia at baseline and 12 months after surgery. The assessors had access to all clinical data, but were blinded to allocation and to delirium status during hospital stay. They first classified all patients independently. The inter-rater agreement upon the dementia diagnosis was satisfactory (kappa 0.87 at baseline and 0.83 at 12 months). Cases with disagreement were discussed until a consensus was reached.

ADL-functions: Proxies were interviewed regarding pre-fracture activities in daily living function (Barthel ADL Index (BADL)(Wade, 1992) and Nottingham Extended ADL Index (NEADL)(Gladman et al., 1993). The proxies were asked to describe the condition of the patients 14 days prior to the fracture in order to tap the function in a stable clinical phase. Proxies were also interviewed the follow up controls, using the same scoring systems as during hospital stay.

Physical function: Hand Grip Strength was examined by hand dynamometry (Jamar, Germany, three repetitions per examination) daily throughout the duration of the hospital stay and at the follow up controls. The Short Physical Performance Battery (SPPB)(Guralnik et al., 2000) was used to assess mobility at follow up controls. SPPB consists of three parts: a test of balance, a test of walking speed, and a test of the ability to rise from a chair. The maximum score is 12 points, and a difference of 0.5 is considered clinically meaningful.

Table 8. Overview of assessments and timing of assessments in the different patient samples

		Index stay				Follow up controls			
Domain	Test/variable	S1	S2	S3	S4	S1	S2	S3	S4
Cognition	IQCODE	•	•	•	•	•	•		
	CDR	•				•			
	MMSE		•	•	•	•	•	•	•
	Clock drawing test		•		•	•	•		•
	CERAD 10 word test				•	•	•		•
	Kendrick OLT				•				•
	Trailmaking A and B				•				•
Delirium	CAM	•	•	•	•	•		•	
	MDAS	•	•						
	DRS-98			•				•	
	Edinburgh Delirium Test Box 1			•				•	
ADL function	BADL	•	•			•	•		
	Katz			•				•	
	Lawton			•	•			•	
	NEADL	•	•			•	•		
Depression	Cornell	•			•	•			
	Geriatric Depression Scale							•	
	MADRS				•				
Clinical data	ASA	•	•	•	•				
	APACHE II	•	•	•					
	ECG	•	•	•					
	Weight, height	•	•			•			•
	CCI	•	•	•	•				
	Medication	•	•	•	•	•	•	•	•
	Surgical and anesthesiological procedures	•	•	•	•				
Physical function	SPPB					•			
	Active PAL	•							
	Hand-dynamometry	•	•		•	•			
Biological material	CSF	•		•	•				
	Blood	•	•	•	•	•		•	

Sample 1 (S1): Watne. Followed up after 4 and 12 months
Sample 2 (S2): Juliebo/Krogseth. Followed up after 6 months
Sample 3 (S3): Hall. Followed up after 1,6 and 12 months. In addition to MMSE were several other cognitive tests included at the follow up controls.
Sample 4 (S4): Idland. Followed up after 1,2,3,4 and 5 years

3.2.2 **Timing of assessments**

During the hospital stay, all patients in the RCT were assessed daily (weekdays) preoperatively and until the fifth postoperative day. Patients with delirium were followed daily until resolution of delirium or discharge from the hospital.

Follow up visits in the RCT were carried out by research nurses four and twelve months after surgery (with a time window of ± three weeks). The patients were most often assessed where they were living, but a few preferred to be assessed at our out patient clinic at the hospital. A

follow-up control typically lasted between two and three hours, and the evaluators started the assessment with the cognitive tests of the primary endpoint.

At each follow-up, proxies were interviewed regarding ADL- and cognitive function. Patients and proxies were asked for re-admissions since surgery.

See table 8 for timing of assessments in sample 2 - 4.

3.2.3 **Blinding of evaluators in the RCT**

The follow up visits were done by research nurses blinded to allocation and to all clinical data during hospital stay. The research nurses registered cases in which they had become unblinded, for instance because patients or relatives disclosed the allocation. This happened in 5-10% of the cases.

Data collection during hospital stay could not be done blinded, since the patients were assessed in the ward they were allocated to.

3.3 Collection and handling of biological samples. Laboratory procedures

Blood from patients included in the RCT was collected pre- and postoperatively and at four and 12 months after surgery. Serum, plasma, EDTA and Pax Gene (only post operatively) were collected. After sampling, the serum tubules were left in the vertical position for 30 minutes at room temperature for clotting, before they were centrifuged. Plasma was centrifuged immediately. Aliquots of 500 microliters were then stored at -80 degrees C in polypropylene tubes. CSF was collected at the onset of spinal anesthesia before administration of the anesthetic agent. Up to 4 ml was collected in polypropylene tubes. The CSF was centrifuged within four hours and the supernatant was stored in aliquots of 100 – 1000 microliters at – 80 degrees C.

Similar procedures were used for collection and handling of CSF and blood also in sample 3 and sample 4.

3.3.1 **Anticholinergic activity (AA)**

AA in serum and CSF was determined by a modified version of the muscarinic radio receptor bioassay developed by Tune and Coyle (Tune and Coyle, 1980, Jakobsen et al., 2011). Samples of 20 microliters were applied in 96 well plates for high throughput analysis of AA. Atropine was used as a reference, and AA was reported in atropine equivalents (pmol/mL). Samples from Edinburgh were transported to Oslo on dry ice. All serum and CSF samples from Oslo and Edinburgh were analyzed at the University of Oslo using the same assay by the same method operator (blinded to all clinical data) within one laboratory sequence. The validation parameters of the bioassay showed good reproducibility with coefficients of variation less than 30 % for the estimated binding/displacement constants of repeated atropine calibration curves.

3.3.2 **Measurement of neopterin**

For measurement of neopterin were samples of serum and CSF from Oslo and Edinburgh sent to Dr Durk Fekkes at Erasmus MC, Rotterdam, The Netherlands. The samples were transported frozen on dry ice. Neopterin in serum and CSF were measured with high performance liquid chromatography with acid oxidation. Neopterin and dihydroneopterin were measured together as described earlier(Van Gool et al., 2003). The analyses were done blinded to all clinical data.

3.4 Inclusion and randomization in the RCT

Patients enrolled in the RCT (sample 1) were included and randomized by the orthopedic surgeon on call in the emergency room at Oslo University Hospital - Ullevaal. All patients with a hip fracture (a femoral neck fracture, a trochanteric or a sub-trochanteric fracture) were eligible for inclusion. Patients from nursing homes and patients with dementia could also be included as we believed that an orthogeriatric intervention could be of particular importance to the frailest patients. Patients were excluded if the hip fracture was a part of a high energy trauma (defined as a fall from higher than one meter) or if they were moribund at admittance. There was no exclusion criteria related to age. We believed that most of the younger hip fracture patients (below 70 years) would have suffered a high energy trauma, and thus were excluded. The small number of patients of this age that suffer a hip fracture from a low energy trauma can be expected to be frail and could thus potentially benefit from an orthogeriatric service.

The randomization was based on computer-generated random numbers, and carried out by a statistician (ES) without any contact with the patients or the personnel involved in the inclusion. We used block randomization (blocks of variable and unknown size) to ensure an equal group size. The randomization was stratified with respect to whether or not the patient was admitted from a nursing home, in order to get the groups balanced regarding pre-fracture frailty and cognitive decline. The allocation of each patient (orthogeriatric or orthopedic care) was by sealed, opaque, numbered envelopes that were held in the Emergency Department (different colors for the two stratification groups). Consent and inclusion procedures were carried out by the orthopedic surgeons on call in the emergency room.

In order to enhance the awareness of the study in the ER, the study physician on several occasions taught the personal in the ER about delirium, and gave updates regarding inclusion rates in the trial. The same was done for the orthopedic surgeons. The study physician hold track of which surgeon that included which patients, and at regular intervals prizes were given to the surgeon that had included most patients. Similar rewards were given to the anesthesiologists who collected CSF samples. The study physician or study nurse checked everyday that the envelope with the lowest number was taken. At 13 occasions occurred an

error which a randomization envelope was opened, but the patient was nevertheless not included.

The reasons were as follows:
• Included in the study before (previous fracture) - 6
• Randomized in a period where the geriatric ward was closed due to outbreak of gastroenteritis - 3
• Wrong diagnosis (patient had no hip fracture) - 2
• Patient sent to another hospital from the ER - 1
• Initially opened envelope from the wrong stratum (stratified whether or not the patients lived in nursing homes), error discovered immediately and new envelope opened - 1.

These patients were not included (except for the first six who already had been included earlier and the last one who was included based on the secondly drawn envelope), no data was registered from these hospital stays, and they were not further analyzed. Thus, 13 more envelopes were opened than the number of included patients. That 13 errors occurred during the inclusion period, must been interpreted in the light of an inclusion period of more than two years with a 24/7 inclusion procedure and a high number of surgeons involved.

3.5 Intervention in the RCT

The intervention for the patients randomized to the acute geriatric ward included medication reviews, early and intensive mobilization, optimizing pre- and postoperative nutrition and early discharge planning. A key element of the intervention was a Comprehensive Geriatric Assessment (CGA) as a basis for the planning of treatment. All team members (geriatrician, nurse, physiotherapist and occupational therapist) were expected to assess patients during their first day on the ward, and the team had daily meetings to co-ordinate treatment and to plan discharge. Clinical routines were developed based on literature search, experience from earlier orthogeriatric models and the pilot phase prior to start of randomization. Checklists were printed out and made immediately available for the treatment team for each patient.

Details about the intervention are described in a separate publication(Wyller et al., 2012).

3.6 Statistics

All statistical analyses were performed using IBM SPSS Statistics version 18 - 20, except for median differences and corresponding 95% confidence intervals in the RCT (paper II) that were estimated by the Hodges Lehmann estimator using StatXact 8.0.

3.6.1 Comparing groups (paper I-IV)

Categorical variables were analysed by Chi-square test. Continues variables were analysed by Mann-Whitney tests and t-tests depending on data distribution.

3.6.2 Linear regression (paper I and II)

Linear regression explores the effect of different independent variables on one continuous outcome variable. In paper I was linear regression used to assess what variables could predict the modified IQCODE score at follow up. Since the outcome had to be interpreted in the light of pre-fracture IQCODE score, we adjusted for pre-fracture IQCODE score in the analysis. The inclusion of other covariates was based on a p-value < 0.1 in univariate analyses.

Regarding the trajectories of the MMSE, we set the date of follow-up as time zero, and counted the time backwards to the points of the pre-fracture MMSE tests. We used a linear regression analysis to calculate the slope of each patient's change in the MMSE scores over time. The regression coefficient of these analyses represents change in the MMSE by time measured in years. These slopes were not normally distributed, and a Mann-Whitney test was used to calculate whether the regression coefficients differed between the patients with and without delirium.

In paper II was it already in the protocol (Wyller et al., 2012)and the SAP(Wyller et al.) established that we should perform a linear regression to adjust for any inequality in the distribution of important prognostic variables between the intervention and control group. Regardless of the effect of the intervention it would be clinically relevant to perform such an analysis in order to explore what variables could predict cognitive performance at the follow-up controls.

Although data was not presented in the paper, linear regression was also used in paper III to assess the effect of center on serum AA (see section 6.3.1 for details).

3.6.3 Logistic regression (paper III and IV)

Logistic regression is useful to explore the effect of different prognostic variables when the outcome variable of interest is categorical, most often binary. In clinical research this is often presence or absence of a condition, i.e. mortality, cancer or delirium(Altman, 1991).

In paper III, logistic regression was used to assess the relationship between AA and delirium when adjusting for other covariates. We performed two separate logistic analyses, one with serum AA and one with CSF AA as covariates, and both using 'delirium any time' as the outcome variable (only the table for CSF AA is shown in the paper). The analyses were performed on pooled data with samples both from Oslo and Edinburgh. The inclusion of other covariates was based on a p-value < 0.1 in univariate analyses. CSF AA and center were forced into the final model.

A similar strategy was used in paper IV to assess the relationship between delirium and neopterin in serum and CSF. The inclusion of other covariates was based on a p-value < 0.1 in univariate analyses. All analyses were on pooled data from both centers. There was a near linear relationship between delirium and neopterin levels in serum. For CSF neopterin levels there was a "cutoff" at the 75th percentile with a steep rise in delirium rates above this "threshold". In the logistic regression analysis, serum neopterin was therefore used as a continuous variable, whereas CSF neopterin was dichotomized at the 75th percentile.

3.6.4 Construction of the composite endpoint in the RCT

The primary outcome was cognitive function four months after surgery, and we expected that included patients would perform within a wide range; from severe dementia to no signs of cognitive impairment. To be able to measure differences in both the higher and the lower spectrum of cognitive function, we combined two scales: The 10 words test from CERAD and the CDR. To construct a combined endpoint, we normalized these scales into a 0 - 100 scoring (CDR had to be reversed since it is scaled in the opposite direction). CDR weighed 50 % and the immediate and delayed recall parts of the 10 word test weighed 25 % each in the

combined measure. Thus, higher score on the primary endpoint means better cognitive performance.

3.6.5 **Statistical analysis plan (SAP) and blinding of analyses in the RCT**

A statistical analysis plan was developed (and published online) prior to un-blinding of the data(Wyller et al.). Pre-planned subgroup analyses were done for patients admitted from nursing homes or not, and patients with and without pre-fracture dementia. The primary analysis was carried out by a statistician (ES) blind to allocation.

3.7 **Ethical considerations**

The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from the patients or substitute decision-makers if patients did not have capacity to consent. The study was approved by the Regional Committee for Ethics in Medical Research in Norway (REK S-09169a) and the Data Protection Officer at Oslo University Hospital (Ref. 1361).

Inclusion in the RCT was not considered to have any substantial harmful effects. Most patients and their relatives were positive for an opportunity of an admission to the acute geriatric ward. Those patients that refused to participate in the study were younger those included (median 81 versus 85 years; $P \leq 0.001$). Several of those who refused explained that they felt much too vigorous to fit in a geriatric ward and considered it an unattractive scenario to be admitted there.

Cognitively intact patients were included on the basis of written, informed consent. We developed a full information leaflet for cognitively intact patients and a simplified and shortened one for patients with somewhat reduced competence. When the latter version was used, a close relative received the full version of the patient information. Those who were totally unable to give a valid informed consent were included on the basis of assent from the nearest relative. Since the relatives often were difficult to reach while the patients were in the ER, some patients could not be included in the trial. After some weeks, we therefore were

allowed by REK to also include such patients in the ER, and obtain assent from the relatives afterwards.

A high proportion of hip fracture patients is either demented or delirious (or both) on admittance. These groups are presumed to be more vulnerable to the quality of hospital care than those cognitively intact, and thus important to include in studies of this kind.

4 Main results

Of 466 eligible patients admitted to Oslo University Hospital - Ullevaal between September 2009 and January 2012, were 329 included in the RCT (see figure 4 for a flowchart of patients). Non-included patients were younger than included patients (median 81 v 85 years; $p \leq 0.001$) and more of them were men (35.3 % v 25.1 %, p=0.01). Half of the included patients were considered to have dementia, and one third was living in nursing homes. Patients randomized to the intervention group and the control group were well matched in all important baseline variables. In total 35 patients (11 %) were lost to the follow up control after four months (and thus the primary endpoint in the RCT), 14 from the intervention group and 21 from the control group (p=0.23). Of patients lost to the four months follow up control, only 2 (7 %) were living in a nursing home before the fracture, compared to 73 (30 %) of patients tested (p=0.002). Patients lost to follow up were younger (median age 83 v 85; p=0.19) and fewer were considered having dementia before the fracture (12/35 (34%) v 112/242 (46%), p=0.18), these differences were, however, not significant. The last twelve months follow up control was done in December 2012.

4.1 Delirium superimposed on dementia (paper I)

Results: 201 of the 287 patients developed delirium in the acute phase. Using linear regression, delirium was a significant predictor of a more prominent cognitive decline at follow-up measured by the IQCODE-SF questionnaire (p=0.002). Among patients having a pre-fracture MMSE score, the patients developing delirium had a median (IQR) yearly decline on the MMSE of 2.4 points (1.1-3.9), compared to 1.0 points (0-1.9) in the group without delirium (p=0.001, Mann-Whitney test).

Conclusions: Hip fracture patients with pre-fracture dementia run a high risk of developing delirium. Delirium superimposed on dementia is a significant predictor of further cognitive decline measured by the IQCODE-SF questionnaire, as well as by the MMSE in a subgroup of our patients.

4.2 The effect of orthogeriatrics on cognitive function (paper II)

Results: 329 patients were included. There was no significant difference in cognitive function four months after surgery between patients treated in the acute geriatric and the orthopaedic ward (mean 54.7 v 52.9, 95 % confidence interval for the difference -5.9 to 9.5; p=0.65). There was also no significant difference in delirium rates (49 % v 53 %, p=0.51) or four month mortality (17 % v 15 %, p=0.50) between the intervention and the control group. In a pre-planned sub-group analysis, participants living in their own home at baseline who were randomised to orthogeriatric care had better mobility four months after surgery compared with patients randomised to the orthopaedic ward, measured with SPPB (median 6 v 4, 95 % confidence interval for the median difference 0 to 2; p=0.04).

Conclusion: Pre- and postoperative orthogeriatric care given in an acute geriatric ward was not effective in reducing delirium or long-term cognitive impairment in patients with hip fracture. The intervention had, however, a positive effect on mobility in patients not admitted from nursing homes.

4.3 Delirium pathophysiology (paper III, paper IV)

Paper III: Anticholinergic activity in CSF and serum in hip fracture patients with and without delirium

Results: Fifty-two (54 %) of the patients in Oslo and 20 (39 %) of the patients in Edinburgh developed delirium. There was no statistically significant difference in AA between patients with and without delirium in Oslo (serum: 7.02 vs 6.08 pmol/mL, p=0.54, CSF: 0.39 vs 0.48 pmol/mL, p=0.26) or in Edinburgh (serum: 1.35 vs 1.62 pmol/mL, p=0.76, CSF: 0.36 vs 0.31 pmol/mL, p=0.93). Neither was there any difference in SAA (Oslo p=0.74, Edinburgh p=0.51) nor in CSF AA (Oslo p=0.21, Edinburgh p=0.93) when patients were subdivided into prevalent, incident, subsyndromal and never delirium. Stratifying the patients according to pre-fracture cognitive status (IQCODE) gave the same results.
Conclusion: This is the first study of AA in CSF of people with and without delirium. The study does not support the hypothesis that central (CSF) or peripheral (serum) AA is an important mechanism of delirium in hip fracture patients.

Paper IV: Cerebrospinal fluid levels of neopterin are elevated in delirium after hip fracture. A role for cellular immunity or oxidative stress?

Results: Sixty-four (46%) of 139 hip fracture patients developed delirium during the peri-operative period. Neopterin levels were higher in the delirium group in both serum (median (IQR) 37.0 (26.2 – 51.1) nmol/mL vs 27.1(22.6 – 40.7) nmol/mL, p=0.003) and in CSF (median (IQR) 29.6 (22.3 – 40.4) nmol/mL vs 24.7 (19.4 – 30.6) nmol/mL, p=0.003, with highest levels in those about to develop delirium in the post-operative period. CSF neopterin remained significantly associated with delirium after controlling for other risk factors using logistic regression analysis. Those with higher neopterin levels were more likely to have a poorer outcome (death or new institutionalization) at one year (CSF: median (IQR) 29.2 (22.8 – 39.6) nmol/L v 24.9 (19.4 – 33.2) nmol/L, p=0.02; serum: median (IQR) 37.9 (26.8 – 54.4) nmol/L v 29.2 (23.1 – 41.7) nmol/L, p=0.03).

Conclusions: This study is the first to examine neopterin in CSF in delirium, and our findings suggest potential roles for activation of cell-mediated immune responses or oxidative stress in the delirium process. High levels may also be useful in predicting poor outcomes. These findings need to be expanded by examining other components of these pathological pathways, and examination in other patient groups.

5 Discussion

5.1 Effect of delirium on cognitive trajectories (paper I)

This study included only patients with pre-fracture cognitive impairment (IQCODE ≥ 3.44). Our findings are in support of a theory that delirium is an independent risk factor for acceleration of cognitive decline in patients with already established cognitive impairment.

Only a few studies have explored the long term cognitive effects of delirium superimposed on dementia (Gross et al., 2012, Fong et al., 2009, Davis et al., 2012), and like in our study they report an acceleration of the cognitive decline. The delirium diagnosis in the earlier studies was, however, based on chart reviews only, a method that is reported to have low sensitivity(Saczynski et al., 2014). Our study is the first where the delirium diagnosis is based on daily evaluations of the patients with validated bed side instruments.

In contrast to earlier studies in this field, a major methodological weakness with our study is the lack of a documented dementia diagnosis before the delirious episode. The use of IQCODE is, however, supported by validations studies(Jorm, 2004), and is commonly used as a measure of cognitive impairment in delirium studies. Our use of a modified IQCODE at the follow up controls, where the care-givers were asked for cognitive changes after the fracture instead of after 10 years, has not been validated and can indeed be criticized.

In order to explore the true effect of delirium on long term cognitive trajectories, one have to design a prospective longitudinal study that combines a pre-delirium objective measure of cognition, repeated bedside delirium assessments and objective cognitive testing several months after the delirious episode has ended. This is an extremely demanding design, and such a study has not been conducted yet. Since hip fracture is an acute event, an objective measure of prefracture cognitive status is hard to obtain. Our strategy to overcome this problem was to include MMSE scores documented in patient charts before the fracture. Patients with delirium had a more rapid decline in MMSE scores from pre fracture to those collected at the follow up controls.

Taken together, we believe that our approach gives some new information regarding cognitive prognosis after delirium. Both strategies gave the same result, and this support our conclusion

that delirium has a negative impact on long term cognition also in patients with established cognitive impairment.

5.2 Orthogeriatrics (paper II)

We found no evidence that cognitive function four months after surgery was improved in patients treated pre- and postoperatively in an acute geriatric ward, compared to usual care in an orthopaedic ward. There was, however, a trend that the intervention had a positive effect on mobility on patients not admitted from nursing homes.

5.2.1 Why so limited effect of our model?

Despite the comprehensive intervention, the effect on the primary endpoint was limited. There are several possible explanations for this. First, the choice of endpoint might have been too audacious. For the intervention to be effective in this regard, two presuppositions had to be true. First, the primary outcome assumes that delirium lies on the causal pathway towards the development of dementia. The major criticism against studies that implies that delirium has a negative impact on cognitive trajectories, is that delirium is only unmasking dementia and is not causing it. If this is true, one could not expect delirium prevention to have any effect on long term outcomes. As described earlier, a growing amount of evidence suggests that delirium can lead to dementia, but since delirium occurs in relation to acute illness it is difficult to design good prospective studies to address this very important question.

The second presupposition was that the orthogeriatric intervention had to be effective in delirium prevention. Other studies have shown that geriatric intervention is effective in reducing delirium in hip fracture patients, also when the intervention is limited to a liaison service (Marcantonio et al., 2001) and an Inpatient Geriatric Consultant Team(Deschodt et al., 2012). Since the limited geriatric intervention given in these studies was effective in reducing delirium, one should expect that continuously pre- and postoperative geriatric care, as provided in our model, should be even more effective. Our intervention failed, however, to prevent delirium or reduce delirium severity. This was surprising and can in part be explained by the good quality of usual care in our study. Compared to other models reported in the literature, waiting time for surgery was short in our study. Introduction of an orthogeriatric service is usually reported to reduce waiting time for surgery, but in our study it was two

hours longer for the patients in the acute geriatric ward. This difference was not statistically significant, but could nevertheless have had a negative impact for patients allocated to intervention since waiting time for surgery is known to have a sincere negative impact on outcomes in hip fracture patients(Pioli et al., 2012b).

The personnel in the orthopaedic ward had also experience from earlier orthogeriatric models and was familiar with usual strategies for delirium prevention (use of single rooms, adequate management of pain, orientation etc.). In order to obtain a precise delirium diagnosis was the personnel at the orthopaedic ward daily interviewed regarding cognitive changes of the patients, and this inevitably raised the awareness of delirium in the orthopaedic ward.

But most importantly were several factors with the orthogeriatric model not optimal. The ward was often over-crowded. During the inclusion period was on average 101 % of the beds occupied. This means that usually there were more patients in the ward than it had capacity to serve so patients had to be treated in the corridor. In order to avoid randomization violations, was the ward was instructed (and managed!) to admit all randomized hip fracture patients. Since patients tend to come in clusters, there were times when several patients had to be treated in the corridor, and the work load was too large to handle and it inevitably influenced quality of care. The orthopaedic ward was equally staffed as the acute geriatric ward and had a 90 % bed occupancy during the project period. The orthopaedic patients are in general less demanding than a geriatric patient.

The hip fracture patients included in the trial was the only surgical patients in the acute geriatric ward, and some of the personnel never got used to handle orthopaedic patients. Especially were many nervous to mobilize the patients postoperatively. Before the inclusion started we had a pilot phase of 14 months, and this was probably too short for implementation of procedures. The fact that the hip fracture patients often represented extra work load and was an unfamiliar patient category impacted negatively on the enthusiasm regarding the project. The hip fracture patients are demanding patients, and one should not underestimate the importance of a factor as enthusiasm.

Despite the lack of effect on the primary endpoint, and the weaknesses with our orthogeriatric model, it is important to point out that the intervention had a positive effect on mobilisation, the most important secondary endpoint in our trial. A difference on SPPB of 0.5 is considered clinically meaningful, and the effect seen in our study (6 *v* 4 points) is likely to be important

and should be further explored in future studies. Data from the subgroup of patients that had mobilization recorded with the activPAL™ body-worn sensor system, indicated that patients in the acute geriatric ward, received a more intensive mobilization compared to patients in the orthopedic ward.

5.2.2 What is the optimal orthogeriatric model?

An integrated model (Kammerlander model 4) is considered the best orthogeriatric model. This is the conclusion in all four reviews on orthogeriatric care, and from a clinical point of view it is logical that this must be the superior model. When hip fracture patients are treated in an integrated ward, one can recruit personnel that are interested in such patients, and it will be easier to implement routines. With daily co-management between orthopedic surgeons and geriatrician planning of surgery and medical optimization is easier and the problem with disintegration of responsibility would be avoided.

A model of integrated care has however never been evaluated in a RCT, and it unlikely that it ever will. In order to design such a study one would need to keep two separate wards for treatment of hip fracture patients. To implement an integrated ward demand a joint effort from orthopedic surgeons and geriatricians, and not least must administrative and financial issues be solved. In order to succeed with such a demanding process there are professional and administrative arguments not to keep two parallel treatment paths, but instead focus all the recourses to build up an integrated ward.

5.3 Delirium pathophysiology (paper III and IV)

5.3.1 Anticholinergic activity

Several studies have reported an increased anticholinergic activity in patients with delirium. Theoretically this makes perfect sense; acetylcholine is a neurotransmitter involved in many of the processes that are impaired in delirium (attention, arousal, learning) and cholinergic deficiency is among the major theories in delirium pathophysiology. Anticholinergic activity in CSF had however never been measured in delirious patients before our study.

We did not find that CSF or serum AA was associated with delirium. AA in serum in hip fracture patients has only been measured in one other study in addition to ours, and like ours they found no difference in AA between patients with and without delirium(van Munster et al., 2012). AA therefore seems to be less important in the pathogenesis of delirium in hip fracture patients, compared to other patient groups. A possible explanation for this is that the hip fracture patients are a particular frail patient group with a high degree of chronic cognitive impairment. In our study CSF AA was associated with severity of delirium in those patients without chronic cognitive impairment, suggesting that AA might be of some importance in patients free from dementia.

Unexplained differences in serum AA between Edinburgh and Oslo

There was no difference in the median CSF AA between Oslo and Edinburgh (0.43 vs 0.35 pmol/mL p=0.29). However there was a significant difference in median SAA between the two hospitals with levels in Oslo more than four times higher than in Edinburgh (6.37 vs 1.48 pmol/mL p<0.001). Center remained a significant predictor of SAA levels after adjusting for IQCODE, delirium status and ACB in a linear regression model with SAA as outcome.

We carefully reviewed the possible sources for the discrepancies between the serum AA values for Edinburgh vs. Oslo. The serum AA analyses from the two centeres were carried out within one laboratory sequence (same run), making potential issues associated to the assay unlikely. As the sampling procedures were merely the same at the two centeres, including type of containers, it is also difficult to point on potential reasons for the discrepancies associated to sample collection or handling. The correlation between AA in serum and CSF was stronger in samples collected in Oslo compared to those collected in Edinburgh (Spearman's Rho 0.62, p<0.001 vs Spearman's Rho 0.26, p=0.07). Other studies have also reported a strong correlation between AA in serum and CSF(Miller et al., 1988, Plaschke et al., 2007, Plaschke et al., 2010), and the weak correlation seen in the samples from Edinburgh could suggest that the serum AA in those samples was falsely low. This could theoretically have been explained with increased adsorption of anticholinergic agents (drugs and metabolites) to the inner 'dry' surface of the containers. This is however also unlikely since CSF and serum was transported to Oslo in identical containers. There have also not been any systematic differences between levels measured in serum and Oslo in other analyses performed (CRP, cytokines, neopterin). Although we can not rule out the possibility that

patients from Edinburgh actually display lower serum AA values than those from Oslo, we suspect that something related to the sample logistic caused lower SAA levels in the serum samples from Edinburgh.

Challenges in the measurements of anticholinergic drug burden

Since medications with anticholinergic properties are associated with a high risk of adverse effects in elderly patients (Lam and Cheung, 2012), tools have been developed to calculate the anticholinergic drug burden. Several scales exist where different medications are ranked based on their anticholinergic activity. The anticholinergic burden is estimated by calculating the total anticholinergic score of all the medications a patient use(Boustani et al., 2008, Rudolph Jl, 2008, Carnahan et al., 2006). By using such anticholinergic scales several researchers have found an association with high anticholinergic burden and adverse outcomes, including an association with delirium and dementia (for an overview, see(Campbell et al., 2009, Kersten and Wyller, 2014).

There has however been critique against such scales(Kersten and Wyller, 2014, Duran et al., 2013). Firstly there is a wide heterogeneity among the scales with different estimates of the anticholinergic potency of the same drug. This makes it difficult to compare studies that use different scales. There is also a lack of adjustment for dose, drug-drug interactions and age of the patients. It has been argued that this simplification of complex pharmacological mechanisms is particularly problematic in a geriatric patient, since biological variation increases with age(Kersten and Wyller, 2014). There have also been difficult to show that a reduction in anticholinergic burden leads to improved clinical outcomes for the patients. In a recently published RCT including nursing home patients was the intervention effective in reducing the anticholinergic burden (measured with the Anticholinergic Drug Scale (ADS), but this had no significant effect on cognitive performance (Kersten et al., 2013).

In 1980, Tune and Coyle developed a bioassay making it possible to quantify the anticholinergic activity (AA) in vitro in biological samples (Tune and Coyle, 1980). The assay technique measures the AA of compounds present in the biological samples by the degree of displacement of a radioactively labeled ligand (^{3}H-QNB) from muscarinic receptors rat brain receptors. High AA in the biological samples is proportional with a high degree of displacement and low radioactive counts per minute (CCPM) from the undisplaced radioligand. Atropine is used as a reference compound and the AA in a biological sample is

given as “atropine equivalents”. The in vitro AA of many drugs have been measured using this bioassay technique (Chew et al., 2008) and there have also been several reports of an association between high serum AA and dementia and delirium(Campbell et al., 2009, Carnahan et al., 2002, Kersten and Wyller, 2014).

There has been some criticism against this assay(Carnahan et al., 2002, Kersten and Wyller, 2014). The assay quantify the total degree of muscarinic receptor displacement of different compounds in the sample solution, but do not distinguish between agonists and antagonists, or between receptor affinity for different muscarinic receptor subtypes. It is also important to understand that not only drugs that are considered to have anticholinergic properties can cause an elevated AA(Chew et al., 2008), and there are also reports of poor correlation between serum AA and anticholinergic burden calculated from the medications patients used(Lampela et al., 2013). Acute illness in itself has been associated with higher AA in serum (Flacker and Lipsitz, 1999). AA has most often been measured in serum, and this does not necessarily reflect anticholinergic burden in the brain which depends on the blood-brain permeability of the drug. There is also a huge difference in AA levels among studies, so a “cutoff” between “low” and “high” serum AA have not been possible to determine(Carnahan et al., 2002). In addition to all these weaknesses the assay is too demanding to perform to be introduced in daily clinical work.

5.3.2 **Neopterin**

Neopterin was elevated in both CSF and serum in hip fracture patients with delirium. These findings suggest potentially greater activation of the cellular immune response in delirium. It may also represent a role for oxidative stress in delirium, and this finding should be combined with other measures of antioxidant levels, enzymes involved in oxidative stress systems and reactive oxygen species.

The relative levels of neopterin demonstrated in delirium and dementia are intriguing, as the pattern is what you might expect to see in microglial priming, where patients with no underlying cognitive impairment and no delirium have the lowest levels, those with dementia who might be expected to have a degree of low level inflammation have slightly higher levels, those with delirium only have even higher levels, but those with delirium super-imposed on

dementia have the highest levels. It may be that both delirium and dementia processes activate these systems with a cumulative effect in those with both diagnoses.

Other factors that influence neopterin levels

Given the "dose-response" pattern seen in CSF from hip fracture patients, with an increase in neopterin with more severe cognitive impairment (as a combination of dementia and delirium), one could suspect that the cognitively healthy controls would have even lower levels. This was not the case, as neopterin in CSF from the healthy controls was as high as hip fracture patients with delirium (median 30.9 vs 29.6 nmol/L, p=0.73) and higher than hip fracture patients without delirium (median 24.7 nmol/L, p=0.003). One possible explanation for the surprisingly high neopterin levels is that 13 of the elective patients had either a history of cancer or an active infection and this group had higher levels of CSF neopterin compared to elective patients without cancer or infection (median 35.4 nmol/L v 27.7 nmol/L, p=0.06). When elective patients with cancer and/or infection were excluded, there were no significant differences in neopterin levels in CSF between the controls and the hip fracture patients, neither in those with (p=0.11) or without (p=0.47) delirium. A possibility is that while neopterin analysis for the hip fracture patients were done in one batch, the analyses for the healthy controls were done in a separate one.

The introduction of an additional control group is strength with this study, although the neopterin levels measured in the healthy controls did not "fit" perfectly in with the levels measured in the hip fracture patients. Firstly it demonstrated that it is not possible to use our data to define a "cutoff" of neopterin to identify patients of particular high risk of delirium in other studies. It also demonstrates some of the difficulties in delirium research. Many of the candidate biomarkers in delirium (such as neopterin), are also associated with other comorbidities. In studies on delirium pathophysiology it is therefor very important to define relevant control groups; e.g. to compare levels of biomarkers in delirious hip fracture patients with healthy age matched controls is probably of limited relevance.

On the other hand, as the variation in risk factors (co-morbidities, medication use, cognitive capacity) increases with age, it is challenging to recruit patients that are phenotypically equally matched in studies on delirium pathophysiology. As the current knowledge of delirium pathophysiology is so limited, compromises in study design must be accepted.

5.3.3 Hip fractures: The perfect setting for delirium pathophysiology research?

Several of the studies that exist on delirium pathophysiology have been performed in hip fracture patients(MacLullich et al., 2011, van Munster et al., 2012, Westhoff et al., 2013). There are several reasons for this. First is delirium extremely prevalent among hip fracture patients, affecting 40 - 50 % of the patients. In most of the patients delirium is triggered by the same exposure; the fracture and surgery. And at last there is the unique possibility to acquire CSF from those operated in spinal anesthesia.

There are however also some disadvantages with this model. A huge part of the hip fracture population has dementia already before the fracture. Since many of the candidate biomarkers in delirium also seems to play a role in dementia, it is difficult to sort out the effect of delirium. The fracture and surgery itself trigger the immune system in all patients, so one can measure pro-inflammatory compounds also in patients without delirium. There is also a possibility that delirium have different pathophysiologic entities depending on the precipitating factor. To study delirium pathophysiology in different patient groups is therefore of great value.

5.3.4 Challenges in delirium pathophysiology research

Although clearly a CNS phenomenon, most studies on delirium pathophysiology have been done by the use of serum samples. This demonstrates the ethical and practical difficulties in acquiring CSF from delirious patients. There is also a lack of animal models in delirium, and all published animal studies so far are from a single research group(Cunningham et al., 2005).

When reading studies about delirium pathophysiology, is it important to take into account the extreme complexity of the different biological systems. In most delirium studies, the biomarkers have only been measured once, and the patients included are often on different time course in their delirium development (there is often a mix of patients with prevalent, incident, subsyndromal and never delirium in studies). Since the explored biologic processes are dynamic, this mix of "delirium phenotypes" makes it very difficult to interpret the results. A longitudinal design with repeated delirium assessments and collection of biomarkers would be valuable, but it would be difficult to overcome practical and ethical challenges involved in repeated sampling of CSF.

5.4 Methodological considerations

5.4.1 Patient selection

RCT

The inclusion of nursing home patients in the RCT can be considered as strength as well as a weakness with the study. It improves the external validity of the study that nursing home patients and demented patients were included since they represent a major part of the hip fracture population and are at high risk of delirium. On the other hand, nursing home patients are so frail and cognitively impaired that they may be unlikely to benefit from the intervention. To assess the efficacy in such patients, other endpoints than we chose might be more feasible(Goldberg et al., 2013).

Pathophysiology

There were different exclusion and inclusion criteria in Oslo and Edinburgh, making the Oslo-cohort significantly frailer. It is difficult to rule out that there might also have been some differences in diagnostic judgment between the two centers. The assessment tools were, however, similar and thorough, and center was not a significant explanatory factor for delirium risk in the logistic regression analyses in any study.

5.4.2 Assessment methods

Measures of cognition

IQCODE has been criticized as a crude measure of cognitive function, since it is based upon proxy information. Because hip fracture is an acute event, ascertaining prefracture cognitive status is challenging. Many community-dwelling patients with dementia do not have a documented diagnosis(Wergeland et al., 2014). Thus, relying on past records alone would underestimate the prevalence of prefracture dementia. IQCODE has been validated(Jorm, 2004) and is often used in delirium studies(van Munster et al., 2012). Most patients in our study had relatives, friends or health care personnel that could inform IQCODE.

DRS conversion to MDAS

The delirium diagnosis both in Oslo and Edinburgh was both based on the CAM. The delirium severity was however measured by two different tools; MDAS in Oslo and DRS-98 in Edinburgh. A literature search did not provide any direct comparisons between the scales, or a clearly defined cut-off for severe delirium in either scale. Advice was sought from an expert in the field with considerable experience administering both scales (David Meagher), and MDAS was therefore rated retrospectively on patients in Edinburgh based on his advice. This was done by transforming scores from the Richmond Agitation Sedation Scale (RASS) (MDAS item 1) and the closest equivalent MMSE (MDAS items 2-4) and DRS-R98 (MDAS items 5-10) items, to produce equivalent MDAS items. This method has not been validated, and can be criticized.

5.4.3 Statistical considerations

Use of composite endpoint

Our combined endpoint was designed to measure cognition in patients representing a broad spectrum of cognitive functioning. It was based upon well validated components, but our specific way of combining them has not been validated and we can thus not be sure that the composite had the intended sensitivity or validity.

Inter-rater agreement

As explained in section 4.2.1, the inter-rater agreement for the CAM based diagnosis of delirium was calculated for LOW and each of the two study nurses, both showing kappa =1. This implies that there was 100 % agreement in the jugdement whether the patients had delirium or not. With a kappa = 1 it should be unnecessary for the study nurses to discuss patients where they were unsure about the delirium diagnosis, but during the inclusion period there were several occasions where it was difficult to decide whether the patients had delirium or not. The reason why the interrater agreement showed a kappa = 1 was presumably that we assessed too few patients together and also that in the assessed patients the diagnosis was quite obvious. In retrospect it is clear that the interrater agreement should have been assessed in more patients in order to obtain a more trustworthy estimate.

Missing values

Missing values for the primary endpoint in the RCT were imputed in different ways in order to explore their potential influence on the results:

- if a patient had the combined endpoint available after 12 but not four months, those values were imputed in the four months dataset (10 patients).
- imputation of the worst possible score for all patients that had died.
- imputation of the worst possible score for all missing patients.
- imputation of the mean score for the randomisation group the patient belonged to for all missing patients.

These analyses showed no substantial differences from the primary analysis.

6 Conclusions

Hip fracture is a serious event with dramatic short and long-term consequences for the patients. Delirium is common and is associated with poorer outcome.

- The orthogeriatric model in use at Oslo University Hospital - Ullevaal between June 2008 and January 2012 was not effective in preventing delirium or long-term cognitive decline.
- The intervention had a positive effect on mobility in patients not admitted from nursing homes.
- Delirium is a common complication, affecting half of the hip fracture patients.
- Chronic cognitive impairment is a strong risk factor for delirium.
- Delirium had a strong negative impact on cognitive function in the long-term.
- Anticholinergic activity in CSF and serum seems not to be an important mechanism in the development of delirium in hip fracture patients. In patients without pre-fracture cognitive impairment, increasing CSF AA might enhance delirium severity.
- Neopterin is elevated in CSF and serum in patients with delirium. This suggests activation of cell-mediated immune responses or oxidative stress in the delirium process.
- High levels of neopterin can predict poor outcome.
- The pathophysiologic mechanisms in delirium are different in patients with and without chronic cognitive impairment.

7 Suggestions for future research

This thesis has focused on orthogeriatrics and delirium; two topics that are receiving an increased interest from researchers. There are however several unanswered questions.

Orthogeriatrics

It is widely believed that to involve geriatricians in the care of elderly patients with fractures improves outcome. An orthogeriatric approach seems to be particular effective in treating hip fracture patients, and orthogeriatric care is already implemented in many countries. Several important questions remains however unanswered and future studies should aim at:

- Further explore how the orthogeriatric care is best organized. More RCTs should be carried out, particularly to evaluate the more integrated models (Kammerlander model 3 and 4).
- Long term outcomes of orthogeriatric care need to be further explored. Most of the studies so far have focused outcomes collected from registers (LOS, re-admissions, mortality). Future studies should aim to include face-to-face evaluation of patients with objective measures of function.
- As an increase in hip fractures can be expected in the future and it would be of great value if future studies could identify those hip fracture patients that benefit most on orthogeriatric care. A comprehensive orthogeriatric model is demanding, and with limited resources available, it is important to know how the resources are best prioritized.

Delirium

Despite an increase in studies on outcomes after delirium and pathophysiology, even the most basic questions remains mostly unanswered. Future studies should aim at:

- To get at more precise estimate of the impact delirium has on cognition in the long term, one should conduct several studies were different cohort of patients were closely monitored for delirium with repeated measures of cognitive function.

- Future studies on delirium prevention should also include objective cognitive testing at follow up controls.

- Large biobanks of CSF and serum should be established. Analysis should be done with methods with sufficient sensitivity.

- All the published animal studies on delirium so far come from one single research group. There is clearly a need for more models for delirium on different genetic backgrounds.

The existing studies on pathophysiology have most often used a simple delirium yes/no dichotomization. This is an oversimplification since 1) delirium in reality is not a binary phenomenon but represent a continuum and 2) because the patients show a wide heterogeneity in terms of predisposing and precipitating factors for delirium as well as in delirium symptomatology. Larger samples sizes are therefor needed in order to do be able to better phenotype patients and to do subgroup analyses. To succeed in this, international collaboration with exchange of samples is needed.

Many of the suggested studies are costly and demanding, but given the magnitude of the problem, it should be possible to write convincing applications to get funding.

8 References

Adamis, D., Sharma, N., Whelan, P. J. & Macdonald, A. J. 2010. Delirium scales: A review of current evidence. *Aging Ment Health,* 14**,** 543-55.

Adamis, D., Treloar, A., Martin, F. C., Gregson, N., Hamilton, G. & Macdonald, A. J. 2007. APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients. *Int J Geriatr Psychiatry,* 22**,** 688-94.

Adunsky, A., Arad, M., Levi, R., Blankstein, A., Zeilig, G. & Mizrachi, E. 2005. Five-year experience with the Sheba model of comprehensive orthogeriatric care for elderly hip fracture patients. *Disability and Rehabilitation.* Informa Allied Health.

Adunsky, A., Lerner-Geva, L., Blumstein, T., Boyko, V., Mizrahi, E. & Arad, M. 2011. Improved Survival of Hip Fracture Patients Treated Within a Comprehensive Geriatric Hip Fracture Unit, Compared With Standard of Care Treatment. *Journal of the American Medical Directors Association,* 12**,** 439-444.

Adunsky, A., Levi, R., Cecic, A., Arad, M., Noy, S. & Barell, V. 2002. The "Sheba" model of comprehensive orthogeriatric care for elderly hip fracture patients: a preliminary report. *Isr Med Assoc J,* 4**,** 259-61.

Adunsky, A., Lusky, A., Arad, M. & Heruti, R. J. 2003. A Comparative Study of Rehabilitation Outcomes of Elderly Hip Fracture Patients: The Advantage of a Comprehensive Orthogeriatric Approach. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences,* 58**,** M542-M547.

Altman, D. G. 1991. *Practical statistics for medical research,* London, Chapman & Hall.

Antonelli Incalzi, R., Gemma, A., Capparella, O., Bernabei, R., Sanguinetti, C. & Carbonin, P. U. 1993. Continuous geriatric care in orthopedic wards: a valuable alternative to orthogeriatric units. *Aging (Milano),* 5**,** 207-16.

Association, A. P. 2000. *Diagnostic and stastical manual of mental disorders DSM-IV-TR. 4th ed text revision. ,* Washington, DC.

Association, A. P. 2013. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* Washington, DC.

Association, T. B. O. 2007. *The Care of Patients with Fragility Fracture ("Blue Book")*

Barca, M. L., Engedal, K., Laks, J. & Selbaek, G. 2010. A 12 months follow-up study of depression among nursing-home patients in Norway. *J Affect Disord,* 120**,** 141-8.

Barone, A., Giusti, A., Pizzonia, M., Razzano, M., Palummeri, E. & Pioli, G. 2006. A comprehensive geriatric intervention reduces short- and long-term mortality in older people with hip fracture. *J Am Geriatr Soc,* 54**,** 711-2.

Bhattacharyya, R., Agrawal, Y., Elphick, H. & Blundell, C. 2013. A unique orthogeriatric model: a step forward in improving the quality of care for hip fracture patients. *Int J Surg,* 11**,** 1083-6.

Boustani, M., Campbell, N., Munger, S., Maidment, I. & Fox, C. 2008. Impact of anticholinergics on the aging brain: a review and practical application. *Aging Health,* 4**,** 311-320.

Boyd, R. V., Hawthorne, J., Wallace, W. A., Worlock, P. H. & Compton, E. H. 1983. The Nottingham orthogeriatric unit after 1000 admissions. *Injury,* 15**,** 193-196.

Brannstrom, B., Gustafson, Y., Norberg, A. & Winblad, B. 1989. Problems of basic nursing care in acutely confused and non-confused hip-fracture patients. *Scand J Caring Sci,* 3**,** 27-34.

Brannstrom, B., Gustafson, Y., Norberg, A. & Winblad, B. 1991. ADL performance and dependency on nursing care in patients with hip fractures and acute confusion in a task allocation care system. *Scand J Caring Sci,* 5**,** 3-11.

Breitbart, W., Rosenfeld, B., Roth, A., Smith, M. J., Cohen, K. & Passik, S. 1997. The Memorial Delirium Assessment Scale. *Journal of Pain & Symptom Management,* 13**,** 128-137.

Bruce, A. J., Ritchie, C. W., Blizard, R., Lai, R. & Raven, P. 2007. The incidence of delirium associated with orthopedic surgery: a meta-analytic review. *Int.Psychogeriatr.,* 19**,** 197-214.

Buecking, B., Timmesfeld, N., Riem, S., Bliemel, C., Hartwig, E., Friess, T., Liener, U., Ruchholtz, S. & Eschbach, D. 2013. Early orthogeriatric treatment of trauma in the elderly: a systematic review and metaanalysis. *Dtsch Arztebl Int,* 110**,** 255-62.

Burkhart, C. S., Dell-Kuster, S., Gamberini, M., Moeckli, A., Grapow, M., Filipovic, M., Seeberger, M. D., Monsch, A. U., Strebel, S. P. & Steiner, L. A. 2010. Modifiable and nonmodifiable risk factors for postoperative delirium after cardiac surgery with cardiopulmonary bypass. *J Cardiothorac Vasc Anesth,* 24**,** 555-9.

Campbell, N., Boustani, M., Limbil, T., Ott, C., Fox, C., Maidment, I., Schubert, C. C., Munger, S., Fick, D., Miller, D. & Gulati, R. 2009. The cognitive impact of anticholinergics: a clinical review. *Clin.Interv.Aging,* 4**,** 225-233.

Carnahan, R. M., Lund, B. C., Perry, P. J. & Pollock, B. G. 2002. A critical appraisal of the utility of the serum anticholinergic activity assay in research and clinical practice. *Psychopharmacol.Bull.,* 36**,** 24-39.

Carnahan, R. M., Lund, B. C., Perry, P. J., Pollock, B. G. & Culp, K. R. 2006. The Anticholinergic Drug Scale as a Measure of Drug-Related Anticholinergic Burden: Associations With Serum Anticholinergic Activity. *The Journal of Clinical Pharmacology,* 46**,** 1481-1486.

Cerejeira, J., Lagarto, L. & Mukaetova-Ladinska, E. B. 2014. The immunology of delirium. *Neuroimmunomodulation,* 21**,** 72-8.

Cerejeira, J., Nogueira, V., Lu+¡S, P., Vaz-Serra, A. & Mukaetova-Ladinska, E. B. 2012. The Cholinergic System and Inflammation: Common Pathways in Delirium Pathophysiology. *Journal of the American Geriatrics Society***,** n/a-n/a.

Charlson, M. E., Pompei, P., Ales, K. L. & Mackenzie, C. R. 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis,* 40**,** 373-83.

Chew, M. L., Mulsant, B. H., Pollock, B. G., Lehman, M. E., Greenspan, A., Mahmoud, R. A., Kirshner, M. A., Sorisio, D. A., Bies, R. R. & Gharabawi, G. 2008. Anticholinergic activity of 107 medications commonly used by older adults. *J Am Geriatr Soc,* 56**,** 1333-41.

Chumlea, W. C., Guo, S. S., Wholihan, K., Cockram, D., Kuczmarski, R. J. & Johnson, C. L. 1998. Stature prediction equations for elderly non-Hispanic white, non-Hispanic black, and Mexican-American persons developed from NHANES III data. *J Am Diet Assoc,* 98**,** 137-42.

Cogan, L., Martin, A. J., Kelly, L. A., Duggan, J., Hynes, D. & Power, D. 2010. An audit of hip fracture services in the Mater Hospital Dublin 2001 compared with 2006. *Ir.J Med Sci.,* 179**,** 51-55.

Cole, M. G., Dendukuri, N., Mccusker, J. & Han, L. 2003. An empirical study of different diagnostic criteria for delirium among elderly medical inpatients. *J Neuropsychiatry Clin Neurosci,* 15**,** 200-7.

Cunningham, C. 2013. Microglia and neurodegeneration: the role of systemic inflammation. *Glia,* 61**,** 71-90.

Cunningham, C. & Maclullich, A. M. J. 2012. At the extreme end of the psychoneuroimmunological spectrum: Delirium as a maladaptive sickness behaviour response. *Brain, Behavior, and Immunity*.

Cunningham, C., Wilcockson, D. C., Campion, S., Lunnon, K. & Perry, V. H. 2005. Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. *J Neurosci,* 25**,** 9275-84.

Danysz, W. & Parsons, C. G. 2012. Alzheimer's disease, beta-amyloid, glutamate, NMDA receptors and memantine--searching for the connections. *Br J Pharmacol,* 167**,** 324-52.

Davis, D. H. J., Terrera, G. M., Keage, H., Rahkonen, T., Oinas, M., Matthews, F. E., Cunningham, C., Polvikoski, T., Sulkava, R., Maclullich, A. M. J. & Brayne, C. 2012. Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study. *Brain,* 135**,** 2809-2816.

Davydow, D. S., Gifford, J. M., Desai, S. V., Needham, D. M. & Bienvenu, O. J. 2008. Posttraumatic stress disorder in general intensive care unit survivors: a systematic review. *Gen Hosp Psychiatry,* 30**,** 421-34.

De Jonghe, A., Van Munster, B. C., Fekkes, D., Van Oosten, H. E. & De Rooij, S. E. 2012. The Tryptophan Depletion Theory in Delirium: Not Confirmed in Elderly Hip Fracture Patients. *Psychosomatics,* 53**,** 236-243.

De Rooij, S. E., Van Munster, B. C. & De Jonghe, A. 2014. Melatonin Prophylaxis in Delirium: Panacea or Paradigm Shift? *JAMA Psychiatry*.

De Rooij, S. E., Van Munster, B. C., Korevaar, J. C. & Levi, M. 2007. Cytokines and acute phase response in delirium. *Journal of Psychosomatic Research,* 62**,** 521-525.

De Rui, M., Veronese, N., Manzato, E. & Sergi, G. 2012. Role of comprehensive geriatric assessment in the management of osteoporotic hip fracture in the elderly: an overview. *Disability and Rehabilitation.* Informa Allied Health.

Deschodt, M., Braes, T., Broos, P., Sermon, A., Boonen, S., Flamaing, J. & Milisen, K. 2011. Effect of an inpatient geriatric consultation team on functional outcome, mortality, institutionalization, and readmission rate in older adults with hip fracture: a controlled trial. *J Am Geriatr Soc,* 59**,** 1299-308.

Deschodt, M., Braes, T., Flamaing, J., Detroyer, E., Broos, P., Haentjens, P., Boonen, S. & Milisen, K. 2012. Preventing delirium in older adults with recent hip fracture through multidisciplinary geriatric consultation. *J Am Geriatr Soc,* 60**,** 733-9.

Devas, M. B. 1974. Geriatric orthopaedics. *Br Med J,* 1**,** 190-2.

Duran, C. E., Azermai, M. & Vander Stichele, R. H. 2013. Systematic review of anticholinergic risk scales in older adults. *Eur J Clin Pharmacol,* 69**,** 1485-96.

Dy, C. J., Dossous, P. M., Ton, Q. V., Hollenberg, J. P., Lorich, D. G. & Lane, J. M. 2012. The medical orthopaedic trauma service: an innovative multidisciplinary team model that decreases in-hospital complications in patients with hip fractures. *J Orthop.Trauma,* 26**,** 379-383.

Eikelenboom, P. & Hoogendijk, W. J. 1999. Do delirium and Alzheimer's dementia share specific pathogenetic mechanisms? *Dement Geriatr Cogn Disord,* 10**,** 319-24.

Ferrucci, L., Ble, A., Bandinelli, S., Lauretani, F., Suthers, K. & Guralnik, J. M. 2004. A flame burning within. *Aging Clin Exp Res,* 16**,** 240-3.

Fick, D. M., Agostini, J. V. & Inouye, S. K. 2002. Delirium Superimposed on Dementia: A Systematic Review. *Journal of the American Geriatrics Society,* 50**,** 1723-1732.

Fisher, A. A., Davis, M. W., Rubenach, S. E., Sivakumaran, S., Smith, P. N. & Budge, M. M. 2006. Outcomes for older patients with hip fractures: the impact of orthopedic and geriatric medicine cocare. *J Orthop.Trauma,* 20**,** 172-178.

Fitzgerald, J. M., Adamis, D., Trzepacz, P. T., O'regan, N., Timmons, S., Dunne, C. & Meagher, D. J. 2013. Delirium: a disturbance of circadian integrity? *Med Hypotheses,* 81**,** 568-76.

Flacker, J. M., Cummings, V., Mach, J. R., Jr., Bettin, K., Kiely, D. K. & Wei, J. 1998. The association of serum anticholinergic activity with delirium in elderly medical patients. *Am J Geriatr Psychiatry,* 6**,** 31-41.

Flacker, J. M. & Lipsitz, L. A. 1999. Serum anticholinergic activity changes with acute illness in elderly medical patients. *J Gerontol A Biol Sci Med Sci,* 54**,** M12-6.

Flacker, J. M. & Lipsitz, L. A. 2000. Large neutral amino acid changes and delirium in febrile elderly medical patients. *J Gerontol A Biol Sci Med Sci,* 55**,** B249-52; discussion B253-4.

Folstein, M. F., Folstein, S. E. & Mchugh, P. R. 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res,* 12**,** 189-98.

Fong, T. G., Jones, R. N., Marcantonio, E. R., Tommet, D., Gross, A. L., Habtemariam, D., Schmitt, E., Yap, L. & Inouye, S. K. 2012. Adverse outcomes after hospitalization and delirium in persons with Alzheimer disease. *Ann Intern Med,* 156**,** 848-56, w296.

Fong, T. G., Jones, R. N., Shi, P., Marcantonio, E. R., Yap, L., Rudolph, J. L., Yang, F. M., Kiely, D. K. & Inouye, S. K. 2009. Delirium accelerates cognitive decline in Alzheimer disease. *Neurology,* 72**,** 1570-1575.

Friedman Sm, M. D., Bingham Kw,Kates Sl 2009. IMpact of a comanaged geriatric fracture center on short-term hip fracture outcomes. *Archives of Internal Medicine,* 169**,** 1712-1717.

Friedman, S. M., Mendelson, D. A., Kates, S. L. & Mccann, R. M. 2008. Geriatric co-management of proximal femur fractures: total quality management and protocol-driven care result in better outcomes for a frail patient population. *Journal of the American Geriatrics Society,* 56**,** 1349-1356.

Gamberini, M., Bolliger, D., Lurati Buse, G. A., Burkhart, C. S., Grapow, M., Gagneux, A., Filipovic, M., Seeberger, M. D., Pargger, H., Siegemund, M., Carrel, T., Seiler, W. O., Berres, M., Strebel, S. P., Monsch, A. U. & Steiner, L. A. 2009. Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery--a randomized controlled trial. *Crit Care Med,* 37**,** 1762-8.

Gaudreau, J. D. & Gagnon, P. 2005. Psychotogenic drugs and delirium pathogenesis: the central role of the thalamus. *Med Hypotheses,* 64**,** 471-5.

Gilchrist, W. J., Newman, R. J., Hamblen, D. L. & Williams, B. O. 1988. Prospective randomised study of an orthopaedic geriatric inpatient service. *BMJ,* 297.

Ginsberg, G., Adunsky, A. & Rasooly, I. 2013. A cost-utility analysis of a comprehensive orthogeriatric care for hip fracture patients, compared with standard of care treatment. *Hip Int***,** 0.

Giusti, A., Barone, A., Razzano, M., Pizzonia, M. & Pioli, G. 2011. Optimal setting and care organization in the management of older adults with hip fracture. *Eur J Phys Rehabil Med,* 47**,** 281-96.

Gjertsen, J. E., Engesaeter, L. B., Furnes, O., Havelin, L. I., Steindal, K., Vinje, T. & Fevang, J. M. 2008. The Norwegian Hip Fracture Register: experiences after the first 2 years and 15,576 reported operations. *Acta Orthopaedica,* 79**,** 583-593.

Gladman, J. R., Lincoln, N. B. & Adams, S. A. 1993. Use of the extended ADL scale with stroke patients. *Age Ageing,* 22**,** 419-24.
Goldberg, S. E., Bradshaw, L. E., Kearney, F. C., Russell, C., Whittamore, K. H., Foster, P. E., Mamza, J., Gladman, J. R., Jones, R. G., Lewis, S. A., Porock, D. & Harwood, R. H. 2013. Care in specialist medical and mental health unit compared with standard care for older people with cognitive impairment admitted to general hospital: randomised controlled trial (NIHR TEAM trial). *Bmj,* 347**,** f4132.
Gonzalez-Montalvo, J. I., Alarcon, T., Mauleon, J. L., Gil-Garay, E., Gotor, P. & Martin-Vega, A. 2010. The orthogeriatric unit for acute patients: a new model of care that improves efficiency in the management of patients with hip fracture. *Hip Int,* 20**,** 229-35.
Grant, P. M., Ryan, C. G., Tigbe, W. W. & Granat, M. H. 2006. The validation of a novel activity monitor in the measurement of posture and motion during everyday activities. *Br J Sports Med,* 40**,** 992-7.
Gregersen, M., Morch, M. M., Hougaard, K. & Damsgaard, E. M. 2012. Geriatric intervention in elderly patients with hip fracture in an orthopedic ward. *J Inj.Violence Res.,* 4**,** 45-51.
Grigoryan, K. V., Javedan, H. & Rudolph, J. L. 2014. Orthogeriatric care models and outcomes in hip fracture patients: a systematic review and meta-analysis. *J Orthop Trauma,* 28**,** e49-55.
Gross, A. L., Jones, R. N., Habtemariam, D. A., Fong, T. G., Tommet, D., Quach, L., Schmitt, E., Yap, L. & Inouye, S. K. 2012. Delirium and Long-term Cognitive Trajectory Among Persons With Dementia. *Arch Intern Med,* 172**,** 1324-31.
Guenther, U., Theuerkauf, N., Frommann, I., Brimmers, K., Malik, R., Stori, S., Scheidemann, M., Putensen, C. & Popp, J. 2013. Predisposing and precipitating factors of delirium after cardiac surgery: a prospective observational cohort study. *Ann Surg,* 257**,** 1160-7.
Guralnik, J. M., Ferrucci, L., Pieper, C. F., Leveille, S. G., Markides, K. S., Ostir, G. V., Studenski, S., Berkman, L. F. & Wallace, R. B. 2000. Lower Extremity Function and Subsequent Disability. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences,* 55**,** M221-M231.
Gustafson, Y., Berggren, D., Brannstrom, B., Bucht, G., Norberg, A., Hansson, L. I. & Winblad, B. 1988. Acute confusional states in elderly patients treated for femoral neck fracture. *J Am Geriatr Soc,* 36**,** 525-30.
Gustafson, Y., Brannstrom, B., Berggren, D., Ragnarsson, J. I., Sigaard, J., Bucht, G., Reiz, S., Norberg, A. & Winblad, B. 1991. A geriatric-anesthesiologic program to reduce acute confusional states in elderly patients treated for femoral neck fractures. *J Am Geriatr Soc,* 39**,** 655-62.
Hall, R. J., Meagher, D. J. & Maclullich, A. M. J. 2012. Delirium detection and monitoring outside the ICU. *Best Practice & Research Clinical Anaesthesiology*

Delirium in the Hospital Setting.
Hall, R. J., Shenkin, S. D. & Maclullich, A. M. J. 2011. A Systematic Literature Review of Cerebrospinal Fluid Biomarkers in Delirium. *Dementia and Geriatric Cognitive Disorders,* 32**,** 79-93.
Han, L., Mccusker, J., Cole, M., Abrahamowicz, M., Primeau, F. O. & +Ëlie, M. 2001. Use of Medications With Anticholinergic Effect Predicts Clinical Severity of Delirium Symptoms in Older Medical Inpatients. *Archives of Internal Medicine,* 161**,** 1099-1105.

Handoll, H. H., Cameron, I. D., Mak, J. C. & Finnegan, T. P. 2009. Multidisciplinary rehabilitation for older people with hip fractures. *Cochrane.Database.Syst.Rev.*, CD007125.

Hebert-Davies, J., Laflamme, G. Y. & Rouleau, D. 2012. Bias towards dementia: are hip fracture trials excluding too many patients? A systematic review. *Injury,* 43**,** 1978-84.

Hempsall, V. J., Robertson, D. R., Campbell, M. J. & Briggs, R. S. 1990. Orthopaedic geriatric care--is it effective? A prospective population-based comparison of outcome in fractured neck of femur. *J R.Coll.Physicians Lond,* 24**,** 47-50.

Ho, W. W., Kwan Dai, D. L., Liu, K. W., Chow, K. M., Lau, E., Woo, J. & Leung, K. S. 2009. To investigate the effect and cost-effectiveness of implementing an orthogeriatric intervention for elderly patients with acute hip fracture: the experience in Hong Kong. *J Am Geriatr Soc,* 57**,** 2153-4.

Hshieh, T. T., Fong, T. G., Marcantonio, E. R. & Inouye, S. K. 2008. Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. *J Gerontol.A Biol.Sci.Med.Sci.,* 63**,** 764-772.

Huang, Y. & Mucke, L. 2012. Alzheimer mechanisms and therapeutic strategies. *Cell,* 148**,** 1204-22.

Hughes, C. G., Patel, M. B. & Pandharipande, P. P. 2012. Pathophysiology of acute brain dysfunction: what's the cause of all this confusion? *Curr Opin Crit Care,* 18**,** 518-26.

Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A. & Martin, R. L. 1982. A new clinical scale for the staging of dementia. *Br J Psychiatry,* 140**,** 566-72.

Inouye, S. K. 1999. Predisposing and precipitating factors for delirium in hospitalized older patients. *Dement Geriatr Cogn Disord.* 1999/09/04 ed.

Inouye, S. K., Van Dyck, C. H., Alessi, C. A., Balkin, S., Siegal, A. P. & Horwitz, R. I. 1990. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann.Intern.Med.,* 113**,** 941-948.

Inouye, S. K., Westendorp, R. G. & Saczynski, J. S. 2013. Delirium in elderly people. *Lancet*.

Jakobsen, S. M. Ñ., Kersten, H. & Molden, E. 2011. Evaluation of Brain Anticholinergic Activities of Urinary Spasmolytic Drugs Using a High-Throughput Radio Receptor Bioassay. *Journal of the American Geriatrics Society,* 59**,** 501-505.

Jones, S. F. & Pisani, M. A. 2012. ICU delirium: an update. *Curr Opin Crit Care,* 18**,** 146-51.

Jorm, A. F. 1994. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation. *Psychol Med,* 24**,** 145-53.

Jorm, A. F. 2004. The Informant Questionnaire on cognitive decline in the elderly (IQCODE): a review. *Int Psychogeriatr,* 16**,** 275-93.

Juliebo, V., Bjoro, K., Krogseth, M., Skovlund, E., Ranhoff, A. H. & Wyller, T. B. 2009. Risk factors for preoperative and postoperative delirium in elderly patients with hip fracture. *J Am Geriatr Soc,* 57**,** 1354-61.

Kammerlander, C., Roth, T., Friedman, S., Suhm, N., Luger, T., Kammerlander-Knauer, U., Krappinger, D. & Blauth, M. 2010. Ortho-geriatric service: a literature review comparing different models. *Osteoporosis International,* 21**,** 637-646.

Karrasch, M., Sinerva, E., Gronholm, P., Rinne, J. & Laine, M. 2005. CERAD test performances in amnestic mild cognitive impairment and Alzheimer's disease. *Acta Neurol Scand,* 111**,** 172-9.

Kates, S., Mendelson, D. & Friedman, S. 2010a. Co-managed care for fragility hip fractures (Rochester model). *Osteoporosis International,* 21**,** 621-625.

Kates, S. L., Blake, D., Bingham, K. W., Kates, O. S., Mendelson, D. A. & Friedman, S. M. 2010b. Comparison of an organized geriatric fracture program to United States government data. *Geriatr Orthop Surg Rehabil,* 1**,** 15-21.

Kates, S. L., Mendelson, D. A. & Friedman, S. M. 2011. The value of an organized fracture program for the elderly: early results. *J Orthop Trauma,* 25**,** 233-7.

Kennedy, M., Enander, R. A., Tadiri, S. P., Wolfe, R. E., Shapiro, N. I. & Marcantonio, E. R. 2014. Delirium risk prediction, healthcare use and mortality of elderly adults in the emergency department. *J Am Geriatr Soc,* 62**,** 462-9.

Kennie, D. C., Reid, J., Richardson, I. R., Kiamari, A. A. & Kelt, C. 1988. Effectiveness of geriatric rehabilitative care after fractures of the proximal femur in elderly women: a randomised clinical trial. *BMJ,* 297.

Kersten, H., Molden, E., Tolo, I. K., Skovlund, E., Engedal, K. & Wyller, T. B. 2013. Cognitive effects of reducing anticholinergic drug burden in a frail elderly population: a randomized controlled trial. *J Gerontol A Biol Sci Med Sci,* 68**,** 271-8.

Kersten, H. & Wyller, T. B. 2014. Anticholinergic drug burden in older people's brain - how well is it measured? *Basic Clin Pharmacol Toxicol,* 114**,** 151-9.

Khan, B. A., Zawahiri, M., Campbell, N. L. & Boustani, M. A. 2011. Biomarkers for Delirium: A Review. *Journal of the American Geriatrics Society,* 59**,** S256-S261.

Khan, R., Fernandez, C., Kashifl, F., Shedden, R. & Diggory, P. 2002. Combined orthogeriatric care in the management of hip fractures: a prospective study. *Ann.R.Coll.Surg.Engl,* 84**,** 122-124.

Khasraghi, F. A., Christmas, C., Lee, E. J., Mears, S. C. & Wenz, J. F., Sr. 2005. Effectiveness of a multidisciplinary team approach to hip fracture management. *J Surg.Orthop.Adv.,* 14**,** 27-31.

Knaus, W. A., Draper, E. A., Wagner, D. P. & Zimmerman, J. E. 1985. APACHE II: a severity of disease classification system. *Crit Care Med,* 13**,** 818-29.

Koponen, H. J., Lepola, U. & Leinonen, E. 1994. A long-term follow-up study of cerebrospinal fluid 5-hydroxyindoleacetic acid in delirium. *Eur Arch Psychiatry Clin Neurosci,* 244**,** 131-4.

Koval, K. 2006. Editorial Comment on: Outcomes for Older Patients With Hip Fracture: The Impact of Orthopedic and Geriatric Medical Cocare. *J Orthop.Trauma,* 20**,** 179.

Koval, K. J., Chen, A. L., Aharonoff, G. B., Egol, K. A. & Zuckerman, J. D. 2004. Clinical pathway for hip fractures in the elderly: the Hospital for Joint Diseases experience. *Clin Orthop.Relat Res.***,** 72-81.

Krogseth, M., Wyller, T. B., Engedal, K. & Juliebo, V. 2011. Delirium Is an Important Predictor of Incident Dementia among Elderly Hip Fracture Patients. *Dementia and Geriatric Cognitive Disorders,* 31**,** 63-70.

Kudoh, A., Takase, H., Takahira, Y. & Takazawa, T. 2004. Postoperative confusion increases in elderly long-term benzodiazepine users. *Anesth Analg,* 99**,** 1674-8, table of contents.

Lam, M. P. & Cheung, B. M. 2012. The use of STOPP/START criteria as a screening tool for assessing the appropriateness of medications in the elderly population. *Expert Rev Clin Pharmacol,* 5**,** 187-97.

Lampela, P., Lavikainen, P., Garcia-Horsman, J. A., Bell, J. S., Huupponen, R. & Hartikainen, S. 2013. Anticholinergic drug use, serum anticholinergic activity, and adverse drug events among older people: a population-based study. *Drugs Aging,* 30**,** 321-30.

Laurila, J. V., Pitkala, K. H., Strandberg, T. E. & Tilvis, R. S. 2002. Confusion assessment method in the diagnostics of delirium among aged hospital patients: would it serve better in screening than as a diagnostic instrument? *Int J Geriatr Psychiatry,* 17**,** 1112-9.

Laurila, J. V., Pitkala, K. H., Strandberg, T. E. & Tilvis, R. S. 2003. The impact of different diagnostic criteria on prevalence rates for delirium. *Dement Geriatr Cogn Disord,* 16**,** 156-62.

Leung, A. H., Lam, T. P., Cheung, W. H., Chan, T., Sze, P. C., Lau, T. & Leung, K. S. 2011. An orthogeriatric collaborative intervention program for fragility fractures: a retrospective cohort study. *J Trauma,* 71**,** 1390-1394.

Liem, I. S., Kammerlander, C., Suhm, N., Blauth, M., Roth, T., Gosch, M., Hoang-Kim, A., Mendelson, D., Zuckerman, J., Leung, F., Burton, J., Moran, C., Parker, M., Giusti, A., Pioli, G., Goldhahn, J., Kates, S. L. & Investigation Performed with the Assistance of The, A. N. 2013. Identifying a standard set of outcome parameters for the evaluation of orthogeriatric co-management for hip fractures. *Injury,* 44**,** 1403-12.

Liptzin, B., Laki, A., Garb, J. L., Fingeroth, R. & Krushell, R. 2005. Donepezil in the prevention and treatment of post-surgical delirium. *Am J Geriatr Psychiatry,* 13**,** 1100-6.

Lundstrom, M., Edlund, A., Lundstrom, G. & Gustafson, Y. 1999. Reorganization of nursing and medical care to reduce the incidence of postoperative delirium and improve rehabilitation outcome in elderly patients treated for femoral neck fractures. *Scand J Caring Sci,* 13**,** 193-200.

Lundstrom, M., Olofsson, B., Stenvall, M., Karlsson, S., Nyberg, L., Englund, U., Borssen, B., Svensson, O. & Gustafson, Y. 2007. Postoperative delirium in old patients with femoral neck fracture: a randomized intervention study. *Aging Clin Exp Res,* 19**,** 178-86.

Macdonald, A., Adamis, D., Treloar, A. & Martin, F. 2007. C-reactive protein levels predict the incidence of delirium and recovery from it. *Age and Ageing,* 36**,** 222-225.

Maclullich, A. M., Edelshain, B. T., Hall, R. J., De, V. A., Howie, S. E., Pearson, A., Middleton, S. D., Gillies, F., Armstrong, I. R., White, T. O., Cunningham, C., De Rooij, S. E. & Van Munster, B. C. 2011. Cerebrospinal fluid interleukin-8 levels are higher in people with hip fracture with perioperative delirium than in controls. *J Am Geriatr Soc,* 59**,** 1151-1153.

Maclullich, A. M., Ferguson, K. J., Miller, T., De Rooij, S. E. & Cunningham, C. 2008. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. [Review] [100 refs]. *Journal of Psychosomatic Research,* 65**,** 229-238.

Maclullich, A. M. J. & Hall, R. J. 2011. Who understands delirium? *Age and Ageing,* 40**,** 412-414.

Maldonado, J. R. 2013. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry,* 21**,** 1190-222.

Marcantonio, E. R., Flacker, J. M., Wright, R. J. & Resnick, N. M. 2001. Reducing Delirium After Hip Fracture: A Randomized Trial. *Journal of the American Geriatrics Society,* 49**,** 516-522.

Mazzola, P., De Filippi, F., Castoldi, G., Galetti, P., Zatti, G. & Annoni, G. 2011. A comparison between two co-managed geriatric programmes for hip fractured elderly patients. *Aging Clin Exp Res,* 23**,** 431-6.

Meagher, D., Adamis, D., Trzepacz, P. & Leonard, M. 2012. Features of subsyndromal and persistent delirium. *The British Journal of Psychiatry,* 200**,** 37-44.

Menzies, I. B., Mendelson, D. A., Kates, S. L. & Friedman, S. M. 2012. The impact of comorbidity on perioperative outcomes of hip fractures in a geriatric fracture model. *Geriatr Orthop Surg Rehabil,* 3**,** 129-34.

Milisen, K., Foreman, M. D., Abraham, I. L., De Geest, S., Godderis, J., Vandermeulen, E., Fischler, B., Delooz, H. H., Spiessens, B. & Broos, P. L. 2001. A nurse-led

interdisciplinary intervention program for delirium in elderly hip-fracture patients. *J Am Geriatr Soc,* 49**,** 523-32.
Miller, P. S., Richardson, J. S., Jyu, C. A., Lemay, J. S., Hiscock, M. & Keegan, D. L. 1988. Association of low serum anticholinergic levels and cognitive impairment in elderly presurgical patients. *Am J Psychiatry,* 145**,** 342-345.
Miura, L. N., Dipiero, A. R. & Homer, L. D. 2009. Effects of a Geriatrician-Led Hip Fracture Program: Improvements in Clinical and Economic Outcomes. *Journal of the American Geriatrics Society,* 57**,** 159-167.
Munster, B. C., Aronica, E., Zwinderman, A. H., Eikelenboom, P., Cunningham, C. & Rooij, S. E. 2011. Neuroinflammation in delirium: a postmortem case-control study. *Rejuvenation.Res.,* 14**,** 615-622.
Murr, C., Widner, B., Wirleitner, B. & Fuchs, D. 2002. Neopterin as a marker for immune system activation. *Curr Drug Metab,* 3**,** 175-87.
Murray, C., Sanderson, D. J., Barkus, C., Deacon, R. M., Rawlins, J. N., Bannerman, D. M. & Cunningham, C. 2012. Systemic inflammation induces acute working memory deficits in the primed brain: relevance for delirium. *Neurobiol Aging,* 33**,** 603-616 e3.
Naglie, G., Tansey, C., Kirkland, J. L., Ogilvie-Harris, D. J., Detsky, A. S., Etchells, E., Tomlinson, G., O'rourke, K. & Goldlist, B. 2002. Interdisciplinary inpatient care for elderly people with hip fracture: a randomized controlled trial. *CMAJ,* 167**,** 25-32.
Nakamura, J., Uchimura, N., Yamada, S. & Nakazawa, Y. 1997. Does plasma free-3-methoxy-4-hydroxyphenyl(ethylene)glycol increase in the delirious state? A comparison of the effects of mianserin and haloperidol on delirium. *Int Clin Psychopharmacol,* 12**,** 147-52.
Neufeld, K. J. & Thomas, C. 2013. Delirium: Definition, Epidemiology, and Diagnosis. *J Clin Neurophysiol,* 30**,** 438-442.
Norden, D. M. & Godbout, J. P. 2013. Review: microglia of the aged brain: primed to be activated and resistant to regulation. *Neuropathol Appl Neurobiol,* 39**,** 19-34.
Organization, W. H. 2008. *International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10),* New York.
Osse, R. J., Fekkes, D., Tulen, J. H. M., Wierdsma, A. I., Bogers, A. J. J. C., Van Der Mast, R. C. & Hengeveld, M. W. 2012. High Preoperative Plasma Neopterin Predicts Delirium After Cardiac Surgery in Older Adults. *Journal of the American Geriatrics Society,* 60**,** 661-668.
Pandharipande, P. P., Girard, T. D., Jackson, J. C., Morandi, A., Thompson, J. L., Pun, B. T., Brummel, N. E., Hughes, C. G., Vasilevskis, E. E., Shintani, A. K., Moons, K. G., Geevarghese, S. K., Canonico, A., Hopkins, R. O., Bernard, G. R., Dittus, R. S. & Ely, E. W. 2013. Long-Term Cognitive Impairment after Critical Illness. *New England Journal of Medicine,* 369**,** 1306-1316.
Pandharipande, P. P., Morandi, A., Adams, J. R., Girard, T. D., Thompson, J. L., Shintani, A. K. & Ely, E. W. 2009. Plasma tryptophan and tyrosine levels are independent risk factors for delirium in critically ill patients. *Intensive Care Med,* 35**,** 1886-92.
Pioli, G., Barone, A., Mussi, C., Tafaro, L., Bellelli, G., Falaschi, P., Trabucchi, M. & Paolisso, G. 2014. The management of hip fracture in the older population. Joint position statement by Gruppo Italiano Ortogeriatria (GIOG). *Aging Clin Exp Res*.
Pioli, G., Frondini, C., Lauretani, F., Davoli, M. L., Pellicciotti, F., Martini, E., Zagatti, A., Giordano, A., Pedriali, I., Nardelli, A., Zurlo, A., Ferrari, A. & Lunardelli, M. L. 2012a. Time to surgery and rehabilitation resources affect outcomes in orthogeriatric units. *Arch Gerontol Geriatr,* 55**,** 316-22.

Pioli, G., Frondini, C., Lauretani, F., Davoli, M. L., Pellicciotti, F., Martini, E., Zagatti, A., Giordano, A., Pedriali, I., Nardelli, A., Zurlo, A., Ferrari, A. & Lunardelli, M. L. 2012b. Time to surgery and rehabilitation resources affect outcomes in orthogeriatric units. *Archives of Gerontology and Geriatrics,* 55**,** 316-322.

Pisani, M. A., Murphy, T. E., Araujo, K. L., Slattum, P., Van Ness, P. H. & Inouye, S. K. 2009. Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. *Crit Care Med,* 37**,** 177-83.

Plaschke, K., Kopitz, J., Mattern, J., Martin, E. & Teschendorf, P. 2010. Increased cortisol levels and anticholinergic activity in cognitively unimpaired patients. *J Neuropsychiatry Clin.Neurosci.,* 22**,** 433-441.

Plaschke, K., Thomas, C., Engelhardt, R., Teschendorf, P., Hestermann, U., Weigand, M. A., Martin, E. & Kopitz, J. 2007. Significant correlation between plasma and CSF anticholinergic activity in presurgical patients. *Neuroscience Letters,* 417**,** 16-20.

Radtke, F. M., Gaudreau, J. D. & Spies, C. 2010. Diagnosing delirium. *Jama,* 304**,** 2125; author reply 2126-7.

Ramirez-Bermudez, J., Ruiz-Chow, A., Perez-Neri, I., Soto-Hernandez, J. L., Flores-Hernandez, R., Nente, F., Montes, S. & Rios, C. 2008. Cerebrospinal fluid homovanillic acid is correlated to psychotic features in neurological patients with delirium. *General Hospital Psychiatry,* 30**,** 337-343.

Ranhoff, A., Holvik, K., Martinsen, M., Domaas, K. & Solheim, L. 2010. Older hip fracture patients: three groups with different needs. *BMC Geriatrics,* 10**,** 65.

Ritchie, C. W., Newman, T. H., Leurent, B. & Sampson, E. L. 2014. The association between C-reactive protein and delirium in 710 acute elderly hospital admissions. *Int Psychogeriatr,* 26**,** 717-24.

Ritter, C., Tomasi, C. D., Dal-Pizzol, F., Pinto, B. B., Dyson, A., De Miranda, A. S., Comim, C. M., Soares, M., Teixeira, A. L., Quevedo, J. & Singer, M. 2014. Inflammation biomarkers and delirium in critically ill patients. *Crit Care,* 18**,** R106.

Roberts, H. C., Pickering, R. M., Onslow, E., Clancy, M., Powell, J., Roberts, A., Hughes, K., Coulson, D. & Bray, J. 2004. The effectiveness of implementing a care pathway for femoral neck fracture in older people: a prospective controlled before and after study. *Age and Ageing,* 33**,** 178-184.

Robinson, T. N., Raeburn, C. D., Angles, E. M. & Moss, M. 2008. Low tryptophan levels are associated with postoperative delirium in the elderly. *Am J Surg,* 196**,** 670-4.

Rolfson, D. B., Mcelhaney, J. E., Jhangri, G. S. & Rockwood, K. 1999. Validity of the confusion assessment method in detecting postoperative delirium in the elderly. *Int Psychogeriatr,* 11**,** 431-8.

Rooney, S., Qadir, M., Adamis, D. & Mccarthy, G. 2014. Diagnostic and treatment practices of delirium in a general hospital. *Aging Clin Exp Res*.

Rudolph Jl, S. M. J. a. M. C. M. R. E. 2008. THe anticholinergic risk scale and anticholinergic adverse effects in older persons. *Archives of Internal Medicine,* 168**,** 508-513.

Ryan, D. J., O'regan, N. A., Caoimh, R. O., Clare, J., O'connor, M., Leonard, M., Mcfarland, J., Tighe, S., O'sullivan, K., Trzepacz, P. T., Meagher, D. & Timmons, S. 2013. Delirium in an adult acute hospital population: predictors, prevalence and detection. *BMJ Open,* 3.

Saczynski, J. S., Kosar, C. M., Xu, G., Puelle, M. R., Schmitt, E., Jones, R. N., Marcantonio, E. R., Wong, B., Isaza, I. & Inouye, S. K. 2014. A tale of two methods: chart and interview methods for identifying delirium. *J Am Geriatr Soc,* 62**,** 518-24.

Saczynski, J. S., Marcantonio, E. R., Quach, L., Fong, T. G., Gross, A., Inouye, S. K. & Jones, R. N. 2012. Cognitive Trajectories after Postoperative Delirium. *New England Journal of Medicine.* Massachusetts Medical Society.

Saltvedt, I., Prestmo, A., Einarsen, E., Johnsen, L., Helbostad, J. & Sletvold, O. 2012. Development and delivery of patient treatment in the Trondheim Hip Fracture Trial. A new geriatric in-hospital pathway for elderly patients with hip fracture. *BMC Research Notes,* 5**,** 355.

Sanders, R. D. 2011. Hypothesis for the pathophysiology of delirium: Role of baseline brain network connectivity and changes in inhibitory tone. *Medical Hypotheses,* 77**,** 140-143.

Scala, R. 2011. Hypercapnic encephalopathy syndrome: a new frontier for non-invasive ventilation? *Respir Med,* 105**,** 1109-17.

Schoen, J., Meyerrose, J., Paarmann, H., Heringlake, M., Hueppe, M. & Berger, K. U. 2011. Preoperative regional cerebral oxygen saturation is a predictor of postoperative delirium in on-pump cardiac surgery patients: a prospective observational trial. *Crit Care,* 15**,** R218.

Schofield, I. 1997. A small exploratory study of the reaction of older people to an episode of delirium. *J Adv Nurs,* 25**,** 942-52.

Shulman, K. I. 2000. Clock-drawing: is it the ideal cognitive screening test? *Int J Geriatr Psychiatry,* 15**,** 548-61.

Shyu, Y. I., Liang, J., Wu, C. C., Su, J. Y., Cheng, H. S., Chou, S. W., Chen, M. C. & Yang, C. T. 2008. Interdisciplinary intervention for hip fracture in older Taiwanese: benefits last for 1 year. *J.Gerontol.A Biol.Sci.Med.Sci.,* 63**,** 92-97.

Shyu, Y. I., Liang, J., Wu, C. C., Su, J. Y., Cheng, H. S., Chou, S. W., Chen, M. C., Yang, C. T. & Tseng, M. Y. 2010. Two-Year Effects of Interdisciplinary Intervention for Hip Fracture in Older Taiwanese. *Journal of the American Geriatrics Society,* 58**,** 1081-1089.

Shyu, Y. I. L., Liang, J., Wu, C. C., Su, J. Y., Cheng, H. S., Chou, S. W. & Yang, C. T. 2005. A Pilot Investigation of the Short-Term Effects of an Interdisciplinary Intervention Program on Elderly Patients with Hip Fracture in Taiwan. *Journal of the American Geriatrics Society,* 53**,** 811-818.

Siddiqi, N., House, A. O. & Holmes, J. D. 2006. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing,* 35**,** 350-64.

Sletvold, O., Helbostad, J. L., Thingstad, P., Taraldsen, K., Prestmo, A., Lamb, S. E., Aamodt, A., Johnsen, R., Magnussen, J. & Saltvedt, I. 2011. Effect of in-hospital comprehensive geriatric assessment (CGA) in older people with hip fracture. The protocol of the Trondheim Hip Fracture Trial. *BMC Geriatr,* 11**,** 18.

Stenvall, M., Berggren, M., Lundstr+Âm, M., Gustafson, Y. & Olofsson, B. 2012. A multidisciplinary intervention program improved the outcome after hip fracture for people with dementiaGÇöSubgroup analyses of a randomized controlled trial. *Archives of Gerontology and Geriatrics,* 54**,** e284-e289.

Stenvall, M., Olofsson, B., Nyberg, L., Lundstrom, M. & Gustafson, Y. 2007. Improved performance in activities of daily living and mobility after a multidisciplinary postoperative rehabilitation in older people with femoral neck fracture: a randomized controlled trial with 1-year follow-up. *J Rehabil.Med,* 39**,** 232-238.

Swanson, C. E., Day, G. A., Yelland, C. E., Broome, J. R., Massey, L., Richardson, H. R., Dimitri, K. & Marsh, A. 1998. The management of elderly patients with femoral fractures. A randomised controlled trial of early intervention versus standard care. *Med J Aust.,* 169**,** 515-518.

Trzepacz, P. T. 2000. Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. *Semin.Clin.Neuropsychiatry,* 5**,** 132-148.
Trzepacz, P. T., Mittal, D., Torres, R., Kanary, K., Norton, J. & Jimerson, N. 2001. Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. *J Neuropsychiatry Clin Neurosci,* 13**,** 229-42.
Tune, L. & Coyle, J. T. 1980. Serum levels of anticholinergic drugs in treatment of acute extrapyramidal side effects. *Arch Gen Psychiatry,* 37**,** 293-7.
Uy, C., Kurrle, S. E. & Cameron, I. D. 2008. Inpatient multidisciplinary rehabilitation after hip fracture for residents of nursing homes: a randomised trial. *Australas J Ageing,* 27**,** 43-4.
Van Den Boogaard, M., Kox, M., Quinn, K., Van Achterberg, T., Van Der Hoeven, J., Schoonhoven, L. & Pickkers, P. 2011. Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients. *Critical Care,* 15**,** R297.
Van Der Cammen, T. J., Tiemeier, H., Engelhart, M. J. & Fekkes, D. 2006. Abnormal neurotransmitter metabolite levels in Alzheimer patients with a delirium. *Int J Geriatr Psychiatry,* 21**,** 838-43.
Van Der Mast, R. C. & Fekkes, D. 2000. Serotonin and amino acids: partners in delirium pathophysiology? *Semin Clin Neuropsychiatry,* 5**,** 125-31.
Van Der Mast, R. C., Fekkes, D., Moleman, P. & Pepplinkhuizen, L. 1991. Is postoperative delirium related to reduced plasma tryptophan? *Lancet,* 338**,** 851-2.
Van Der Mast, R. C., Van Den Broek, W. W., Fekkes, D., Pepplinkhuizen, L. & Habbema, J. D. 2000. Is delirium after cardiac surgery related to plasma amino acids and physical condition? *J Neuropsychiatry Clin Neurosci,* 12**,** 57-63.
Van Eijk, M. M., Roes, K. C., Honing, M. L., Kuiper, M. A., Karakus, A., Van Der Jagt, M., Spronk, P. E., Van Gool, W. A., Van Der Mast, R. C., Kesecioglu, J. & Slooter, A. J. 2010. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *The Lancet,* 376**,** 1829-1837.
Van Gool, A. R., Fekkes, D., Kruit, W. H., Mulder, P. G., Ten Hagen, T. L., Bannink, M., Maes, M. & Eggermont, A. M. 2003. Serum amino acids, biopterin and neopterin during long-term immunotherapy with interferon-alpha in high-risk melanoma patients. *Psychiatry Res,* 119**,** 125-32.
Van Gool, W. A., Van De Beek, D. & Eikelenboom, P. 2010. Systemic infection and delirium: when cytokines and acetylcholine collide. *Lancet,* 375**,** 773-775.
Van Munster, B. C., De Rooij, S. E. & Korevaar, J. C. 2009. The role of genetics in delirium in the elderly patient. *Dement Geriatr Cogn Disord,* 28**,** 187-195.
Van Munster, B. C., Korevaar, J. C., De Rooij, S. E., Levi, M. & Zwinderman, A. H. 2007. The association between delirium and the apolipoprotein E epsilon4 allele in the elderly. *Psychiatr.Genet.,* 17**,** 261-266.
Van Munster, B. C., Thomas, C., Kreisel, S. H., Brouwer, J. P., Nanninga, S., Kopitz, J. & De Rooij, S. E. 2012. Longitudinal assessment of serum anticholinergic activity in delirium of the elderly. *Journal of Psychiatric Research*.
Vidan, M., Serra, J. A., Moreno, C., Riquelme, G. & Ortiz, J. 2005. Efficacy of a comprehensive geriatric intervention in older patients hospitalized for hip fracture: a randomized, controlled trial. *J Am Geriatr Soc,* 53**,** 1476-82.
Wade, D. 1992. Measurment in Neurological Rehabilitation. *Oxford, Oxford University Press*.
Wagner, P., Fuentes, P., Diaz, A., Martinez, F., Amenabar, P., Schweitzer, D., Botello, E. & Gac, H. 2012. Comparison of complications and length of hospital stay between

orthopedic and orthogeriatric treatment in elderly patients with a hip fracture. *Geriatr Orthop Surg Rehabil,* 3**,** 55-8.
Welsh, K. A., Butters, N., Mohs, R. C., Beekly, D., Edland, S., Fillenbaum, G. & Heyman, A. 1994. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. *Neurology,* 44**,** 609-14.
Wergeland, J. N., Selbaek, G., Hogset, L. D., Soderhamn, U. & Kirkevold, O. 2014. Dementia, neuropsychiatric symptoms, and the use of psychotropic drugs among older people who receive domiciliary care: a cross-sectional study. *Int Psychogeriatr,* 26**,** 383-91.
Westhoff, D., Witlox, J., Koenderman, L., Kalisvaart, K. J., De Jonghe, J. F., Van Stijn, M. F., Houdijk, A. P., Hoogland, I. C., Maclullich, A. M., Van Westerloo, D. J., Van De Beek, D., Eikelenboom, P. & Van Gool, W. A. 2013. Preoperative cerebrospinal fluid cytokine levels and the risk of postoperative delirium in elderly hip fracture patients. *J Neuroinflammation,* 10**,** 122.
White, S., Calver, B. L., Newsway, V., Wade, R., Patel, S., Bayer, A. & O'mahony, M. S. 2005. Enzymes of drug metabolism during delirium. *Age Ageing,* 34**,** 603-8.
Witlox, J., Eurelings, L. S. M., De Jonghe, J. F. M., Kalisvaart, K. J., Eikelenboom, P. & Van Gool, W. A. 2010. Delirium in Elderly Patients and the Risk of Postdischarge Mortality, Institutionalization, and Dementia. *JAMA: The Journal of the American Medical Association,* 304**,** 443-451.
Wong, C. L., Holroyd-Leduc, J., Simel, D. L. & Straus, S. E. 2010. Does this patient have delirium?: value of bedside instruments. *JAMA,* 304**,** 779-86.
Wong Tin Niam, D. M., Bruce, J. J. & Bruce, D. G. 2005. Quality project to prevent delirium after hip fracture. *Australasian Journal on Ageing,* 24**,** 174-177.
Wyller, T. B., Watne, L. & Skovlund, E. *Statistical analysis plan - the Oslo Orthogeriatric Study* [Online]. Available: http://www.med.uio.no/klinmed/forskning/grupper/klinisk-geriatrisk-forskning/dokumenter/statistical_analysis_plan_oslo_orthogeriatric_study_final.pdf [Accessed January 8, 2014.
Wyller, T. B., Watne, L. O., Torbergsen, A., Engedal, K., Frihagen, F., Juliebo, V., Saltvedt, I., Skovlund, E., Raeder, J. & Conroy, S. 2012. The effect of a pre- and post-operative orthogeriatric service on cognitive function in patients with hip fracture. The protocol of the Oslo Orthogeriatrics Trial. *BMC Geriatr,* 12**,** 36.
Yokota, H., Ogawa, S., Kurokawa, A. & Yamamoto, Y. 2003. Regional cerebral blood flow in delirium patients. *Psychiatry Clin Neurosci,* 57**,** 337-9.
Zhang, Z., Pan, L., Deng, H., Ni, H. & Xu, X. 2014. Prediction of delirium in critically ill patients with elevated C-reactive protein. *J Crit Care,* 29**,** 88-92.
Zlokovic, B. V. 2011. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci,* 12**,** 723-38.
Zuckerman, J. D., Sakales, S. R., Fabian, D. R. & Frankel, V. H. 1992. Hip fractures in geriatric patients. Results of an interdisciplinary hospital care program. *Clin Orthop.Relat Res.***,** 213-225.

9 Paper I - IV

I

II

Watne et al. BMC Medicine 2014, 12:63
http://www.biomedcentral.com/1741-7015/12/63

BMC Medicine

RESEARCH ARTICLE Open Access

The effect of a pre- and postoperative orthogeriatric service on cognitive function in patients with hip fracture: randomized controlled trial (Oslo Orthogeriatric Trial)

Leiv Otto Watne[1,2*], Anne Cathrine Torbergsen[2,3], Simon Conroy[4], Knut Engedal[2,5], Frede Frihagen[6], Geir Aasmund Hjorthaug[6], Vibeke Juliebo[7], Johan Raeder[2,8], Ingvild Saltvedt[9,10], Eva Skovlund[11] and Torgeir Bruun Wyller[1,2*]

Abstract

Background: Delirium is a common complication in patients with hip fractures and is associated with an increased risk of subsequent dementia. The aim of this trial was to evaluate the effect of a pre- and postoperative orthogeriatric service on the prevention of delirium and longer-term cognitive decline.

Methods: This was a single-center, prospective, randomized controlled trial in which patients with hip fracture were randomized to treatment in an acute geriatric ward or standard orthopedic ward. Inclusion and randomization took place in the Emergency Department at Oslo University hospital. The key intervention in the acute geriatric ward was Comprehensive Geriatric Assessment including daily interdisciplinary meetings. Primary outcome was cognitive function four months after surgery measured using a composite outcome incorporating the Clinical Dementia Rating Scale (CDR) and the 10 words learning and recalls tasks from the Consortium to Establish a Registry for Alzheimer's Disease battery (CERAD). Secondary outcomes were pre- and postoperative delirium, delirium severity and duration, mortality and mobility (measured by the Short Physical Performance Battery (SPPB)). Patients were assessed four and twelve months after surgery by evaluators blind to allocation.

Results: A total of 329 patients were included. There was no significant difference in cognitive function four months after surgery between patients treated in the acute geriatric and the orthopedic wards (mean 54.7 versus 52.9, 95% confidence interval for the difference −5.9 to 9.5; $P = 0.65$). There was also no significant difference in delirium rates (49% versus 53%, $P = 0.51$) or four month mortality (17% versus 15%, $P = 0.50$) between the intervention and the control group. In a pre-planned sub-group analysis, participants living in their own home at baseline who were randomized to orthogeriatric care had better mobility four months after surgery compared with patients randomized to the orthopedic ward, measured with SPPB (median 6 versus 4, 95% confidence interval for the median difference 0 to 2; $P = 0.04$).

Conclusions: Pre- and postoperative orthogeriatric care given in an acute geriatric ward was not effective in reducing delirium or long-term cognitive impairment in patients with hip fracture. The intervention had, however, a positive effect on mobility in patients not admitted from nursing homes.

Trial registration: ClinicalTrials.gov NCT01009268 Registered November 5, 2009

Keywords: Hip fracture, Orthogeriatrics, Delirium, Cognitive decline

* Correspondence: l.o.watne@gmail.com; t.b.wyller@medisin.uio.no
[1]Oslo Delirium Research Group, Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway
[2]University of Oslo, Institute of Clinical Medicine, Oslo, Norway
Full list of author information is available at the end of the article

Background

More than 30% of individuals 65-years-old or older experience at least one fall each year, and the prevalence increases with age [1]. Ten percent of falls result in serious injuries [2], with hip fracture as one of the most feared consequences. In the European Union it was estimated that 615,000 new hip fractures occurred in 2010, and the number of hip fractures is expected to increase in the years to come [3].

Patients with hip fracture are often frail, have multiple co-morbidities including cognitive impairment, and there is usually polypharmacy [4]. To address these patients' needs, different models of orthogeriatric co-management have been developed. Models range from a limited consultation or liaison service through to integrated orthogeriatric units [5]. Few of these models have been evaluated in randomized controlled trials (RCTs), and the heterogeneity of interventions, outcomes and populations makes it difficult to draw conclusions regarding the superiority of one particular model [5-7]. Geriatric intervention might be especially beneficial in the vulnerable period prior to surgery, but most studies are limited to postoperative orthogeriatric intervention [8].

A common complication of hip fracture is delirium, a syndrome of acute change in cognition and alertness, and altered, often psychotic, behavior [9]. About 40% to 50% of hip fracture patients are reported to develop delirium in the peri-operative period [10]. Delirium is particularly common in patients with pre-existing dementia [11], despite which patients with dementia are often excluded from studies [12]. Delirium in the perioperative phase is associated with increased risk of death, institutionalization and subsequent dementia [13]. Multifactorial intervention can prevent delirium in hip fracture patients [14-16], but it is not yet established if preventing delirium can reduce long-term cognitive decline.

In 2008, we established an orthogeriatric service at our hospital, comprising pre- and postoperative care of hip fracture patients in the acute geriatric ward. We evaluated this model by a RCT in which hip fracture patients receiving usual care in the orthopedic ward comprised the control group. We hypothesized that the intervention could prevent delirium-associated long-term cognitive decline and, thus, chose cognitive function four months after surgery as the primary outcome.

Methods

Project context

In 2008, orthogeriatric care at Oslo University Hospital was reorganized and became a part of the acute geriatric ward. The new service had the capacity to serve approximately half of the patients admitted with hip fracture. The remaining patients were treated in the orthopedic ward. To evaluate the new model, we randomly allocated patients between the acute geriatric and the orthopedic wards. The first hip fracture patient was admitted to the acute geriatric ward in June 2008 and after a pilot period inclusion in the study started in September 2009. The recruitment ended in January 2012. The study protocol containing further information is published elsewhere [17].

Study design

We carried out a randomized, controlled, single-blind trial comparing pre- and postoperative orthogeriatric care integrated in the acute geriatric ward to usual care in the orthopedic ward. Inclusion and randomization took place in the emergency department, overseen by the duty orthopedic surgeon. Allocation was by sealed, opaque, numbered envelopes. Randomization was based on computer-generated random numbers (blocks of variable and unknown size) and was carried out by a statistician (ES) not involved in the clinical service. Randomization was stratified according to whether or not the patients were admitted from nursing homes. Included patients were transferred directly from the emergency department to the allocated ward, and had their entire hospital stay in the same ward except for time in the operating theater and a few hours in the postoperative care unit. Operative and anesthetic procedures were the same in the two groups.

Study participants

All patients admitted acutely to Oslo University Hospital with a hip fracture (a femoral neck fracture, a trochanteric or a sub-trochanteric fracture) were eligible for inclusion. Patients were excluded if the hip fracture was a part of a high energy trauma (defined as a fall from higher than one meter) or if they were moribund on admission.

Intervention and control

Patients randomized to intervention were treated in the acute geriatric ward (Table 1). This was a 20 bed ward, mainly admitting patients suffering from acute medical disorders superimposed upon frailty, co-morbidities and polypharmacy. The only surgical patients treated in the ward were the hip fracture patients included in the trial. On average during the inclusion period, two to four beds were used for hip fracture patients. The acute geriatric ward was regularly full or over-crowded. To avoid randomization violation, the ward was instructed to admit included hip fracture patients even if the ward was full. Thus, some hip fracture patients had to be treated in the corridor until a room was available, usually within the first 24 hours.

A key element of the intervention was a Comprehensive Geriatric Assessment (CGA) as a basis for treatment planning. All team members (geriatrician, nurse, physiotherapist and occupational therapist) were expected to assess patients during their first day on the ward, and the team had daily meetings to co-ordinate treatment and to

Table 1 Organization of treatment in the acute geriatric ward and the orthopedic ward

Description of ward	Acute geriatric ward	Orthopedic ward
Department	Clinic of Internal Medicine, Department of Geriatrics	Department of Orthopedic Surgery
Number of beds	20	52
Average number of beds occupied	101%	90%[a]
Organization of ward	Hip fracture patients spread among other medical patients	Hip fracture patients spread among other surgical patients
Staff-order (number per bed)		
- nurses	1	1.18
- nursing assistants	0.28	0.06
- physiotherapists	0.08	0.07
- occupational therapists	0.07	0
- nutritionists	available on request	0
- social worker	available on request	0.02
Interdisciplinary meetings	Daily	No
Intervention after discharge	Patients offered control at orthopedic outpatient clinic four months after surgery	Patients offered control at orthopedic outpatient clinic four months after surgery

[a]For the orthopedic ward, only figures from 2011 were available.

plan discharge. Clinical routines were developed based on a literature search, experience from earlier orthogeriatric models and the pilot phase prior to the start of randomization. Checklists were printed out and made immediately available for the treatment team for each patient. Details about the clinical routines have been published [17] and included medication reviews, early and intensive mobilization, optimizing pre- and postoperative nutrition and early discharge planning.

The control group was treated in the orthopedic ward, a 52 bed ward admitting a range of elective and non-elective orthopedic patients. The staff-patient ratio was similar to that of the acute geriatric ward (Table 1). There were, however, no multidisciplinary meetings and no geriatric assessments. Early mobilization was emphasized, and hip fracture patients were seen by a physiotherapist soon after surgery. The postoperative care unit was within the orthopedic ward, where all patients (including those allocated to intervention) were observed after surgery.

All patients included in the trial were offered a control in the orthopedic outpatient clinic four months after surgery. There was no additional intervention after discharge from hospital.

Measurements

Social and demographic information was collected during the acute stay. Information regarding surgical and anesthetic procedures, medical diagnoses (Charlson comorbidity index [18]), drug use and complications was also collected. Proxies were interviewed regarding pre-fracture Activities of Daily Living (Barthel ADL Index (BADL [19]) and Nottingham Extended ADL Index (NEADL [20])) and cognitive function (Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE [21])). Estimated height was derived using knee-heel length [22] and the patients were weighed using a chair scale. Mobilization after surgery was used as a process measure, recorded on day two post-surgery from case notes and observations. From September 2011, mobility was recorded with the activPAL™ body-worn sensor system [23]. The sensor was attached on the anterior aspect of the non-affected thigh as soon as possible after surgery and worn until discharge.

All patients were screened once daily for delirium using the Confusion Assessment Method (CAM) [24] preoperatively and until the fifth postoperative day (all) or until discharge (delirious patients). The study geriatrician or a study nurse completed all the assessments. If the nurse was unsure about the diagnosis, the study geriatrician was consulted. The CAM score was based on information from nurses, close relatives and hospital records related to the preceding 24 hours, in combination with a 10 to 30 minute interview with the patient. Tests of cognition, attention and alertness included the digit span test (forward and backward), orientation and delayed recall (from the Memorial Delirium Assessment Scale (MDAS) [25]). Delirium severity was measured with MDAS. Patients were assessed regularly on weekdays, but staff members who had been working during weekends were interviewed every Monday, and the case notes scrutinized in order to ascertain potential episodes of delirium. The mean number of delirium assessments during the stay was 5.7 (SD 2.7).

Follow up visits were carried out four and twelve months after surgery (with a time window of ± three weeks) by study nurses blind to allocation and to all clinical data

during the original hospital stay. The patients were assessed in their current place of residence. Each visit typically lasted for two to three hours, and the evaluators started the assessment with the cognitive tests of the primary outcome.

At each follow-up visit, proxies were interviewed regarding physical (ADL) and cognitive function, using the same scoring systems as during the index stay. Mobility at the follow-up visits was assessed with the short physical performance battery (SPPB) [26]. Weight at follow-up was assessed using a standing scale that was calibrated to the chair scale used during hospital stay. Patients and proxies were asked about any hospital readmissions since surgery.

One specialist in geriatric medicine (TBW) and one specialist in old age psychiatry (KE) independently assessed whether the patients fulfilled the International Classification of Diseases, version 10 (ICD-10) criteria for dementia at baseline and 12 months after surgery. The assessors had access to all clinical data, but were blinded to allocation and delirium status during hospital stay. The inter-rater agreement upon the dementia diagnosis was satisfactory (kappa 0.87 at baseline and 0.83 at 12 months); disagreements were resolved through discussion.

Primary outcome

The primary outcome was cognitive function four months after surgery, which was expected to show a wide range of severity from severe dementia to no cognitive impairment. To be able to measure differences in both the higher and the lower spectrum of cognitive function, we combined two scales:

– The 10 words test from the Consortium to Establish a Registry for Alzheimer's disease battery (CERAD) [27]. In this memory test patients are asked to recall 10 words after having them presented orally or visually. We used the immediate and delayed recall tasks of the test. This test is shown to be sensitive for memory changes in persons with good cognitive functioning [28].

– The Clinical Dementia Rating scale (CDR [29]). CDR is based on information from the best available sources as a combination of patient and proxy information and is sensitive for cognitive changes in patients with dementia. We used the 'sum of boxes' scoring adding up to a sum score ranging from zero (no dementia symptoms) to 18 (severe dementia). In most studies the sum score is shown to correlate highly with the original categorical score of zero to three [30].

To construct the combined outcome measure, we normalized these scales into a 0 to 100 scoring (CDR had to be reversed since it is scaled in the opposite direction). The CDR carried a 50% weighting, and the immediate and delayed recall parts of the 10 word test each contributed 25% in the combined measure. Thus, a higher score on the primary outcome indicated better cognitive performance.

Secondary outcomes

Secondary outcomes included preoperative delirium, delirium severity, length of stay, mortality, mobility, place of residence, ADL function and weight changes at the follow up controls. CDR and the 10 words test were analyzed separately, in addition to other measures of cognition (Mini-mental state examination (MMSE) [31], clock drawing test [32], IQCODE).

Statistical analyses

No pre-trial data were available to carry out precise power estimates. Based upon previous experience with the CDR, we judged 300 patients to be sufficient to detect clinically meaningful differences [30]. As 20% of hip fracture patients can be expected to die within four months of surgery, we aimed to randomize 370 patients. Recruitment ended after randomization of 332 patients due to resource constraints.

A statistical analysis plan (SAP) was developed (and published online) prior to un-blinding of the data [33]. The primary analysis was carried out blind to allocation by the study statistician (ES).

The primary analysis was carried out as a modified intention-to-treat analysis including patients with CDR and a complete 10-word test at the four-month control. Two patients were sent to the ward opposite to randomization allocation, and these patients were analyzed according to the group in which they were treated (Figure 1). Three moribund patients (two randomized to the acute geriatric ward and one to the orthopedic ward) were recruited in error, and were excluded from the primary analysis.

The primary outcome was not normally distributed but the sample size was large and parametric methods could therefore be applied. To adjust for any inequality in the distribution of important prognostic variables between the intervention and control group, we performed a linear regression with the primary outcome as the dependent variable, and variables with known or believed influence on the outcome were included in the model in a stepwise manner, in addition to the randomization group. If their introduction to the model changed the effect estimate for the randomization variable by 10% or more, they were included in the final model. Variables were removed by stepwise backwards elimination until the final model was reached. Age (negatively skewed) and waiting time to surgery (positively skewed) had non-normal distributions, and were squared and log transformed, respectively, to achieve better fit of the model. Secondary outcomes were analyzed by the Mann–Whitney test, t-tests and Chi-square tests depending on data distribution. Pre-planned subgroup analyses were carried out in patients admitted from nursing homes, and in patients with and without pre-fracture dementia.

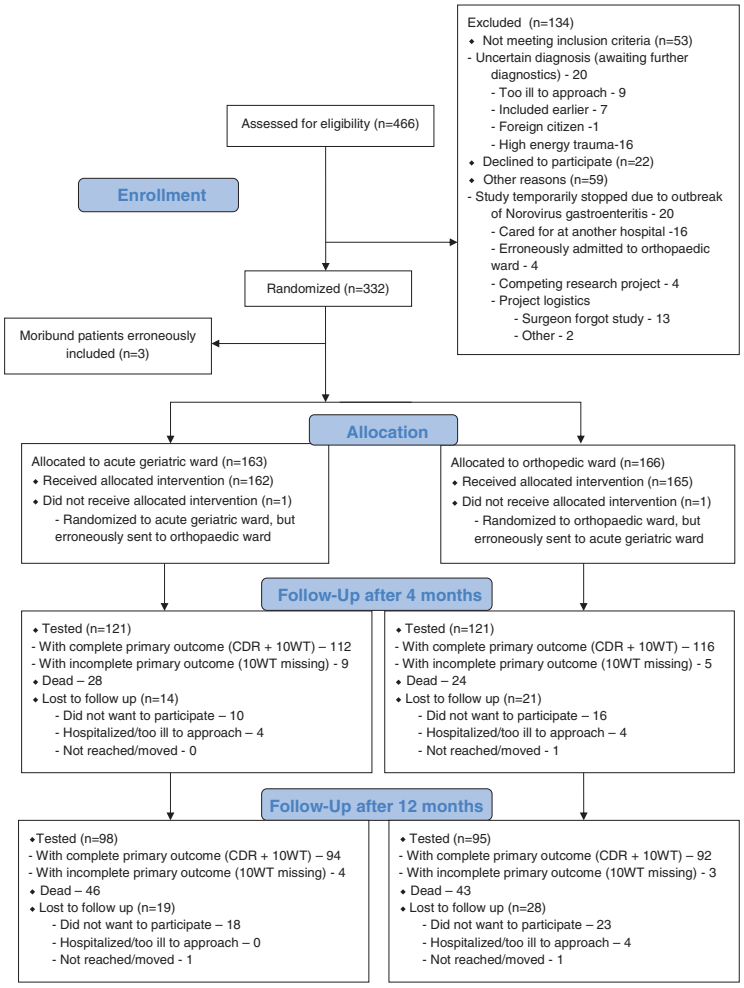


Figure 1 CONSORT flow diagram. CDR, Clinical Dementia Rating; 10 WT, 10 word test (from CERAD, Consortium to Establish a Registry for Alzheimer's Disease).

All statistical analyses were performed using IBM SPSS Statistics version 20, except for median differences and corresponding 95% confidence intervals that were estimated by the Hodges Lehmann estimator using StatXact 8.0.

Sensitivity analyses

As a sensitivity analysis we analyzed the primary outcome with the non-parametric Mann–Whitney test. We also carried out sensitivity analyses including the three moribund patients who were erroneously recruited, and a strict intention to treat analysis with all patients analyzed according to allocation. Missing values for the primary outcome were imputed in different ways in order to explore their potential influence on the results:

– if a patient had the combined outcome available after twelve but not four months, those values were imputed in the four-month dataset (ten patients).
– imputation of the worst possible score for all patients who had died.
– imputation of the worst possible score for all missing patients.
– imputation of the mean score for the randomization group the patient belonged to for all missing patients.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from the patients or substitute decision-makers if patients did not have capacity to consent. The study was approved by the Regional Committee for Ethics in Medical Research in Norway (REK S-09169a) and the Data Protection Officer at Oslo University Hospital (Ref. 1361).

Results

Between 17 September 2009 and 5 January 2012, 446 patients were assessed for eligibility and 332 were included (Figure 1). Non-included patients were younger than included patients (median 81 versus 85 years; $P \leq 0.001$) and more were men (35.3% versus 25.1%, $P = 0.01$). Half of the included patients at baseline were considered to have dementia, and one third were living in nursing homes. Patients randomized to the intervention group and the control group were well matched in all important baseline variables (Table 2). In total, 35 patients (11%) were lost to follow up at four months, 14 from the intervention group and 21 from the control group ($P = 0.23$). Of patients lost to the four month follow up, only 2 (7%) were living in a nursing home before the fracture, compared to 73 (30%) patients who were followed-up ($P = 0.002$). Patients lost to follow up were younger (median age 83 versus 85, $P = 0.19$) and fewer were considered to have dementia before the fracture (12/35 (34%) versus 112/242 (46%), $P = 0.18$); however, these differences were not significant. The final twelve month follow up was completed in December 2012.

Impact of intervention during hospital stay

There was no difference in delirium rates between the intervention and control groups (49% versus 53%, $P = 0.51$) (Table 3). There was also no difference in delirium duration (median three versus four days, $P = 0.85$) or delirium severity measured with MDAS (median 21.5 versus 20, $P = 0.44$). Fewer patients treated in the acute geriatric ward were discharged with ongoing delirium (15% versus 26%, $P = 0.01$).

The median length of stay was three days longer in the intervention group (median eleven versus eight days, $P \leq 0.001$). Patients in the intervention group had a longer waiting time for surgery, but this difference was not statistically significant (median 26 versus 24 hours, $P = 0.54$).

There was a trend to greater mobilization in the intervention group on the second day after surgery (86% versus 80%). In 46 patients, mobilization after surgery was assessed with activPAL™ activity sensors. During the first five days after surgery, the patients were mobilized for a longer time in the standing or stepping position in the intervention group (median 29 minutes versus 17 minutes).

Table 2 Baseline characteristics

Characteristics	Acute geriatric ward (number = 163)	Orthopedic ward (number = 166)
Age, median (range)	84 (55 to 99)	85 (46 to 101)
Male (%)	42 (26)	38 (23)
IQCODE >3.44 (%)[a]	93 (58)	91 (58)
Dementia, expert opinion (%)[b]	80 (49)	82 (49)
BADL, median (IQR)[c]	18 (13 to 20)	18 (15 to 20)
NEADL, median (IQR)[d]	28 (9 to 52)	30.5 (12 to 52)
APACHE II score, mean (SD)	9.5 (2.8)	9.3 (2.7)
CCI, median (IQR)	1 (0 to 2)	1 (0 to 2)
Number of medications used regularly, median (IQR)	5 (2 to 7)	4 (2 to 6)
BMI, mean (SD)[e]	24.4 (4)	24.4 (4.6)
Living in an institution (%)	52 (32)	50 (30)
Type of fracture (%):		
- Femoral neck	98 (60)	97 (58)
- Intertrochanteric	64 (39)	67 (40)
- Subtrochanteric	1 (1)	2 (1)
Type of surgery (%):		
- Hemiarthroplasty	74 (45)	71 (43)
- Osteosynthesis	88 (54)	91 (55)
- Total hip replacement	0 (0)	1(1)
- Girdlestone	1 (1)	0 (0)
- Not operated	0 (0)	3 (2)
Type of anesthesia (%)		
- General	8 (5)	14 (9)
- Spinal	147 (94)	143 (91)
- Epidural	2 (1)	0 (0)
Injury occurred indoors (%)	136 (84)	139 (84)

[a]IQCODE was missing in two patients from the acute geriatric ward and in eight patients from the orthopedic ward; [b]based upon consensus in an expert panel (TBW and KE); [c]Barthel ADL was missing in one patient from the acute geriatric ward and three patients from the orthopedic ward; [d]NEADL was missing in four patients from the acute geriatric ward and in two patients from the orthopedic ward; [e]BMI was missing in 30 patients from the acute geriatric ward and in 69 patients from the orthopedic ward. APACHE II, Acute Physiology and Chronic Health Evaluation II; BADL, Barthel Activities of Daily Living; BMI, body mass index; CCI, Charlson Comorbidity Index score; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; IQR, interquartile range; NEADL, Nottingham Extended ADL Index.

Primary outcome - cognitive function four months after surgery

The primary outcome could be computed in 228 patients and there was no significant difference between patients treated in the acute geriatric ward and the orthopedic ward after four months (mean 54.7 versus 52.9, 95% confidence interval for the difference −5.9 to 9.5; $P = 0.65$) (Table 4). There was also no difference in the combined outcome after twelve months (mean 51.0 versus 49.1, 95% confidence interval for the difference −7.7 to 11.4; $P = 0.69$).

Table 3 Impact of intervention during hospital stay

Variable	Acute geriatric ward (number = 163)	Orthopedic ward (number = 166)	*P*-value
Delirium any time during hospital stay (%)[a]	80 (49)	86 (53)	0.51
Pre-operative delirium (%)[b]	47 (31)	50 (35)	0.41
Delirium severity MDAS, median (IQR)[c]	21.5 (15.3 to 25)	20 (13.8 to 26)	0.44
Delirium duration in days, median (IQR)[d]	3 (2 to 7)	4 (2 to 6)	0.85
Discharged with ongoing delirium (%)	24 (15)	43 (26)	0.01
Waiting time for surgery in hours, median (IQR)[e]	26.2 (15.9 to 42.7)	23.9 (16.5 to 38.1)	0.54
Length of stay in days, median (IQR)	11 (8 to 15)	8 (4.8 to 11)	≤ 0.001
Medical complications, any	72 (44)	76 (46)	0.82
- Cardiac complications	22 (14)	19 (11)	0.58
- Cerebral complications	2 (1)	0 (0)	0.25
- Thrombo-embolic complications	2 (1)	0 (0)	0.25
- Pulmonary complications	21 (13)	13 (8)	0.15
- Renal failure	6 (4)	2 (1)	0.18
- Urinary tract infections	26 (16)	41 (25)	0.05
- Pressure ulcer	3 (2)	8 (5)	0.22
- Gastro-intestinal complications	5 (3)	4 (2)	0.75
Surgical complications, any	4 (3)	6 (4)	0.75
- surgical site infection	1 (1)	1 (1)	1
- wound problem	2 (1)	4 (2)	0.69
- osteosynthesis failure	1 (1)	0 (0)	1
- dislocation of prosthesis	0 (0)	1 (1)	0.5
Fall (%)	14 (9)	11 (7)	0.5
In-hospital mortality (%)	6 (4)	3(2)	0.21
Mobilized out of bed the second day after surgery (%)[f]	139 (86)	119 (80)	0.13
Time mobilized in standing or stepping position the first five days after surgery in minutes, median (IQR)[g]	29.3 (10.8 to 42.7)	16.8 (4.3 to 68.2)	0.24

[a]Delirium status defined by CAM. CAM was missing in four patients from the orthopedic ward; [b]preoperative delirium status unknown in nine patients from the acute geriatric ward and in 23 patients from the orthopedic ward; [c]highest MDAS in patients with delirium. MDAS was missing in four patients in the acute geriatric ward and in eight patients from the orthopedic ward; [d]number of days from first to last positive CAM; [e]time from admission to start of anesthesia. Three patients from the orthopedic ward did not undergo surgery; [f]missing in two patients from the acute geriatric ward and in 17 patients from the orthopedic ward; [g]masured with activPAL™ in 22 patients from the acute geriatric ward and in 24 patients from the orthopedic ward. CAM, Confusion Assessment Method; IQR, interquartile range; MDAS, Memorial Delirium Assessment Scale.

The Mann–Whitney test gave essentially the same results as the t-test at four and twelve months. A linear regression with the primary outcome as the dependent variable (Table 5) identified four significant predictors associated with poorer score: if the patient was admitted from a nursing home, IQCODE at baseline above 3.44, older age, and delirium during the hospital stay.

Secondary outcomes and subgroup analyses

Patients treated in the acute geriatric ward performed better on all cognitive measures; CERAD immediate recall (median 12.5 versus 11.5) and delayed recall (median 3 versus 2) , approved clock drawing test (49% versus 40%), MMSE (median 24 versus 23) and CDR (1.5 versus 2.5). They also had better ADL function measured with the BADL Index (median 17 versus 16) and NEADL (median 26.5 versus 22). None of these differences were, however, statistically significant.

Patients randomized to the acute geriatric ward had better mobility four months after surgery, measured with SPPB (median 4 versus 3, 95% confidence interval for the median difference 0 to 2; $P = 0.13$) (Table 4). This difference was statistically significant in the pre-specified subgroup analysis restricted to patients living in their own home before the fracture (median 6 versus 4, 95% confidence interval for the median difference 0 to 2; $P = 0.04$). Subgroup analyses stratified according to pre-fracture dementia status and nursing home residence gave no other significant

Table 4 Impact of intervention four and twelve months after surgery

Outcome	Four months follow up		*P*-value	Twelve months follow up		*P*-value
	Acute geriatric ward (n = 121)	Orthopedic ward (n = 121)		Acute geriatric ward (n = 98)	Orthopedic ward (n = 95)	
Primary outcome, mean (SD)[a]	54.7 (30.3)	52.9 (29.1)	0.65	51.0 (33.4)	49.1 (32.3)	0.69
CERAD 10 word test, median (IQR)						
- immediate recall,	12.5 (6 to 17)	11.5 (5.3 to 18)	0.77	11.5 (5 to 18)	11 (5 to 17.8)	0.89
- delayed recall	3 (0 to 6)	2 (0 to 5)	0.35	3 (0 to 6)	2.5 (0 to 5)	0.41
- recognition	18 (13.4 to 19)	17.5 (13 to 19.8)	0.93	17 (11 to 20)	17 (12 to 20)	0.93
CDR sum of boxes, median (IQR)	1.5 (0 to 9)	2.5 (0 to 9.5)	0.39	1.75 (0 to 14)	2.5 (0 to 14)	0.52
MMSE, median (IQR)[b]	24 (16 to 28)	23 (16 to 27)	0.28	24 (16.3 to 27)	22 (13.3 to 26)	0.34
Approved clock drawing test (%)[c]	48 (49)	42 (40)	0.20	39 (46)	28 (35)	0.12
NEADL, median (IQR)[d]	26.5 (7.8 to 50.3)	22 (9 to 46.5)	0.85	25 (8.8 to 51)	18 (10 to 47)	0.65
BADL, median (IQR)[e]	17 (10 to 20)	16 (12 to 20)	0.80	17 (9.5 to 19)	16 (11 to 19)	0.44
SPPB, median (IQR)[f]	4 (1 to 8)	3 (1 to 6)	0.13	3 (1 to 7)	3 (1 to 6)	0.14
IQCODE, median (IQR)[g]	3 (3 to 3.25)	3 (3 to 3.19)	0.74	3.69 (3 to 5)	3.75 (3.13 to 4.94)	0.45
Weight change from index stay in kg, mean (SD)[h]	- 3.4 (4.3)	- 4.4 (5.0)	0.25	- 2.4 (6.3)	- 3.4 (7)	0.43
New nursing home admissions (%)	19 (16)	18 (15)	0.86	16 (16)	18 (19)	0.63
Incident dementia[i]				7 (7)	3 (3)	0.33
Re-admissions	21 (17)	21 (17)	0.95	32 (33)	33 (35)	0.76

[a]To construct the primary outcome, we normalized CDR and the 10 word test from CERAD into a 0 to 100 scoring (CDR had to be reversed since it is scaled in the opposite direction). CDR weighed 50% and the immediate and delayed recall parts of the 10 word test weighed 25% each in the combined measure. The primary outcome was missing in nine patients from the acute geriatric ward and five patients from the orthopedic ward at four months and in four patients from the acute geriatric and three from the orthopedic ward at twelve months; [b]MMSE was missing in 11 patients from the acute geriatric ward and in nine patients from the orthopedic ward at the four-month control and in six and three patients, respectively, at the 12-months control; [c] ≥ 4 points. Clock drawing test was missing in 23 patients from the acute geriatric ward and in 16 patients from the orthopedic ward at the four-month control and 14 and 14 patients, respectively, at the 12-month control; [d]NEADL was missing in seven patients from the acute geriatric ward and in eight from the orthopedic ward at the four-month control and in two patients from the orthopedic ward from the 12-month control; [e]Barthel ADL was missing in two patients from the acute geriatric ward and in one from the orthopedic ward at four months and in one and two patients, respectively, at the 12-month control; [f]SPPB was missing in seven patients from the acute geriatric ward and two from the orthopedic ward at four months and in five and three patients, respectively, at the 12-month control; [g]a modified version of IQCODE was used at the four-month control; instead of asking for changes in the last 10 years, we asked for changes since just before the hip fracture. At the 12-month control we used the regular IQCODE. This was missing in two patients from the acute geriatric ward and three from the orthopedic ward at the four-month control and in three and four patients, respectively, at the 12-month control; [h]weight was missing in 33 patients from the acute geriatric ward and 29 patients from the orthopedic ward at the four-month control and in 19 and 22 patients, respectively, at the 12-month control; [i]based upon consensus in an expert panel (TBW and KE). BADL, Barthel Activities of Daily Living; CDR, The Clinical Dementia Rating scale; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; IQR, interquartile range; MMSE, Mini Mental State Examination; NEADL, Nottingham Extended ADL Index; SD, standard deviation; SPPB, Short Physcial Performance Battery.

differences, except that patients from nursing homes randomized to intervention were more often mobilized the second day after surgery (Additional files 1, 2 and 3).

Twenty-eight (17%) patients treated in the acute geriatric ward and 24 (15%) treated in the orthopedic ward were dead four months after the surgery ($P = 0.50$). In both groups, 21% of the patients were readmitted during the first four months after surgery. The results at the 12-month follow up were similar to those after four months.

Sensitivity analyses

Several sensitivity analyses were performed and they showed no substantial differences from the primary analysis.

Discussion

In this randomized controlled trial of patients with hip fracture, we found no evidence that cognitive function four months after surgery was improved in patients treated pre- and postoperatively in an acute geriatric ward, compared to usual care in an orthopedic ward. Delirium rates were equally high in both groups. There was, however, a trend that the intervention had a positive effect on mobility.

Strength and weaknesses

The main strength of this study was the randomized controlled design with blinded outcome assessments. Also, the inclusion of process measures, such as objective mobilization scores, confirms that the intervention was being delivered as intended. The inclusion of patients from nursing homes and those with dementia enhances generalizability as such patients are frequently excluded from trials [34]. On the other hand, nursing home patients are so frail and cognitively impaired that they may be unlikely to benefit from the intervention. To assess the efficacy in such patients, other outcomes than those we chose might be more feasible [35]. The combined

Table 5 Multiple linear regression model with the primary outcome at the four-month follow up control as the dependent variable (number = 228)

Variable	Unadjusted coefficients (95% CI)	*P*-value	Adjusted coefficients (95% CI)	*P*-value
Randomization group (reference: orthopedic ward)	1.8 (−5.9 to 9.5)	0.65	−2.5 (−7.1 to 2.2)	0.29
Admitted from nursing home	−44.5 (−50.8 to −38.2)	≤0.001	−25.0 (−31.1 to −18.8)	≤0.001
Age[a]	−0.006 (−0.009 to −0.004)	≤0.001	−0.002 (−0.003 to 0.000)	0.03
Gender (reference: male)	6.94 (−2.4 to 16.3)	0.14		
Delirium during hospital stay[b]	−31.7 (−38.3 to −25.0)	≤0.001	−11.7 (−17.1 to −6.3)	≤0.001
Number of years of higher education[c]	2.17 (−0.19 to 4.16)	0.03		
IQCODE >3.44[d]	−42.3 (−47.9 to 36.7)	≤0.001	−23.4 (−29.4 to −17.5)	≤0.001
Preoperative waiting time[e]	1.93 (−4.0 to 7.85)	0.52		
APACHE II	−0.78 (−2.2 to 0.66)	0.29		

R = 0.82. [a]Age squared; [b]number = 226; [c]number = 203; [d]IQCODE obtained during hospital stay (number = 222); [e]natural logarithm of preoperative waiting time. APACHE II, Acute Physiology and Chronic Health Evaluation II; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly.

outcome measure was designed to measure cognition in patients representing a broad spectrum of cognitive function and was based upon well-validated components. However, the scale combination has not been validated and, thus, we cannot be sure that it was sensitive to the intervention. As with all service evaluations, blinding of assessments during hospital stay was impossible and may have introduced bias.

Inclusion was terminated before the intended sample size aim was reached. However, as there were few differences between the groups in any of the secondary cognitive outcomes, and sub-group analyses also failed to show any substantial differences, it is reasonable to conclude that this intervention had no effect on cognition.

Comparison with other studies

The impact of orthogeriatric intervention on long-term cognitive function has not previously been assessed. Several studies have demonstrated that orthogeriatric care can prevent delirium in hip fracture patients. A recently published non-randomized controlled trial from Belgium [15] showed that an intervention provided by an inpatient geriatric consultation team was effective in reducing the incidence of delirium (37.2% versus 53.2%, $P = 0.04$), in keeping with a similar American RCT [16]. In both the American and the Belgian studies, all patients received standard treatment from the orthopedic team, whereas in our model orthopedic treatment (besides surgery) was limited to consultation service. A possible explanation for the lack of effect of our model could, therefore, be limited access to orthopedic expertise.

Few studies have compared pre- and postoperative intervention provided in a geriatric ward with usual care in an orthopedic ward. In comparison with usual care, such models have shown promising results, but cognition has seldom been assessed [5,6]. To our knowledge, the only RCT evaluating a geriatrician-led fracture service (were geriatricians have the primary responsibility for the patients) is a Swedish study [36]. Although no preoperative intervention was included, the study showed that significantly more patients allocated to intervention regained independence in personal ADL performance at four and twelve months after surgery. The model was also effective in preventing postoperative delirium and reducing delirium duration [14]. In spite of the fact that we also included preoperative intervention, we were not able to prevent delirium. A likely explanation is that usual care was better in our study since the delirium rates both in the intervention and the control group were lower than in the Swedish study. The orthopedic ward in our study provided a short waiting time for surgery, similar staffing as in the geriatric ward, personnel with earlier experience with orthogeriatric models and delirium prevention, physiotherapy for most hip fracture patients, and an integrated post-operative care unit.

Orthogeriatric intervention is often reported to reduce waiting time for surgery (see Liem [37] for an overview). In our study, however, the waiting time for surgery was two hours longer in the intervention group. Both the intervention (26 hours) and the control group (24 hours) waited, however, for a short time compared to other orthogeriatric studies reporting a waiting time of two to three days and even longer [38-42], indicating that the control group received a good quality service.

Mobility has been assessed in several studies, but mostly by questionnaire. Some, but not all, studies have found that orthogeriatric services provide better mobility [36,40,43,44]. In our study there was an overall trend that patients treated in the intervention group performed better at SPPB four months after surgery, and the difference was statistically significant in those living in their own homes before surgery. A difference on SPPB of 0.5 is considered clinically meaningful, and the effect seen in our study (six versus four points) is likely to be important and should be further explored in future studies.

Interpretation of the results

Despite our comprehensive intervention, the effect on the primary outcome was limited. There are several possible explanations for this. First, the choice of cognitive function as the primary outcome may have been too ambitious. For the intervention to be effective in this regard, two pre-suppositions had to be true. First, the orthogeriatric intervention had to be effective in reducing delirium. However, our intervention failed to prevent delirium or reduce delirium severity. This might be explained by the good quality of usual care at the orthopedic ward in our hospital, combined with sub-optimal circumstances in an often over-crowded acute geriatric ward.

Secondly, the primary outcome assumes that delirium lies on the causal pathway towards the development of dementia. Since delirium usually occurs in relation to acute illness, it is challenging to design studies that can address this question, but some evidence exits suggesting that delirium is associated with long term cognitive decline [13,45,46]. Our study is in keeping with this; the regression analysis showed that delirium was associated with a poorer score on the primary outcome, also when adjusting for potential confounders.

The study may have influenced treatment in the control group. The patients in the orthopedic ward were assessed daily, and in order to make a precise delirium diagnosis personnel in the orthopedic ward were interviewed regarding the patients cognitive status. This inevitably raised the awareness of delirium in the orthopedic ward.

Conclusions

This randomized controlled trial of hip fracture patients found no evidence that cognitive function four months after surgery was improved in patients treated with pre- and postoperative orthogeriatric care provided in an acute geriatric ward, compared to usual care in an orthopedic ward. The intervention had a positive effect on mobility in patients not admitted from nursing homes. Delirium had a strong negative impact on long-term cognitive performance, and delirium prevention and treatment should be given high priority in orthogeriatric care. For further orthogeriatric improvements, we recommend a model with stronger integration of orthopedic and geriatric input than we achieved, in line with recommendations from recent reviews [5,7].

Additional files

Additional file 1: Impact of intervention during hospital stay. Patients stratified according to prefracture residential status (1a) and dementia status (1b).

Additional file 2: Impact of intervention four months after surgery. Patients stratified according to prefracture residential status (2a) and dementia status (2b).

Additional file 3: Impact of intervention 12 months after surgery. Patients stratified according to prefracture residential status (3a) and dementia status (3b).

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TBW initiated the study, led the work on the study design and was involved in analyzing and interpreting the data. TBW is the manuscript's guarantor. LOW had the daily responsibility for running the study and collecting data. LOW was also involved in planning of the study, has analyzed and interpreted the data and drafted the manuscript. ACT had particular responsibility for collecting nutritional data and was involved in planning the study. FF and GH had the primary responsibility to remind and motivate the orthopedic surgeons to include patients in the study. KE participated in all aspects of the planning, in particular regarding the cognitive outcomes. ES carried out the randomization procedure and was extensively involved in the statistical planning and analyses. Together with LOW and TBW, she wrote the statistical analysis plan. FF, VJ, IS, JR, ES and SC all made important contributions to the planning of the study and writing the protocol. All authors participated in critical revision of the article for intellectual content. All authors read and approved the final version of the manuscript.

Acknowledgments

The authors would like to thank the patients and staff at the Orthopedic Department and the Geriatric Department at Oslo University Hospital. They also thank research nurses Elisabeth Fragaat, Tone Fredriksen, Camilla Marie Andersen, Julie Ask Ottesen and Linda Feldt for assisting in data collection. The manuscript's guarantor affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding

The Oslo Orthogeriatric Trial was mainly funded by the Research Council of Norway through the program 'Improving mental health of older people through multidisciplinary efforts' (grant no. 187980/H10). Further, we have received funding from Oslo University Hospital, The Sophies Minde Foundation, The Norwegian Association for Public Health and Civitan's Research Foundation. The sponsors had no role in the design, methods, subject recruitment, data collection, analysis or preparation of the manuscript.

Author details

[1]Oslo Delirium Research Group, Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway. [2]University of Oslo, Institute of Clinical Medicine, Oslo, Norway. [3]Department of General Internal Medicine, Oslo University Hospital, Oslo, Norway. [4]Department of Cardiovascular Sciences, University of Leicester School of Medicine, Leicester, UK. [5]Norwegian Centre for Ageing and Health, Vestfold Mental Health Trust, Vestfold, Norway. [6]Department of Orthopaedic Surgery, Oslo University Hospital, Oslo, Norway. [7]Department of Cardiology, Oslo University Hospital, Oslo, Norway. [8]Department of Anesthesiology, Oslo University Hospital, Oslo, Norway. [9]Department of Geriatrics, St. Olav Hospital, University Hospital of Trondheim, Trondheim, Norway. [10]Department of Neuroscience, Norwegian University of Science and Technology (NTNU), Trondheim, Norway. [11]School of Pharmacy, University of Oslo, Oslo, Norway.

Received: 28 January 2014 Accepted: 17 March 2014
Published: 15 April 2014

References

1. Rubenstein LZ, Josephson KR: **The epidemiology of falls and syncope.** *Clin Geriatr Med* 2002, **18:**141–158.
2. Tinetti ME, Kumar C: **The patient who falls: "It's always a trade-off".** *JAMA* 2010, **303:**258–266.
3. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jonsson B, Kanis JA: **Osteoporosis in the European**

Union: medical management, epidemiology and economic burden: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos* 2013, **8:**136.
4. Juliebo V, Bjoro K, Krogseth M, Skovlund E, Ranhoff AH, Wyller TB: **Risk factors for preoperative and postoperative delirium in elderly patients with hip fracture.** *J Am Geriatr Soc* 2009, **57:**1354–1361.
5. Kammerlander C, Roth T, Friedman S, Suhm N, Luger T, Kammerlander-Knauer U, Krappinger D, Blauth M: **Ortho-geriatric service: a literature review comparing different models.** *Osteoporos Int* 2010, **21:**637–646.
6. Giusti A, Barone A, Razzano M, Pizzonia M, Pioli G: **Optimal setting and care organization in the management of older adults with hip fracture.** *Eur J Phys Rehabil Med* 2011, **47:**281–296.
7. Grigoryan KV, Javedan H, Rudolph JL: **Orthogeriatric care models and outcomes in hip fracture patients: a systematic review and meta-analysis.** *J Orthop Trauma* 2014, **28:**e49–e55.
8. Buecking B, Timmesfeld N, Riem S, Bliemel C, Hartwig E, Friess T, Liener U, Ruchholtz S, Eschbach D: **Early orthogeriatric treatment of trauma in the elderly: a systematic review and metaanalysis.** *Dtsch Arztebl Int* 2013, **110:**255–262.
9. *Diagnostic and Statistical Manual of Mental Disorders.* Fifthth edition. Washington DC: American Psychiatric Association; 2013.
10. Bruce AJ, Ritchie CW, Blizard R, Lai R, Raven P: **The incidence of delirium associated with orthopedic surgery: a meta-analytic review.** *Int Psychogeriatr* 2007, **19:**197–214.
11. Inouye SK: **Predisposing and precipitating factors for delirium in hospitalized older patients.** *Dement Geriatr Cogn Disord* 1999, **10:**393–400.
12. de Jonghe A, van de Glind EM, van Munster BC, de Rooij SE: **Underrepresentation of patients with pre-existing cognitive impairment in pharmaceutical trials on prophylactic or therapeutic treatments for delirium: a systematic review.** *J Psychosom Res* 2014, **76:**193–199.
13. Krogseth M, Wyller TB, Engedal K, Juliebo V: **Delirium is an important predictor of incident dementia among elderly hip fracture patients.** *Dement Geriatr Cogn Disord* 2011, **31:**63–70.
14. Lundstrom M, Olofsson B, Stenvall M, Karlsson S, Nyberg L, Englund U, Borssen B, Svensson O, Gustafson Y: **Postoperative delirium in old patients with femoral neck fracture: a randomized intervention study.** *Aging Clin Exp Res* 2007, **19:**178–186.
15. Deschodt M, Braes T, Flamaing J, Detroyer E, Broos P, Haentjens P, Boonen S, Milisen K: **Preventing delirium in older adults with recent hip fracture through multidisciplinary geriatric consultation.** *J Am Geriatr Soc* 2012, **60:**733–739.
16. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM: **Reducing delirium after hip fracture: a randomized trial.** *J Am Geriatr Soc* 2001, **49:**516–522.
17. Wyller TB, Watne LO, Torbergsen A, Engedal K, Frihagen F, Juliebo V, Saltvedt I, Skovlund E, Raeder J, Conroy S: **The effect of a pre- and post-operative orthogeriatric service on cognitive function in patients with hip fracture. The protocol of the Oslo Orthogeriatrics Trial.** *BMC Geriatr* 2012, **12:**36.
18. Charlson ME, Pompei P, Ales KL, MacKenzie CR: **A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.** *J Chronic Dis* 1987, **40:**373–383.
19. Wade D: *Measurment in Neurological Rehabilitation.* Oxford: Oxford University Press; 1992.
20. Gladman JR, Lincoln NB, Adams SA: **Use of the extended ADL scale with stroke patients.** *Age Ageing* 1993, **22:**419–424.
21. Jorm AF: **A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation.** *Psychol Med* 1994, **24:**145–153.
22. Chumlea WC, Guo SS, Wholihan K, Cockram D, Kuczmarski RJ, Johnson CL: **Stature prediction equations for elderly non-Hispanic white, non-Hispanic black, and Mexican-American persons developed from NHANES III data.** *J Am Diet Assoc* 1998, **98:**137–142.
23. Grant PM, Ryan CG, Tigbe WW, Granat MH: **The validation of a novel activity monitor in the measurement of posture and motion during everyday activities.** *Br J Sports Med* 2006, **40:**992–997.
24. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI: **Clarifying confusion: the confusion assessment method. A new method for detection of delirium.** *Ann Intern Med* 1990, **113:**941–948.
25. Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S: **The Memorial Delirium Assessment Scale.** *J Pain Symptom Manage* 1997, **13:**128–137.
26. Guralnik JM, Ferrucci L, Pieper CF, Leveille SG, Markides KS, Ostir GV, Studenski S, Berkman LF, Wallace RB: **Lower extremity function and subsequent disability.** *J Gerontol A Biol Sci Med Sci* 2000, **55:**M221–M231.
27. Welsh KA, Butters N, Mohs RC, Beekly D, Edland S, Fillenbaum G, Heyman A: **The Consortium to Establish a Registry for Alzheimer's Disease (CERAD), Part V. A normative study of the neuropsychological battery.** *Neurology* 1994, **44:**609–614.
28. Karrasch M, Sinerva E, Gronholm P, Rinne J, Laine M: **CERAD test performances in amnestic mild cognitive impairment and Alzheimer's disease.** *Acta Neurol Scand* 2005, **111:**172–179.
29. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL: **A new clinical scale for the staging of dementia.** *Br J Psychiatry* 1982, **140:**566–572.
30. Barca ML, Engedal K, Laks J, Selbaek G: **A 12 months follow-up study of depression among nursing-home patients in Norway.** *J Affect Disord* 2010, **120:**141–148.
31. Folstein MF, Folstein SE, McHugh PR: **"Mini-mental state". A practical method for grading the cognitive state of patients for the clinician.** *J Psychiatr Res* 1975, **12:**189–198.
32. Shulman KI: **Clock-drawing: is it the ideal cognitive screening test?** *Int J Geriatr Psychiatry* 2000, **15:**548–561.
33. *Statistical analysis plan - the Oslo Orthogeriatric Study.* Available at: [http://www.med.uio.no/klinmed/forskning/grupper/klinisk-geriatrisk-forskning/dokumenter/statistical_analysis_plan_oslo_orthogeriatric_study_final.pdf]
34. Handoll HH, Cameron ID, Mak JC, Finnegan TP: **Multidisciplinary rehabilitation for older people with hip fractures.** *Cochrane Database Syst Rev* 2009, **4**, CD007125.
35. Goldberg SE, Bradshaw LE, Kearney FC, Russell C, Whittamore KH, Foster PE, Mamza J, Gladman JR, Jones RG, Lewis SA, Porock D, Harwood RH, Medical Crises in Older People Study Group: **Care in specialist medical and mental health unit compared with standard care for older people with cognitive impairment admitted to general hospital: randomised controlled trial (NIHR TEAM trial).** *BMJ* 2013, **347:**f4132.
36. Stenvall M, Olofsson B, Nyberg L, Lundstrom M, Gustafson Y: **Improved performance in activities of daily living and mobility after a multidisciplinary postoperative rehabilitation in older people with femoral neck fracture: a randomized controlled trial with 1-year follow-up.** *J Rehabil Med* 2007, **39:**232–238.
37. Liem IS, Kammerlander C, Suhm N, Blauth M, Roth T, Gosch M, Hoang-Kim A, Mendelson D, Zuckerman J, Leung F, Burton J, Moran C, Parker M, Giusti A, Pioli G, Goldhahn J, Kates SL, Investigation performed with the assistance of the AOTrauma Network: **Identifying a standard set of outcome parameters for the evaluation of orthogeriatric co-management for hip fractures.** *Injury* 2013, **44:**1403–1412.
38. Cogan L, Martin AJ, Kelly LA, Duggan J, Hynes D, Power D: **An audit of hip fracture services in the Mater Hospital Dublin 2001 compared with 2006.** *Ir J Med Sci* 2010, **179:**51–55.
39. Adunsky A, Arad M, Levi R, Blankstein A, Zeilig G, Mizrachi E: **Five-year experience with the Sheba model of comprehensive orthogeriatric care for elderly hip fracture patients.** *Disabil Rehabil* 2005, **27:**1123–1127.
40. Vidan M, Serra JA, Moreno C, Riquelme G, Ortiz J: **Efficacy of a comprehensive geriatric intervention in older patients hospitalized for hip fracture: a randomized, controlled trial.** *J Am Geriatr Soc* 2005, **53:**1476–1482.
41. Mazzola P, De Filippi F, Castoldi G, Galetti P, Zatti G, Annoni G: **A comparison between two co-managed geriatric programmes for hip fractured elderly patients.** *Aging Clin Exp Res* 2011, **23:**431–436.
42. Gonzalez-Montalvo JI, Alarcon T, Mauleon JL, Gil-Garay E, Gotor P, Martin-Vega A: **The orthogeriatric unit for acute patients: a new model of care that improves efficiency in the management of patients with hip fracture.** *Hip Int* 2010, **20:**229–235.
43. Shyu YI, Liang J, Wu CC, Su JY, Cheng HS, Chou SW, Chen MC, Yang CT: **Interdisciplinary intervention for hip fracture in older Taiwanese: benefits last for 1 year.** *J Gerontol A Biol Sci Med Sci* 2008, **63:**92–97.
44. Naglie G, Tansey C, Kirkland JL, Ogilvie-Harris DJ, Detsky AS, Etchells E, Tomlinson G, O'Rourke K, Goldlist B: **Interdisciplinary inpatient care for elderly people with hip fracture: a randomized controlled trial.** *CMAJ* 2002, **167:**25–32.

45. Davis DH, Terrera GM, Keage H, Rahkonen T, Oinas M, Matthews FE, Cunningham C, Polvikoski T, Sulkava R, MacLullich AM, Brayne C: **Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study.** *Brain* 2012, **135:**2809–2816.
46. Fong TG, Jones RN, Shi P, Marcantonio ER, Yap L, Rudolph JL, Yang FM, Kiely DK, Inouye SK: **Delirium accelerates cognitive decline in Alzheimer disease.** *Neurology* 2009, **72:**1570–1575.

doi:10.1186/1741-7015-12-63
Cite this article as: Watne *et al.*: The effect of a pre- and postoperative orthogeriatric service on cognitive function in patients with hip fracture: randomized controlled trial (Oslo Orthogeriatric Trial). *BMC Medicine* 2014 **12**:63.

III

IV