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A Real-life Prospective Cohort Study

Roope Jaatinen

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ABSTRACT

The aim of this study was to investigate new cognitive disorders and the significance of other related psychocognitive factors during hospital care and recovery after hip fracture in an older patient population.

The data for this study comprised hip fracture patients aged 65 years or more suffering their first hip fracture and treated in Seinäjoki Central Hospital between 2007 and 2019 (n=2,320). Data were collected on admission, during hospital care, in an outpatient comprehensive geriatric assessment (CGA) 4–6 months post-hip fracture and by telephone interviews after the index fracture.

New diagnosed cognitive disorder extracted manually from the electronic patient files was documented in almost one in four patients (23.3%). Cognitive disorders had usually advanced to a moderate to severe stage before diagnosis. Higher age, multiple comorbidities and malnutrition were associated with new cognitive disorders. The array of diagnoses did not differ from general occurrence as Alzheimer's disease with or without vascular cognitive impairment was the most common diagnosis. Delirium during acute hospital care was a significant predictor of an imminent diagnosis of a cognitive disorder.

Depressive mood assessed at the outpatient clinic was associated with poorer physical and cognitive performance, and also with malnutrition. Depressive mood was seldom severe. Fear of falling (FoF) was more common in female patients and in patients with multiple medications in regular use and moreover associated with poorer physical performance. Patients with pre-fracture cognitive disorders reported less FoF than those without. Neither depressive mood nor FoF explained the decreased mobility level, change to more supported living arrangements or mortality in one-year follow-up.

Previously undiagnosed cognitive disorders are common in older hip fracture patients. Delirium during hospital care is associated with development of subsequent new diagnoses of cognitive disorders. Depressive mood and FoF are common multifactorial conditions which deserve attention during recovery but do not explain the changes in outcomes one year after the hip fracture. There seems to be significant overlap and co-occurrence of psychocognitive factors in this remarkably heterogeneous population, and thus, CGA should be considered as a standardized protocol throughout the post-hip fracture pathway.

KEYWORDS: cognitive disorders, hip fracture, delirium, depressive mood, fear of falling

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TIIVISTELMÄ

Tutkimuksen tavoitteena oli tutkia lonkkamurtuman jälkeisessä seurannassa todettavia uusia muistisairauksia sekä muiden psykokognitiivisten tekijöiden merkitystä sairaalahoidon ja toipumisen aikana.

Aineisto koostui Seinäjoen keskussairaalassa vuosina 2007–2019 hoidetuista yli 65-vuotiaista lonkkamurtumapotilaista (n=2320). Tiedot kerättiin sairaalahoidon aikana, polikliinisessä kokonaisvaltaisessa geriatrisessa arvioinnissa (CGA) 4–6 kuukautta murtuman jälkeen, sekä puhelinhaastatteluilla.

Muistisairauteen sairastuminen oli yleistä toipumisen aikana. Sairauden vaihe oli yleensä ehtinyt edetä kohtalaiseen tai vakavaan vaikeusasteeseen ennen diagnoosia. Uutta muistisairautta ennusti korkeampi ikä, komorbiditeetit ja vajaaravitsemus. Todettujen muistisairausdiagnoosien kirjo ei poikennut yleisistä esiintyvyyksistä. Sairaalahoidon aikainen delirium oli selvästi yhteydessä uuteen muistisairauteen.

Depressiivistä mielialaa todettiin lähes joka kolmannella ja kaatumisen pelkoa lähes joka toisella potilaalla lonkkamurtuman jälkeisessä CGA:ssa. Depressiivinen mieliala oli yhteydessä huonompaan toiminnalliseen, fyysiseen ja kognitiiviseen suorituskykyyn, sekä vajaaravitsemukseen. Vaikeusasteeltaan depressiivinen mieliala oli harvoin vakavaa. Kaatumisen pelko oli yleisempää naisilla ja monilääkityillä. Kaatumisen pelko liittyi myös heikompaan fyysiseen suorituskykyyn. Potilaat, joilla oli todettu muistisairaus ennen lonkkamurtumaa, kokivat vähemmän kaatumisen pelkoa, kuin potilaat, joilla ei ollut todettua muistisairautta. Depressiivinen mieliala tai kaatumisenpelko eivät yksinään selittäneet heikentynyttä liikuntakykyä, muuttoa tuetumpaan asumismuotoon tai kuolleisuutta vuoden kuluttua murtumasta.

Aiemmin diagnosoimattomat muistisairaudet ovat yleisiä iäkkäillä lonkkamurtumapotilailla. Sairaalahoidon aikainen delirium on yhteydessä uusiin lonkkamurtuman jälkeen todettuihin muistisairauksiin. Depressiivinen mieliala ja kaatumisen pelko ovat yleisiä, monitekijäisiä ongelmia, jotka on syytä huomioida kuntoutumisen aikana, mutta eivät yksinään selitä tilannetta vuoden kuluttua murtumasta. Psykokognitiiviset tekijät voivat esiintyvät limittäin tai samanaikaisesti tässä hauraassa potilasryhmässä ja siksi lonkkamurtuman jälkeinen CGA olisi tärkeää saada osaksi standardoitua hoitopolkua.

AVAINSANAT: cognitive disorders, hip fracture, delirium, depressive mood, fear of falling

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Abbreviations

AD	Alzheimer's disease
ASA	American Society of Anesthesiology
BADL	Basic Activities of Daily Living
CAM	Confusion Assessment Method
CDR	Clinical Dementia Rating
CDT	Clock Drawing Test
CERAD	Consortium to Establish Registry for Alzheimer's disease
CGA	Comprehensive Geriatric Assessment
CI	Confidence interval
CNS	Central Nervous System
DSM	Diagnostic and Statistical Manual for Mental Disorders
DSN	Dynamic Symptom Network
EMS	Elderly Mobility Scale
FoF	Fear of Falling
FTLD	Frontotemporal Lobe Degeneration
GDS-15	15-item version of the Geriatric Depression Scale
HADS	Hospital Anxiety and Depression Scale
HR	Hazard Ratio
IADL	Instrumental Activities of Daily Living
ICD-10	International Classification of Diseases, 10th revision
LBD	Lewy Body Disease
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
MNA-SF	Short-form of the Mini-Nutritional Assessment
MCR	Motor Cognitive Risk syndrome
NDCD	New diagnosis of cognitive disorder
OR	Odds Ratio
PD	Parkinson's disease related dementia
TUG	Timed-Up and Go
VCI	Vascular Cognitive Impairment

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Jaatinen R, Luukkaala T, Viitanen M, Nuotio MS. Combining diagnostic memory clinic with rehabilitation follow-up after hip fracture. *Eur Geriatr Med.* 2020 Aug 11(4):603-611. doi: 10.1007/s41999-020-00334-x.

II Jaatinen R, Luukkaala T, Hongisto MT, Helminen H, Nuotio MS. In-hospital delirium as a prognostic factor for new cognitive disorder in a 1-year post-hip fracture follow-up. *Dement Geriatr Cogn Disord* 2021 Oct 3(50):296-302. doi: 10.1159/000518487

III Jaatinen R, Luukkaala T, Helminen H, Hongisto MT, Viitanen M, Nuotio MS. Prevalence and prognostic significance of depressive symptoms in a geriatric post-hip fracture assessment. *Aging Ment Health*. 2021 Nov 3:1-8. doi: 10.1080/13607863.2021.1998357.

IV Jaatinen R, Luukkaala T, Hongisto MT, Kujala MA, Nuotio MS. Factors associated with and 1-year outcomes of fear of falling in a geriatric post-hip fracture assessment. *Aging Clin Exp Res*. 2022 Jun 21. doi: 10.1007/s40520-022-02159-z.

1 Introduction

Cognitive disorders and falls are common, globally emerging issues due to an ageing population. According to the World Health Organization, the proportion of individuals aged 60 years or more will increase from 12% in 2016 to 22% in 2050 (1). The most rapid increase is expected in the oldest age groups: worldwide, the population aged 80 and over is projected to more than triple between 2015 and 2050 (2). Aging itself is a significant risk factor for both falls and cognitive disorders, and therefore, the prevalence of these is expected to rise in the coming years. However, aging is not uniform. Although chronological age is a well established predictor of mortality on population level, among individuals the effect of genetic, environmental and socioeconomic factors can be remarkable (3,4). Hip fractures may be counted as significant events that may have an impact on subsequent course of life (5).

Most hip fractures are caused by a fall which, in addition to traumatic injuries, also affects psychological wellbeing (6). Cognitive disorders and hip fractures are related to one another, especially in geriatric patients: a fall may be caused by an issue related to cognitive capability and cognitive decline can be hastened by serious trauma such as a hip fracture (7). Older patients are more susceptible to complicating conditions during rehabilitation, such as delirium, depressive mood or fear of falling (FoF), all of which are linked to cognitive disorders (8).

Colligation between cognitive disorders and falls has been the subject of much research. They share common causal pathways and risk factors leading to increased co-occurrence (7). Hip fracture patients may have a high prevalence of undiagnosed cognitive disorders, strengthening the suspicion that impairment in cognitive functions increases the risk for a fall to cause hip fracture (9). Yet little is known of the factors effecting new cognitive disorders after hip fracture. To the best of our knowledge, no studies have been carried out to distinguish the specific diagnoses of cognitive impairments after hip fracture. Moreover, the impact of delirium during hospitalization, depressive mood or fear of falling on rehabilitation outcomes and new cognitive disorders are not clear even though they are frequently observed simultaneously (10–12).

The unique features and complexity of health conditions in older people emphasize the role of a comprehensive assessment (13). In addition to the somatic

factors, patients' psychological and cognitive wellbeing should be acknowledged together with caregivers' point of view (13). Nutritional status has a substantial impact on the patient's health, and thus, requires recognition (14). Multimorbidity, and thus multiple medications for concurrent conditions can have unfavourable interactions which deserve attention (15). Early detection and reliable diagnosis of cognitive disorders and management of other psychocognitive factors are important to initiate beneficial treatment modalities for improved efficacy, functionality and quality of life (16,17). Bearing these factors in mind, geriatric expertise is important during the hospital care and rehabilitation process.

The aim of this study was to identify the new diagnoses of cognitive disorders (NDCD) after hip fracture and to understand the interaction and clinical significance of other related psychocognitive factors: delirium, depression and fear of falling (FoF) during the recovery period. We seek to elucidate the importance of comprehensive geriatric assessment (CGA) of hip fracture patients at the acute phase and during the rehabilitation process from a pragmatic point of view.

2 Review of the Literature

2.1 Hip fractures

2.1.1 Epidemiology

Hip fracture is a fracture of the proximal part of the femur (thighbone). The hip joint is a ball-and-socket synovial joint consisting of the head of the femur (ball) and the acetabulum of the pelvis (socket). Hip fractures are usually caused by a fall and are devastating sequelae of these, especially in frail older patients often with osteoporosis (18,19). Only 1% of falls lead to a hip fracture, but 90% of these fractures are related to a fall from standing height, i.e., a fragility fracture (20,21). A decrease in bone mass and increase in falls causes the strong association between age and the risk of hip fractures (22).

Risk of hip fracture has a tenfold range worldwide, while the age-standardized incidence in men is approximately half of that in women (21,23). A slight downward trend has been seen in the proportion of female patients from 84% (1960s) to 70% (2010s) (24). Socioeconomic status and urbanization are linked to the increased risk of hip fractures but these indicators do not completely explain the variation between countries (25,26). The highest risk for hip fracture has been observed in countries that are far from the Equator and in countries with clothing covering vast amounts of skin area, indicating that vitamin D influences hip fracture incidence (25). Incidences tend to increase from south to north in Europe and the USA (27). Also, hard surfaces, dense population in urban areas and lower physical activity contribute to the risk of hip fractures (26). Scandinavia has been reported to suffer the greatest incidence of hip fractures according to many reports with Norway at the unfortunate first place (20,27,28). Low risk for hip fractures has been observed, for example, in Ecuador, Tunisia and Saudi Arabia (21). Discrepancies between countries may be related to life expectancies, differences in the documentation of hip fractures in medical records and variation in hospital discharge data (20,21,27).

Hip fractures are subcategorized to intracapsular (femoral neck) or extracapsular (inter- or subtrochanteric) fractures according to the anatomical location of the fracture in relation to the hip capsule (29). Classification can be further specified by presenting the level of separation at the fracture site (30). A descriptive

categorization of the fracture location and stability has been made to guide the surgical treatment. The most widely used categorization is the Garden classification (types I to IV), which is based on the anteroposterior radiograph of the hip and describes fracture displacement to facilitate the surgical treatment strategy (29).

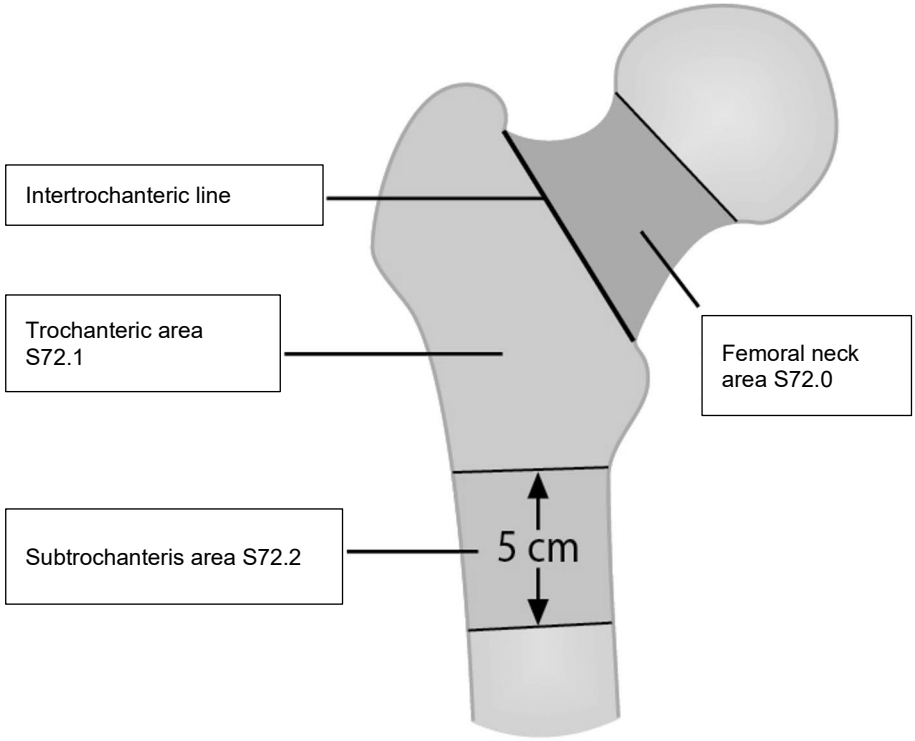

Figure 1. Classification and diagnostic codes (ICD-10) of fractures in the proximal femur. Adapted and modified from Current Care Guidelines of Hip Fracture (Working group appointed by the Finnish Medical Society Duodecim and the Finnish Orthopedic Association 2011).

2.2 Characteristics of an older hip fracture patient

The most notable risk factor for a hip fracture is age (31). Incidence of falls and the severity of fall-related complications increase steadily with age and are the leading causes for injury-related mortality in older patients (32). Between 35 and 40% of community-dwelling individuals aged 65 years and older fall annually (33). Even a mild accident may cause severe trauma due to the combined effect of the high incidence of falls and high susceptibility to injury. This is, however, a decidedly heterogeneous group of patients (34). The patient's previous condition may range from that of an immobile nursing home resident with dementia and osteoporosis

among other comorbidities to that of an independent individual living in his or her own home with no chronic diseases or need for any assistance.

A hip fracture patient is most commonly at least 75 years of age, has the characteristics of frailty (poor mobility, malnutrition, polypharmacy, cognitive disorders and other neurosensory deficits) and has comorbidities, such as osteoporosis or arthritis (21,33,35). An increasing mean age trend has been observed over the past five decades from 73 to approximately 82 years (24,36). Hence, characteristics of poor health and functionality are known to predispose to falls and hip fractures.

Gait and cognitive functioning are closely related: walking requires the integration of attention, planning, memory and motor and perceptual cognitive properties (37). Normal gait consists of three primary components: initiation and maintenance of movement, balance and ability to adapt to the environment (38). Co-ordinated walking requires constant and intact function of multiple regulatory circuits, making gait a sensitive marker of failure in any of these structures (39). In the studies by Montero-Odasso and co-workers, degree of cognitive impairment has been directly linked to the change in gait pattern (40,41). A cognitive disorder may affect every component of normal pacing, and yet, far too often patients with cognitive disorders are excluded from trials, thereby ignoring an important patient population (42). It has been observed that a significant proportion (from 19-40%) of older hip fracture patients have a known cognitive disorder or cognitive impairment on admission to hospital (43).

Patients falling outdoors are generally healthier than those falling indoors (44). In a study by Kelsey and colleagues, indoor falls were associated with inactive lifestyle, disabilities and poor health overall, whereas outdoor falls were associated with better functionality and more active lifestyle (45). However, most falls causing a hip fracture occur indoors. In a study by Ranhoff and co-workers up to 83% of such falls had occurred indoors (46).

2.2.1 Outcomes of hip fracture

A study by Salkeld and colleagues reported that hip fracture has a more severe impact on subsequent quality of life than breast cancer or myocardial infarction (47). Loss of confidence after a fall and hip fracture can contribute to FoF, compromising stability, and thus, increasing the risk of future falls and fractures (48). Indeed, previous fall has been recognized as a common risk factor for future falls (31,45,49). In patients with cognitive disorders, falls and hip fractures are among the most common reasons for hospital admissions (50,51).

Mortality at one month after the fracture is high; almost one in ten patients (4-9.5%), and patients who survive the acute accident are at substantial risk for

disability. Among those who are community-dwelling before the hip fracture, 11% may not regain individual mobility, 16% are transferred to a long-term care facility, and 80% are using a mobility aid one year after hip fracture (30,52). One-year mortality is even higher: up to one in five patients (20%) (24). In a study by Dakhil and co-workers with 726 patients and a follow-up of one year, none of the four groups into which the patients were divided according to baseline functionality, regained prefracture levels of functioning (53). Even if a patient should recover from the fracture itself, a silently developing disabling condition may be progressing simultaneously, impairing wellbeing after the recuperation from the fracture itself has peaked (54).

2.3 Comprehensive geriatric assessment

Aging affects everyone (55). However, since each individual possesses different levels of resilience – the assemblage of biochemical processes designed to maintain the identity, integrity and autonomy of individual organisms against the disturbance caused by both internal and external environments – the effect of ageing seems to be different (56,57). The health of an older patient is a consequence of biological, social and environmental events, all of which are subjectively interpreted and expressed (55). Conditions that are common in older adults and have multifactorial aetiologies are collectively referred to as "geriatric syndromes" (13). Collectively, geriatric syndromes are a result of several declining processes simultaneously with a decreasing ability to withstand stressors (57,58). Geriatric expertise is needed to take this complexity into account.

CGA determines an older patient's medical, psychosocial, functional and environmental resources and problems together with an overall plan for treatment and follow-up (59). Furthermore, an important aspect of CGA is monitoring the response and revising the plan, if necessary (60). CGA is interdisciplinary, collecting the knowledge of the patient's wellbeing from all available authorities (such as nurses, therapists, social workers and next of kin) and also multidimensional, including evaluation of somatic, physiological, social, spiritual, financial and environmental components that influence a patient's health. CGA is thus both a diagnostic and a therapeutic process (59,60).

The most vulnerable and complicated patients, a group which commonly includes older hip fracture patients, have been found to benefit the most from geriatric care (15). According to a comprehensive review by Ellis and co-workers, older patients receiving inpatient CGA increases the odds of being alive and living in one's own home after an unplanned hospitalization (61). Stuck and colleagues reported in their meta-analysis the favourable effect of CGA on mortality, physical and cognitive functions and living arrangements within a follow-up time ranging

from six to 36 months (59). A recent comprehensive review by Veronese and colleagues found that CGA is beneficial in the hospital setting with a strong level of evidence reducing the risk of falls, nursing home admission and pressure ulcers. In older hip fracture patients, CGA significantly prevented delirium (62). Another review by Briggs and co-workers discovered that CGA for frail older patients delivered in primary health care circumstances to patients' homes had no impact on nursing home admissions or mortality, but may reduce unplanned hospital admissions (63). A review by Chen and colleagues reported that a CGA intervention had a positive effect on quality of life and significantly reduced caregiver burden but did not affect the length of hospital stay (64). In summary, older patients benefit from CGA but the beneficial effect depends on the modality and circumstances of delivery.

2.4 Orthogeriatric care

Collaboration between orthopaedic surgeons and geriatricians in the treatment of hip fracture patients was initiated in the UK in the late 1950s (65). It has subsequently been adopted as a standard treatment protocol in many locations worldwide. The benefits of orthogeriatric models of care have been demonstrated by several studies (61,65–68).

Because of diminished functional reserves, vulnerability, frailty and a high risk for both intra- and postoperative complications, these patients are a unique challenge in hospital care. There is substantial variation in the rehabilitation potential and prognoses of these patients (69). Orthogeriatric care is a specified setting for implementing CGA in clinical practice.

In hip fracture patients, orthogeriatric care includes a multidisciplinary approach from the preoperative phase to discharge with a patient-specific rehabilitation plan (70). The preoperative phase aims for optimal preparation (pain management, electrolyte balancing, stabilization of comorbid conditions) and endorses early surgery (operation within 48h of admission). The postoperative phase pursues early mobilization and seeks to prevent complications (delirium, thromboembolism, infections, pressure ulcers etc.). Nutritional management and physiotherapy are initiated. Before discharge a patient-specific rehabilitation plan is conceived (21,70).

The orthogeriatric care models differ according to local resources (66,70).

1. Patients are treated on an orthopaedic ward with geriatric consultation available upon request. The role of the geriatrician is consultative and the responsibility rests solely with orthopaedic surgeons.

2. Patients are treated on a geriatric or rehabilitative ward either from admission or immediately after operative care until discharge. The role of the orthopaedic surgeon is consultative.
3. Patients are treated on an orthopaedic ward but patients are managed jointly by a geriatrician and an orthopaedic surgeon with a multidisciplinary team integrated into that care. Responsibility is shared between the geriatrician and the orthopaedic surgeon.

Geriatric and orthopaedic collaboration has been associated with better outcomes reducing complications, delirium and mortality after hip fracture, and it is also cost-effective (67,68,71,72). However, there is significant variation in the implementation and degree of integration between disciplines in real-life circumstances making comparison of the models challenging (66,68). None of the models has been proven superior to any others (21). A comprehensive review by Min and co-workers resulted in a strong recommendation for a multidisciplinary approach in post-hip fracture rehabilitation: a significant improvement was observed in daily functionality and mobility compared to conventional care (73). Co-management of a standardized clinical pathway and geriatrician-led care and rehabilitation have been associated with shorter preoperative waiting time, which reduces complications; shorter length of stay in hospital and lower readmission rate, which reduces health care costs; lower short-term mortality, which highlights the importance of geriatric expertise; improved independence and lower rates of nursing home admissions (74–76).

Overall, only a few randomized studies have been carried out to investigate the benefits of orthogeriatric care as an alternative to conventional surgical treatment as mentioned by Prestmo and co-workers. In their study, a significant improvement in mobility and activities of daily living was achieved with orthogeriatric care when compared to standard orthopaedic care. Moreover, their comprehensive geriatric care was less costly than orthopaedic care in a 12-month follow-up (77). Patients with dementia, a well-known risk factor for mortality in hip fracture patients, have been reported to benefit from geriatric assessment (78,79). A randomized study by Huusko and colleagues reported patients with mild or moderate dementia benefitting from active multidisciplinary geriatric rehabilitation when compared to standard postoperative rehabilitation in the local health care centre wards (80). A comprehensive review by Van Heghe and co-workers concluded a positive effect of orthogeriatric care in hip fracture patients on length of hospital stay, in-hospital mortality, one-year mortality and delirium during hospital care (68). Substantial heterogeneity and limited number of trials, and an almost complete lack of direct comparison between orthogeriatric care models complicate the evaluation of different modes of orthogeriatric implementation.

2.5 Cognitive disorders and dementia

"Age robs us of everything, even our memories" – a line wrote by Vergil (70-19 BC) in Eclogue IX. A dialogue between two shepherds, where the elder (Moeris) tells the younger (Lycidas) how in the past he used to sing all day while tending his sheep but now, as he has become older, he can no longer remember the songs. Hence, the term *dementia* has been known since ancient times: allusions have been discovered from ancient Egyptians, Greek philosophy (Pythagoras, Aristoteles, Plato) and Roman literature (Vergil, Cicero) (81). The first documentation of age-related decline in behaviour and cognitive abilities as a consequence of pathologies in the nervous systems was in 1776 by a Scottish pathologist, William Cullen (82). A more elaborate scientific perspective has been adopted since the beginning of the 20th century after Alois Alzheimer identified and reported the characteristics of progressive dementia in 1907 (83).

The ability to acquire new information or skills and then use them to solve problems can be called intelligence (84). Intelligence requires smoothly co-operating memory, adaptation and the ability to follow through in practice. Each of these abilities can be further subcategorized depending on the domain under investigation such as short-term memory, visual processing or attention among many others. Age affects all of these in a different way but the changes may not prevent an aged individual from functioning (85). A cognitive disorder is a malfunction in some cognitive feature disturbing normal performance in everyday life (85).

Cognition is a complex term including a vast array of brain functions related to the acquisition, storage, manipulation, application and retrieval of information (86). Distinctive domains of cognitive functions can be measured from tests with pen and pencil to computerized assessment procedures assessing the chosen function alone (17). The underlying mechanisms are embedded in brain circuits and neuromodulators which constantly interact with other sensory input and are perceived according to previous habits and experiences (87–89). Thus, a similar event creates individual experience, which is then acted upon. In the clinical context, the result of an assessment is interpreted by others by the same scheme. Therefore, knowledge of the actual functionality of a person's cognition is always a subjective analysis and calls for more than one encounter (87,90,91).

Cognitive disorders include amnesia, delirium and dementia (92). Dementia is not a specific disease but an umbrella term for symptoms affecting a person's cognitive abilities, such as comprehension, reasoning, remembering, learning and planning, to such an extent that it disrupts normal daily life and activities (82). Dementing diseases are becoming increasingly common due to ageing populations. A new case of dementia is detected somewhere every three seconds, and yet they are underdiagnosed worldwide (93). In high-income countries only 20-50% of dementia cases are identified whereas in low and middle-income countries the lack of

diagnosed cases is even higher (up to 75-90%) (93). There are roughly 55 million people globally living with dementia and the number is anticipated to more than double by 2050, up to 139 million (93,94).

Mild Cognitive Impairment (MCI) is commonly described as a transitionary phase between normal cognition and dementia (95). Patients with MCI are defined as having an objective deficit in cognitive functions with preserved daily functioning (96). The trajectory of MCI may proceed to a more specific diagnosis of dementia depending on the subtype or revert to normal cognition, which is why it deserves attention in clinical practice (97–99). Clinical significance of MCI is a subject of extensive research due to its heterogeneous presentation, neuropathological correlations and subsequent course (98,99).

2.5.1 Prevalence, risk factors and outcomes

The cellular and molecular changes in brain structure and central nervous system (CNS) metabolism are under extensive research (100,101). A recent article by Logroscino and colleagues described the two major challenges in the epidemiology of neurodegenerative diseases: first, the distinction between normal and a specific disease is demanding, and second, the symptoms may be subtle and at least partly overlapping (102). Furthermore, both healthy individuals and subjects with neurodegenerative diseases have similar depositions of neuropathological proteins and other changes – processes which become more complex and less specific as age advances (103,104). Distribution of the major age-related neurodegerative diseases is illustrated in *Figure 2*.

Alzheimer's disease (AD), which is the most common cause of dementia accounting for approximately 60-70% of all cases (105). Other types are vascular cognitive impairment (VCI), Lewy Body disease (LBD), Parkinson's disease-related cognitive disorder (PD) and frontotemporal lobe degeneration (FTLD). Often a combination of aetiologies (two or more) is identified, especially in older patients (94). Rarer pathologies manifesting in similar symptoms include among others Normal Pressure Hydrocephalus, Multisystem atrophy, Creutzfeldt-Jacob disease, Huntington's disease, Chronic Traumatic Encephalopathy and HIV-associated dementia (94,106). Additionally, other conditions, such as the side effects of certain medications, vitamin deficiencies, hypothyreosis, sleep apnea, stress, depression or delirium may resemble dementia symptoms. Unlike other dementias, these are not chronic, progressive conditions and may thus be reversed with treatment (106,107).

There is a significant lack of data on the epidemiology of dementia diagnoses. Moreover, variation exists in the diagnostic processes, instruments and documentation, even though global consensus of diagnostic criteria are available (108,109). This knowledge gap is explained by the difficulty of obtaining the

required data in a longitudinal follow-up manner including recurrent clinical investigations (110). The clinical symptoms of cognitive decline are commonly the result of mixed brain pathology together with age-related degenerative processes and demand recurring assessments to be distinguished from each other (111). Reports suggest that, at best, the accuracy of clinical diagnosis is in the range of 70-80%. More specific diagnosis would require post-mortem neuropathological examinations (112,113). The clinical features of common neurodegenerative disorders are presented in *Table 1*.

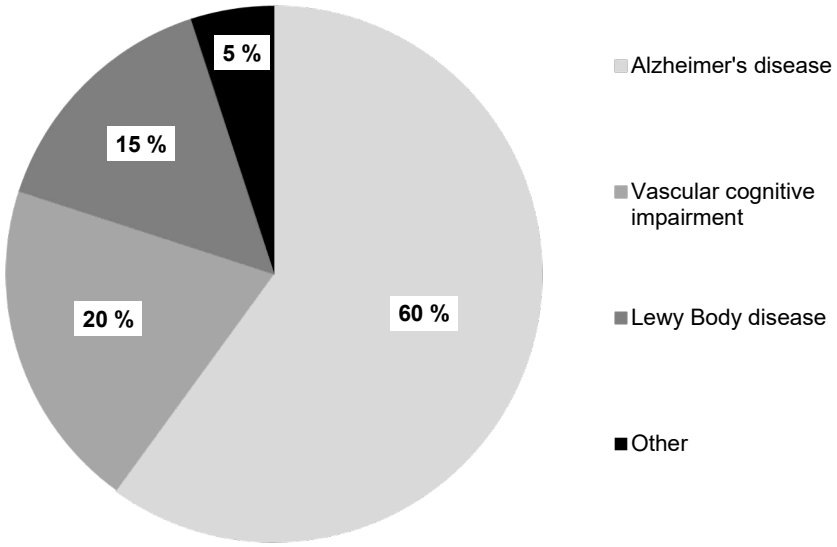

Figure 2. Distribution of major age-related neurodegenerative diseases. Adapted from Niedowicz et al., 2011 (114).

As Vergil thought, age alone is the most significant risk factor for AD. According to a recent summary, approximately five per cent of people aged 60 to 74 years, 13.1% of people aged 75 to 84 years and 33.2% of people aged 88 years and older have dementia because of AD (115). It is estimated that by focusing interventions on the potentially modifiable risk factors, the number of cases could be reduced by one third (116).

Cognitive disorders and dementia share multiple risk factors with cardiovascular diseases including hypertension, hypercholesterolemia, obesity and type 2 diabetes (117,118). The association is explained by impaired brain perfusion and parenchymal changes (119). Family history and genetic predisposition have also

been acknowledged as risk factors for cognitive disorders (120). A thorough report of *The Lancet Commission* lists 12 theoretically modifiable risk factors which may account for up to 40% of dementia cases worldwide. These include, in addition to the previous cardiovascular factors, less education, hearing impairment, smoking, depression, physical inactivity, low social contact, excessive alcohol consumption, traumatic brain injuries and air pollution (121). However, the effects of some of these factors change with age. For example, obesity in midlife increases the risk of cognitive decline but may act as a protective factor in later life. The same applies to elevated blood pressure (115). Age at and duration of exposure seem to be the important factors (118,122). Physical activity, or more broadly an active lifestyle, socially stimulating participation and frequent mentally stimulating activities are also known to preserve cognitive abilities (115,123).

According to WHO, Alzheimer's disease and other dementias are the world's seventh leading cause of death. In high-income countries, they have become the second leading cause of death overtaking stroke, respiratory infections, obstructive pulmonary disease and neonatal conditions (124). In Finland, an alarming shift has been seen in recent years: mortality due to Alzheimer's disease and other dementias, the third leading cause of death after diseases of the circulatory system and neoplasms, grew most from 2020 to 2021 (125). Dementia has been observed as a major contributor to disability and the need for long-term care (126).

Diligent research has been conducted to study the combination of health attributes and brain health. Such an example is the Finnish Geriatric Intervention Study (FINGER), which showed slower cognitive decline in high-risk patients with an intervention including four components: diet, exercise, cognitive training and management of cardiovascular risk factors (127).

Table 1. Known clinical features of common neurocognitive disorders.

	Alzheimer's Disease (128)	**Vascular Cognitive Impairment** (119)	**Dementia with Lewy Bodies** (129)	**Frontotemporal Lobe Degeneration** (130)
Clinical onset and progression	Insidious, gradual and progressive decline	May be abrupt onset, stepwise decline	Progressive cognitive decline before or concurrently with Parkinson's Disease related symptoms.	Insidious, gradual progressive decline, often before 65 years of age
Pathology	Neuronal accumulation of beta-amyloid plaques and neurofibrillary tangles, cholinergic deficits	Global or focal effect of cerebrovascular disease. Cerebral perfusion deficits, ischaemic stroke, cerebral ischaemic injury	Neuronal accumulation of Lewy Bodies (alpha-synuclein aggregates)	Atrophy, hypoperfusion and hypometabolism located in frontal and temporal lobes of the brain
Major clinical features	Impairment in memory, aphasia, apraxia, agnosia. Deficits in executive functions. Subtypes: - Posterior cortical atrophy: visual impairment and deficits in spatial awareness, difficulties in identify objects or distances - Logopenic aphasia: language impairment, non-fluent vocabulary	Deficits in executive functions, attention, motor control and praxis. Problems in planning, organising, problem solving and decision making. Fluctuating performance of memory.	Decline in cognitive performance, fluctuation in attention and alertness, recurrent visual hallucinations, impaired mobility, REM-sleep disturbances, parkinsonism	Progressive development of behavioural and personality change, deficits in executive functions (behavioural variant) and/or language impairment: progressive aphasia, impoverished content of speech, paraphasic errors and difficulties of naming objects (semantic variant, progressive nonfluent aphasia, logopenic variant)

2.5.2 Diagnostic investigations

Neuropathological changes accompanied by changes in cognitive functions proceed in continuum with no clear biological cutpoint to distinguish between normality and disease (91,103,104). Some of the factors and consequences of brain ageing are presented in *Figure 3*. AD, for instance, has been conceptualized as a condition that begins with an asymptomatic pathophysiologic process that develops over time from mild cognitive disorder to severe end-stage dementia (91).

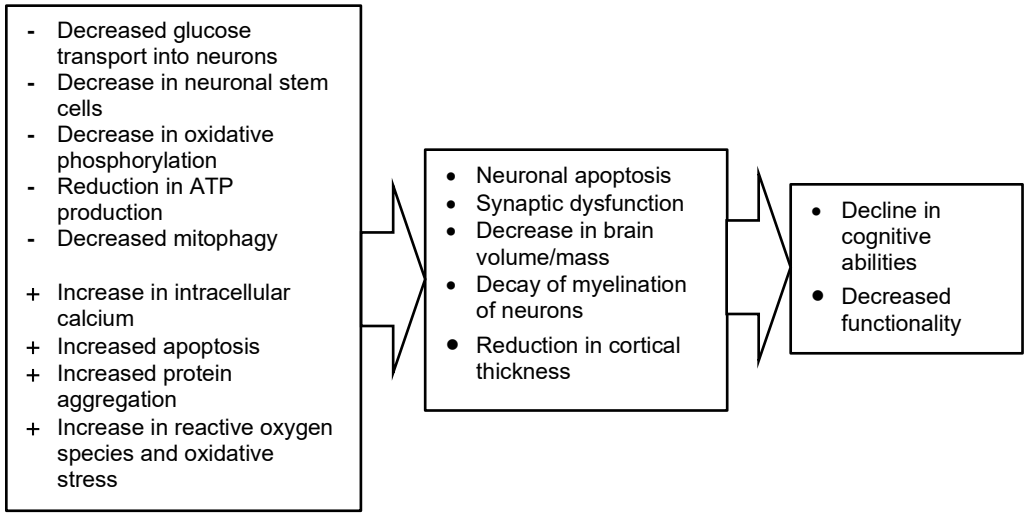

Figure 3. Factors and consequences of brain ageing. Adapted from Morley J.E., Clin Geriatr Med 34 (2018) 505-513.

Subjective memory complaints are common in older population. Studies have reported that 31-88% of community-dwelling adults aged 65 years or more experience memory disturbances (131,132). Accurate diagnosis is fundamental for better planning, treatment, care and social support. Cognitive disorders are not only a burden for the patient, but also for the family, caregivers and the health care system. Thus, an early diagnosis allows for appropriate treatment initiation, social support, education and future planning in agreement with the patient and the next of kin considering financial and legal matters (86,115).

Diagnostic pathways may differ across countries depending on local resources. In Finland, general practioners at public health care centres play a vital role in the diagnostic process. First-line investigations – medical history, family background, level of education, comorbid conditions, cognitive tests (Mini-Mental State Examination - MMSE, Consortium to Establish Registry for Alzheimer's Disease-test - CERAD, Montreal Cognitive Assessment - MoCA) and blood tests – can be

assessed before referring the patient to specialists (either a neurologist or a geriatrician). Some health care centres include these specialities as a part of the full-time staff or offer scheduled appointments. Brain imaging, cerebro-spinal fluid analysis and assessment of behavioural and neuropsychiatric symptoms may be needed. The Finnish diagnostic pathway follows the national care guideline, which is constantly updated according to globally accepted criteria for different subtypes of cognitive disorders (109,133). Diagnoses are set by a specialist in neurology or geriatric medicine according to these guidelines.

Sometimes, reaching the most reliable diagnosis requires regular follow-up and repetition of interview and diagnostic tests (115). Ageing itself accounts for a variety of cellular and structural changes in the brain and cognitive capabilities which should not be considered pathological (88). The diagnosis of the cognitive impairment may change during follow-up or remain unexplained, as is suggested in a study by Boyle and co-workers: the majority of age-related cognitive decline is due to factors other than the pathological indices of major neurodegenerative diseases (110).

2.5.3 Relationship between cognitive disorders and hip fractures

A cognitive disorder may change vital functions needed for maintaining balance. Cognitive decline has been reported as an independent risk factor for falls with a direct relationship between the severity of the decline and gait abnormalities (37,134,135). Of the cognitive domains, executive functions, attention and visuospatial abilities have been associated with motor behaviour, stability control and falls (37,136–138). Neuroimaging studies support these relationships with consistent findings of brain atrophy and/or reduced neural activity in association with instability or gait variability (37). The integrity of frontal-subcortical circuits has been recognized to have an important role in mobility and balance, but also in executive functions (139). These regions have been reported to be especially susceptible to cerebrovascular damage caused by diseases and biological ageing, which may partly explain the association with gait impairment (140). Indeed, there is increasing evidence that poor motor performance is caused by brain damage related to cognitive decline (137).

A meta-analysis by Seitz and colleagues reported the prevalence of cognitive impairment in older hip fracture patients to be from 8.6 to 78.7% (weighted average 41.8%). Prevalence of dementia varied from 15 to 32% (weighted average 19.2%) (43). In another study by Yiannopoulou and co-workers, 60 patients out of 80 older hip fracture patients were diagnosed with dementia (141). Prevalence of dementia is reported to increase when ageing is combined with hip fractures: a study by Kasai and colleagues reported an overall prevalence of 66% in their sample of patients aged

70 years or more. The prevalence increased to 76% in a subgroup analysis with patients aged 75 years or more (142). Thus, the results of earlier studies support the notion of a significant link between cognitive impairment and hip fractures.

Verghese and co-workers proposed motor cognitive risk syndrome (MCR) as a subtype of MCI after their earlier observation of slower gait in patients with MCI compared to healthy controls (143,144). They hypothesized that slowing gait may be an early clinical sign of cognitive impairment. Diagnosis of MCR was based on four criteria: cognitive impairment, slower gait, preserved activities of daily living and absence of dementia at the time of the assessment. In this follow-up study (median follow-up of 36.9 months) of 997 individuals aged 70 or more, MCR was associated with a twelve-fold risk of vascular dementia (143). However, Montero-Odasso and colleagues observed in their study that patients with an amnestic variant of MCI, which is more likely to develop in AD than VCI, had greater deficit in gait than those with non-amnestic MCI (145). They conclude that other cognitive domains beyond executive functions seem to be involved in balance control and safe gait (145).

Several pathological mechanisms underlying the relationship between gait and cognition have been detected (39,137,139,143,145). *Neuroinflammation*, manifesting as microglial activation, may cause increased oxidative stress, synaptic destruction and impaired neuroplasticity. *Vascular damage* includes diffuse micro-damage to small vessels compromising the integrity of frontal and subcortical circuits and hypoperfusion decreasing brain metabolic demands, which is associated with the demyelination of neurons and brain volume loss (37,39). *Neurodegeneration* in multiple systems simultaneously, such as cortical degeneration, frontal areas and brainstem nuclei are involved in impaired motor and cognitive responses (39,146). Deterioration of motor performance is more likely to predict non-AD dementia although vascular changes may cause cytokine release that increases the production of amyloid precursor and amyloid beta proteins, resulting in AD (147). Thus, changes in gait abnormalities and difficulties in stability control seem to be linked to a range of conditions causing cognitive impairment.

2.6 Delirium

Delirium is a serious, underrecognized, costly, potentially fatal condition affecting 20-80% of hospitalized older adults (148,149). Delirium has been associated with longer hospital stays and poor subsequent prognosis afterwards (150,151). However, in up to 30-40% of cases the condition could be prevented with appropriate interventions and care (149,152).

2.6.1 Definition

Delirium is defined as an acute disturbance in cognitive functions provoked by an underlying cause. It is characterized by a recent onset and fluctuating course, alternating awareness, disorganized thinking, impaired attention and memory deficits. It can be thought of as an acute brain failure analogous to an acute episode of heart failure: a multifactorial condition indicating the reduced resilience and vulnerability of the target organ system (153).

The phenomena can also be explained with five key domains (90,154):

1. Cognitive distortion: impairments in memory, executive functions, comprehension, orientation and perception
2. Attention deficits: reduced ability to direct, focus, sustain and shift attention
3. Dysregulation of the circadian rhythm: fragmentation in sleep-wake cycle
4. Emotional dysregulation: characterized by fear, anxiety, anger, irritability
5. Psychomotor disturbances: the various phenotypic presentations
    - Hyperactive subtype: often recognized, characterized by agitation, aggression, vigilance and hallucinations
    - Hypoactive subtype: most often unrecognized, characterized by fatigue, lethargy, absent presence and reduced psychomotor functions
    - Mixed subtype: patients fluctuating between the hyper- and hypoactivity.

It has been hypothesized that the clinical manifestation of delirium, i.e., its motor subtype, is a reflection of the patient's reaction to delirium phenomenology (155).

2.6.2 Prevalence, risk factors and outcomes

Depending on the circumstances, the prevalence of delirium ranges from 1 to 82% (149). In community-dwelling older adults, delirium is uncommon (1-2% or lower) due to the lack of precipitating factors, insufficient detection and incomplete documentation (149,156). In a general practitioner's appointment, delirium cases may be documented as somatic illness or dementia (156). The significantly higher prevalence figures in hospital settings are multifactorial and can be explained by hospital care, pathophysiological consequences of an acute illness and drug effects (149,157). In general hospital admission the prevalence is 14-24% and may increase

up to 56% during a hospital stay (157). In more specialized settings, such as palliative, intensive or post-operative care units incident delirium has been detected in up to 82% of patients (149,157).

Delirium as a geriatric entity can be the result of a single factor but is generally a complex, multifactorial event defined by the sum of the patient's predisposing and precipitating factors. This is conceptualized in *Figure 4*: the more vulnerability, the less is required to cause delirium (149,158). In older patients, pre-existing cognitive impairment is a common risk factor and acts as an indicator of already diminished cognitive reserves (159). Polypharmacy, impaired sensory functions, malnutrition and depressive mood, along with acute illnesses, pain and sleep deprivation are other common predisposing factors increasing the risk of delirium in older patients (159).

Delirium has been observed as an indicator of poor prognosis despite the differences in study designs: an agreement on the influence of delirium on prolonged hospital stay, increased costs of hospital treatment, institutionalization, long-term functional decline, and development of subsequent cognitive disorders has been established in various studies (149,151,153,160–162). There are mixed results on the effect of delirium on mortality although an increase is usually reported (149,163,164).

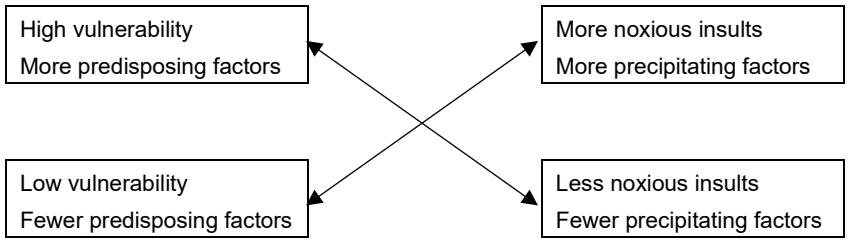

Figure 4. Model of delirium onset as a sum of contributing factors. Adapted from Inouye S, et al., Lancet, 2013.

2.1.1 Assessment tools

The diagnosis of delirium is based on clinical assessment with diagnostic criteria in both the *Diagnostic and Statistical Manual for Mental Disorders, 5th revision* (DSM-V) and the *International Classification of Diseases, 10th revision* (ICD-10). Determining the fluctuating course distinguishing delirium from dementia, requires that the screening is conducted frequently over a period of time. Studies suggest that delirium is unrecognized in up to two-thirds of cases partly because of perceived lack of significance, lack of suitable screening tool and insufficient staff training (165,166). Selecting the best tool suitable for delirium assessment is complicated by the vast selection of options available: a review by De and co-workers lists 21 different instruments for delirium assessment (167).

The most commonly used screening tool is the Confusion Assessment Method (CAM) test (165). This has a strong evidence-based background, good specificity and has been modified to suit specific contexts, such as the emergency room, intensive care unit and long-term care facilities (168,169). Instruction and training are recommended to ensure optimal accuracy (165). However, staff turnover and application by untrained operators may reduce the sensitivity. Another option is the 4 A's test (4AT) which has shown good sensitivity and specificity with higher completion rate compared to CAM (166,170). Additionally, the 4AT has proven useful when delirium co-occurs with dementia and with drowsy patients (167,171). The 4AT is a brief tool that requires no specific training. Sum of scores of 4 or higher may indicate either delirium or dementia which calls for consideration in clinical use (171). The Delirium Rating Scale (DRS) is a 10-item scale based on available patient information over a 24-h period (172). Items are scored from 0 to either 2, 3 or 4 with a maximum score of 32. It has shown good sensitivity and specificity with a cut-off score of 10 or more indicating delirium. Use of this tool requires psychiatric training on the part of the user for better accuracy (167,172). The properties of these tools are presented in *Table 2*.

Table 2. Overview of common screening tools for delirium.

Tool	Applicability	Content	Result
CAM	Identification of and diagnosing delirium	Assessment of presence, severity and fluctuation of nine features of delirium (acute onset, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbance, psychomotor disturbance, altered sleep-wake cycle) Four domains: 1 – acute onset and fluctuating course 2 – inattention 3 – disorganized thinking 4 – altered level of consciousness	"Yes" in domains 1, 2 and 3 or 4
4AT	Identification of delirium and cognitive impairment	Four domains: 1 – Bedside assessment of alertness 0 if normal or mildly drowsy 4 if clearly abnormal 2 – The Abbreviated Mental Test 4 0 if no mistakes 1 if one mistake 2 if more than one mistake 3 – Months of The Year Backwards task 0 if more than 7 correctly 1 if less than 7 correctly or refuses to start 2 if untestable 4 – Evaluation of recent change or fluctuation of mental status 0 if no 4 if yes	≥4 = possible delirium and/or cognitive impairment 1-3 = possible cognitive impairment 0 = delirium or cognitive impairment unlikely

Tool	Applicability	Content	Result
DRS	Assessment of delirium symptoms	10-item scale using available patient information over a 24h period, scored from 0 to 2, 3 or 4 1 – Temporal onset of symptoms 2 – Perceptual disturbances 3 – Hallucination type 4 – Delusions 5 – Psychomotor behaviour 6 – Cognitive status during formal testing 7 – Physical disorder 8 – Sleep-wake cycle disturbance 9 – Lability of mood 10 – Variability of symptoms	Maximum of 32 points, ≥10 = delirium

CAM=Confusion Assessment Method, 4AT=The 4A test, DRS=Delirium Rating Scale

2.6.3 Delirium in hip fracture patients

Older hip fracture patients often suffer from cognitive disturbances during hospitalization (54,69,162). Studies have reported the incidence of delirium in hip fracture patients to range from 5 to 41% (151,161,174,175). Most commonly the incidence varies between 20 and 35% (176,177). An episode of delirium may be present on admission or may develop during hospital care (69). Pain, noxious medications (sedatives, pain medication), stress, surgery, the hospital environment and sleep disturbances contribute to this turmoil (178). Cognitive impairment is acknowledged as an independent risk factor for delirium in older patients (161,179) and is a common underlying, undiagnosed and exacerbating contributor to poor outcomes in older hip fracture patients (161,174,180,181). Malnutrition is another common, independent risk factor for delirium in hip fracture patients and has also been recognized as a prodromal syndrome of AD (182,183). An episode of delirium has been acknowledged to predict subsequent cognitive decline in various settings (164,184,185). Belleli and co-workers observed the postoperative delirium duration as a prognostic factor and reported that each day of postoperative delirium during care on the ward increased the risk of mortality in the next six months by 17% (186). Properties and results of studies of postoperative delirium and associated factors in hip fracture patients are summarized in *Table 3*.

Table 3. Characteristics of studies and associations of postoperative delirium in hip fracture patients.

Authors	*n*	Study population and settings	Screening tool	Observations of the results
Bellelli et al., *Journal of the American Geriatrics Society* 2014 (186)	199	- Hip fracture patients aged 65 years or more admitted to OGU in an Italian university hospital - Daily assessment of delirium during hospital care - Follow-up telephone interview	CAM	- 157 (78.9%) patients without preoperative delirium - Postoperative delirium (57/199, 28.6%) was associated with mortality in the following 6-month period, HR 1.17, 95% CI 1.07-1.28
Bickel et al., *Dementia & Geriatric Cognitive Disorders,* 2008 (187)	200	- Patients aged 60 years or more who underwent hip surgery in a German university hospital - Patients with known dementia were excluded - Daily assessment of delirium during hospital care - Follow-up telephone interview at on average 38 months (SD=5.7) after discharge	CAM	- Hip fracture patients: n=12, 6% - Postoperative delirium (41/200, 20.5%) was associated with cognitive impairment/dementia at 38 months after discharge, OR 41.2, 95% CI 4.3-396.2
Juliebø et al., *Journal of the American Geriatrics Society*, 2009 (174)	364	- Hip fracture patients aged 65 years or more treated in two Norwegian hospitals - Daily assessment of delirium during hospital care	CAM	- 187 (51.4%) patients without preoperative delirium - Postoperative delirium (68/187, 36.4%) was associated with prefracture cognitive impairment (OR 2.93, 95% CI 1.40-6.11), BMI<20kg/m^2 (OR 2.92, 95% CI 1.27-6.74) and injury occurring indoors (OR 2.93, 95% CI 1.25-6.83)
Krogseth et al., *Dementia and Geriatric Cognitive Disorders*, 2011 (189)	106	- Hip fracture patients aged 65 years or more treated in two Norwegian hospitals - Patients with known dementia were excluded - Daily assessment of delirium (not weekends) - Follow-up assessment at patients' home 6 months after the fracture	CAM	- 29 (27.4%) patients developed delirium during the acute phase, 21 of these postoperatively. Of the patients who developed delirium during the acute phase, 11/29 (38%) had developed dementia during follow-up (OR 6.4, 95% CI 1.6-26.1)
Lenze et al., *Journal of the American Geriatrics Society*, 2007 (190)	126	- Hip fracture patients aged 60 years or more in an American university hospital - Assessment of delirium at the end of the hospital care	DRS	- Delirium during hospital care was not associated with post-hip fracture depressive disorder (OR 1.07, 95% CI 0.99-1.16) - An assumption that delirium is a risk factor for developing depression, and that depressive symptoms are a feature of delirium

Authors	*n*	Study population and settings	Screening tool	Observations of the results
Luger et al., *Geriatric Orthopedic Surgery & Rehabilitation*, 2014 (175)	329	- Hip fracture patients aged 80 years or more without preexisting cognitive impairment treated in an Austrian university hospital - 5-year follow-up data scrutinized from medical records	DSM-IV	- Postoperative delirium (18/329, 5.5%) was significantly associated with dementia within the following 5 years (P-value=0.001)
Lundström et al., *Journal of the American Geriatrics Society*, 2003 (184)	78	- Hip fracture patients aged 65 years or more without known prefracture dementia treated in a Swedish university hospital - Screening for delirium symptoms on admission and days 1, 3 and 7 after surgery - Follow-up interview at 5 years after surgery and data scrutinized from medical records	DSM-IV	- 67 (85.9%) patients without preoperative delirium - Postoperative delirium (30/78, 38.5%) was associated with development of dementia during 5-year follow-up (OR 5,66, 95% CI 1.31-23.56)
Marcantonio et al., *Journal of the American Geriatrics Society*, 2000 (151)	126	- Hip fracture patients aged 65 years or more admitted to an American medical center - Daily assessment of delirium during hospital care - Follow-up interview via telephone or in-person if cognitive function was inadequate to allow telephone interview	CAM	- Delirium during hospital care (52/126, 41.3%) was associated with death or new nursing home placement (OR 3.0, 95% CI 1.1-8.4), ADL decline (OR 2.6, 95% CI 1.1-6.1) and decline in mobility (OR 2.6, 95% CI 1.03-6.5) during 1-month follow-up. The associations were no longer significant at 6 months
Olofsson et al., *International Journal of Geriatric Psychiatry,* 2018 (191)	135	- Hip fracture patients aged 70 years or more without a known prefracture dementia treated in a Swedish university hospital - Daily screening for symptoms of delirium during hospital care - Follow-up re-assessment 36 months after surgery at patients' homes	DSM-IV	- 115 (85.2%) patients were without preoperative delirium - Postoperative delirium (56/115, 48,7%) was associated with development of dementia during 3-year follow-up (OR 15.58, 95% CI 2.65-91.64)
Radinovic et al., *Journal of the American Geriatrics Society*, 2014 (192)	277	- Hip fracture patients aged 60 years or more treated in a Serbian university hospital - Patients with severe dementia or delirium within 48h of hospital admission were excluded - Daily assessment of delirium during hospital care	CAM	- Delirium during hospital care (88/277, 31.8%) was associated with history of depression (OR 10.75, 95% CI 2.31-50.05) - High incidence (21.7%) of overlapping syndrome of both depressive mood and delirium

BMI=Body Mass Index, CAM=Confusion Assessment Method, CI=Confidence Interval, DRS=Delirium Rating Scale, DSM-IV (TR)=Diagnostic and Statistical Manual of Mental Health, Fourth Edition (Text Revision), HR=Hazard Ratio, OGU=Orthogeriatric Unit, OR=Odds Ratio, SD=Standard Deviation

2.7 Depressive mood

In addition to cognitive impairment and delirium, a common neuropsychiatric comorbidity affecting especially hospitalized older adults is depressive mood and depression (192,193). In fact, depressive mood has been identified as the most common psychological illness in hip fracture patients (194). Neuropsychiatric symptoms of depressive mood, dementia and delirium (3 D's) often co-occur (195,196). These syndromes may overlap, exist concurrently or emerge exclusively in the same patient which complicates accurate diagnostics (197). For example, a patient may have low daily activity levels due to decreased energy levels, loss of interest or inability to engage in activities, each of which may be caused by any one of the 3 D's (195,198–200). A study by Vaughan and co-workers discovered that frailty and depression in late life share remarkable common aetiologies and manifestations as well as similar symptomology and adverse sequelae (199). Another study by Soysal and colleagues reported that approximately 40% of depressed older adults have frailty and a similar proportion of those who have frailty are depressed (201). Regardless of the challenges in identification, depressive mood has been repeatedly associated with poor functionality, institutionalization and mortality (202,203) and thus, warrants attention as a part of the comprehensive treatment protocol.

2.7.1 Prevalence, risk factors and outcomes

Major depression affects from 1 to 7% of community-dwelling older adults but depressive symptoms may be present in 4-86% depending on the circumstances of assessment and patient population (198,199,204,205). Depression in older age is more common in female than in male patients, similar to the distribution among younger adults (204). The prevalence of depressive mood increases towards later life from 20-25% in 80-89 years of age to 30-50% at the age of 90 or more, as Luppa and colleagues discovered in their meta-analysis (206). However, depressive symptoms in later life are more often recurrent events than first-ever episodes (204). Evidence suggests that prevalence of depressive symptoms increase linearly with medical burden: from 0-10% in community to 25% in primary care settings and onward to 30% in hospital care and up to 45-50% in long term care facilities (205). Higher prevalences have been reported in studies including patients with cognitive disorders (204).

The association between depression and dementia has been identified as a complex pattern with depression being simultaneously an individual risk factor, a prodromal syndrome, a complication or a consequence of dementia (195,200). Somatic concurrence between these symptoms includes hippocampal damage

through depression-initiated alterations in glucocorticoid steroid levels and atrophy of the frontal and parietal lobes contributing to lack of initiative and apathy (200).

The outcomes of depressive symptomology in different studies vary substantially depending on the patient population, timing and the tool used for assessment and length of the follow-up period. Generally, depressive mood has been associated with loss of autonomy, increased experience of postoperative pain and poorer quality of life (11,207). Triolo and colleagues recently performed a retrospective analysis from a 15-year follow-up period of 3,042 Swedish individuals aged 60 years or more (208). They reported an accelerated accumulation of somatic comorbidity over time in patients with any level of depressive symptoms (no depression, subsyndromal depression, minor depression, major depression) compared to non-depressed (208).

2.7.2 Assessment tools

A variety of tools are available for the assessment of depressive symptoms. Among the most widely used are the Centre for Epidemiological Studies Depression Scale (CES-D), the 15-item Geriatric Depression Scale (GDS-15), the Beck Depression Inventory (BDI), the Patient Health Questionnaire 9 (PHQ-9) and the Hospital Anxiety and Depression Scale (HADS) (209–213). The properties of the various instruments are presented in *Table 4*.

The GDS-15 is a shortened form of the 30-item GDS-30 designed to both assess the severity of depressive symptoms and to screen for depression among older patients in particular (210). There has been debate on the exact cut-off point for depressive mood: a study by Cullum and colleagues identified a score of ≥7 points on the GDS-15 to be the more sensitive and specific (73.7% and 81.2%) than diagnosing depression according to the ICD-10 criteria (214). Another study by Friedman and co-workers found a score of six points to be the optimal cut-off according to the DSM-IV criteria (215). The GDS-15 has been found useful in patients with MMSE scores of 10 or more, making it a suitable instrument for geriatric patients (216).

Some studies define depression according to the diagnostic criteria whereas others look for the result of a depressive symptoms screening tool (202,206). Thus, the results vary depending on the aim of the study. Comparing results can be difficult given the widely acknowledged co-occurrence of dementia, delirium and depression in older hospitalized patients, variation in narrative decisions and the ambiguity of study concepts.

Table 4. Overview of screening tools for depressive mood.

Tool	Applicability	Content	Result
GDS-15	Screening for depressive mood in geriatric patients	15-item short form of the original 30-item tool including 15 dichotomous questions related to affective and cognitive domains of depression	0-5 = non or mild depressive mood 6-9 = moderate depressive mood >10 = severe depressive mood[1]
CES-D	Evaluation of current level of depressive symptoms	20 items, each scored from 0 to 3 related to affective, somatic and social aspects of depression	Higher score indicating more severe symptoms of depression
BDI	Evaluation of depression severity	21 items, each scored from 0 to 3 measuring the cognitive, affective, somatic and vegetative symptoms of depression	0-13 = Minimal 14-19 = Mild 20-28 = Moderate 29-63 = Severe
PHQ9	Screening for symptoms of depression	Nine items, each scored from 0 to 3 including the nine categorical symptoms of depression according to the DSM-IV	0-4 = Minimal 5-9 = Mild 10-14 = Moderate 15-19 = Moderately severe 20-27 = Severe
HADS	Evaluation of current level depressive symptoms and anxiety	14-items, each scored from 0 to 3, seven questions related to depressive symptoms and seven to anxiety	0-7 = No depression/anxiety 8-10 = Mild depression/anxiety 11-14 = Moderate depression/anxiety 15-21 = Severe depression/anxiety

GDS-15=15-item Geriatric Depression Scale (210), CES-D=Centre of Epidemiological Studies Depression scale (209), BDI=Beck Depression Inventory (211), PHQ-9=Patient Health Questionnaire (212), HADS=Hospital Anxiety and Depression Scale (213)
1) Cut-off scores may differ between studies

2.7.3 Depressive mood in hip fracture patients

Hip fracture is a sudden accident which threatens all aspects of individuality. Loss of autonomy, impaired mobility and exacerbating comorbidities due to long and slow rehabilitation comprehensively changes the functional state of the patient. Three out of four older hip fracture patients have been reported to have depressive symptoms on hospital admission (217). Depressive mood in hip fracture patients has been associated in many studies with poor rehabilitation outcomes and mortality (202,218,219). Moreover, it contributes to hip fractures as an individual risk factor in several ways. First, the hormonal and homeostatic changes due to depressive mood increase bone resorption and decrease bone formation, increasing the risk of fragility fractures. The effect is explained via the deregulation of the hypothalamic-pituitary-adrenocortical axis resulting in hypercortisolemia, and the decrease in oestrogen and growth hormone concentrations due to depression (220,221). Second,

accelerated decrease in femoral neck bone mineral density has been associated with the use of tricyclic antidepressants and selective serotonin reuptake inhibitors further adding the risk of hip fractures (222). According to Rauma and colleagues, the effect is caused by antidepressants blocking the same cell transporters and receptors found in bone cells inhibiting their functions (222). Third, depressive mood has been associated with poor health behaviours, such as smoking, excessive consumption of alcohol and physical inactivity, which may impact bone metabolism (220,223). Depressive mood may also affect judgement, gait, balance and coordination, further increasing the risk for falls and fractures (220).

Assessment of depressive mood in hip fracture patients may be complicated due to fluctuation of symptoms according to pain and distress (35). Some studies have assessed depressive mood during the acute phase of the injury (on admission, before or immediately after operative care), which may increase the probability for confounding factors, such as adverse effects of medications, hospital environment and pain (224,225). Hip fracture and subsequent hospital care may act as a stressor for vulnerable older patients who are initially more prone to comorbid conditions due to depleted reserves (226). A follow-up study by Chang and co-workers reported that the majority of new-onset depressive symptoms arise within the first 200 days post-hip fracture (227). In addition, Nightingale and colleagues observed that depression increases mortality up to two years after the fracture (194).

2.8 Fear of falling

Older people fear falling more than robbery (228). This fear has been recognized in numerous studies as an even more serious health problem than the fall itself (229–233).

FoF has been associated with pain, depression and cognitive impairments, although due to overlap in manifestations the impact of one single element is uncertain (12). Fear is characterized by debilitating anxiety about falling, loss of self-confidence or activity restriction which affects rehabilitation by reducing participation in physiotherapy and other exercise activity (12,234). The assessment and identification are commonly made from a functional point of view as the patient's own perception of their capabilities to perform or succeed in a particular task (230). The latter is often referred to as self-efficacy (235). Falls and FoF are a bidirectional problem – each acting as a risk factor for the other. FoF has been associated with a two to three-fold risk for falling, the risk being higher in those with a previous fall (236).

2.8.1 Prevalence, risk factors and outcomes

FoF is common in both fallers and non-fallers. A study by Jørstad and colleagues reported a prevalence in non-fallers from 12-65% and from 29-92% in those who had fallen (230). Another study by Painter and co-workers estimated the prevalence of FoF in community-dwelling older adults to range from 35 to 55%, regardless of any previous fall (237). The wide variation in prevalence figures has been explained by the lack of a fundamental definition of FoF. Research has used multiple terms to describe the same condition, such as "fear of falling", "self-/falls efficacy" and "loss of confidence" (142,238). Moreover, studies often lack sufficient background information, rendering difficult the interpretation of this complex psychological outcome (239). Given that the older population is a heterogeneous group with widely different capabilities, it is easy to understand why the prevalence of FoF in this patient group is variable.

A history of falls and female gender are regularly acknowledged as risk factors of FoF (237). FoF has also been associated with higher age, balance and gait problems, functional dependency in ADLs, decreased aerobic endurance, impaired joint mobility and dizziness (32,237,240).

A study by Delbaere and co-workers detected a disparity between perceived and physiological risk of falls (239). In this study, a categorization of patient characteristics according to physical measurements and neuropsychological assessment was made and four groups emerged:

- Vigorous: Good physiological capability and low fall risk, low perceived fall risk
- Anxious: Good or decent physiological capability and low fall risk, high perceived fall risk
- Stoic: Low physiological capability and high fall risk, low perceived fall risk
- Aware: Low physiological capability and high fall risk, high perceived fall risk

Two thirds of the patients were included in the "Vigorous" or the "Aware" groups (239). They presented a congruent association between the physiological and the perceived falls risk. The rest were assigned to the groups in which the self-rated falls risk was inappropriately high ("Anxious") or low ("Stoic"). Patients in the "Anxious" group had more commonly depressive symptoms, higher levels of self-rated disability, problems in executive functions and lower reported quality of life. They performed more poorly in the coordinated stability tests compared to the group with an accurate perception of their fall risk ("Vigorous"). Patients in the "Stoic" group were younger, demonstrated a positive attitude to life, had fewer symptoms of

depression, did more planned exercise and had lower levels of self-rated disability than the patients in the "Aware" group, and were therefore better protected against future falls (239). Thus, it seems that the perception of subjective risk of fall - the psychological component of FoF - is likely to contribute to future falls.

The co-occurrence of cognitive impairment and FoF has been studied with mixed results. Symptom unawareness or "anosognosia" is a particular characteristic of patients with cognitive impairments and thus these patients may be incapable of acknowledging the functional deficits or FoF (241,242). A study by Sakurai and colleagues observed that FoF in older adults was associated with subjective memory complaints that might indicate a preliminary stage of cognitive disorders (243). Moreover, FoF has been identified in combination with psychological inflexibility which is linked to depressive mood and dementia (244,245).

FoF has been associated with decreased physical activity, problems in balance and gait and new falls (32). The adverse effect of FoF on functional capability seems to be higher in patients with higher baseline functions (234). Additionally, FoF generates social consequences by reducing functional independence, preventing participation in social activities and damaging identity (32,231).

2.8.2 Assessment tools

The tools used for the assessment of FoF can be divided into two groups: those which assess fear directly with a single question and those that survey performance and experience during a certain manoeuvre (246). Fear is a dynamic phenomenon, which evolves as rehabilitation progresses. As mentioned before, older patients represent a heterogeneous population with the whole spectrum of mental, cognitive and functional abilities. Pain, change in mobility level, amount of social support among other properties are affecting the sensation of fear. Tools should therefore be selected to best suit the target population, the scope of the intervention and practicality (230,247).

Scheffer and colleagues distinguished 15 different instruments with which to assess FoF (32). The most widely used are the Falls Efficacy Scale (FES), the Activities Specific Balance Confidence (ABC) scale or the Survey of Activities and Fear of Falling in the Elderly (SAFFE), which have subsequently been modified to suit different circumstances (32,248–250). The properties of common instruments are presented in *Table 5*.

Single-item tools are easy to use and inclusive since the question can elicit all the aspects of fear simultaneously (231). Furthermore, they are practical and feasible in patients with cognitive impairment although patients with cognitive impairment may often be excluded (244,246). However, a single-item tool does not distinguish the nature of fear (rational/irrational), its particular aspects or its magnitude (251).

Multi-item instruments are based on a solid theoretical background and focus on the specific characteristics of fear but they may include components that are irrelevant or impossible for patients with functional limitations or cognitive impairments (231,244,246,251).

Table 5. Overview of common screening tools for fear of falling.

Tool	Applicability	Content	Result
FES	Assessment of balance confidence or self-efficacy related to falls while performing normal daily activities	16 items scored with a 4-point scale from 1 to 4	16-19 = low concern about falls 20-27 = moderate concern about falls 28-64 = high concern about falls
ABC	Measurement of individual's confidence of not losing balance while performing activities	16 items each measured from 0-100% (0% = certainty of falling, 100% = complete confidence of stability). Final result is the average of the given answers	≤ 67% = individual is likely to experience fear of falling
SAFFE	To assess the role fear of falling in activity restriction	11 items each scored with a 4-point scale from 0-3	Higher score indicates greater fear of falling

FES=Falls Efficacy Scale (248), ABC=Activities-specific Balance Confidence scale (249), SAFFE=Survey of Activities and Fear of Falling in the Elderly (250)

2.8.3 Fear of falling in hip fracture patients

In addition to the physical injury, falling can cause psychological trauma. In fact, the psychological consequences of falling have been observed to have a more significant impact on disability than the fall itself (251). FoF is thus a common and important factor in older hip fracture patients. It has a more profound impact on rehabilitation outcomes than pain or depression (32,246). In hip fracture patients, FoF seems to cancel out the benefits of high baseline functions in achieving successful recovery (234).

FoF may not be present or may not have a significant effect on rehabilitation outcomes if measured immediately after surgery (234). Due to the dynamic nature of fear as an emotion, it may evolve during rehabilitation according to current health status (246). Oude Voshaar and colleagues speculate that level of fear during rehabilitation is a more important predictor for functional outcomes than fear immediately after surgery (12). Therefore, FoF should be assessed repeatedly throughout the rehabilitation process.

2.9 Summary of the literature

> "*If it were not for the great variability among individuals, medicine might as well be a science and not art.*" – Sir William Osler, 1892

Because of the globally ageing population, fragility fractures are becoming an increasing burden on societies and health care systems (252). Falls and fractures in geriatric patients seem to be multidimensional issues including concurring and overlapping somatic and psychological components (21,208). The body's ability to compensate and maintain homeostasis under stress is decreasing due to increase of chronological age alone, hindering the recovery process in this group of patients (194,253). Simultaneously exacerbating or silently developing comorbidities seem to be additional burden to the process (7,21,252).

At the core of geriatric care is the patient's ability to function in daily circumstances. Cognitive disorders, depressive mood and FoF have each been separately associated with decreased daily abilities with an additive effect when these symptoms act simultaneously. A comprehensive assessment is needed to determine the most beneficial interventions. When combined with orthopaedics, different models of orthogeriatric care have been associated with decreased complication rates, better cost-effectiveness and lower mortality rates (77,254). No single model of care has yet been proven to be superior, therefore, future research is warranted.

A major challenge in geriatric medicine is the heterogeneity of the patient population and multiple, possibly overlapping domains: cases often include, in addition to medical morbidity, social and functional properties (253–256). Patients with cognitive impairment are often excluded from trials, thereby omitting a significant patient population (42). This attitude of exclusion is also seen in studies on hip fracture patients (257). Patients often retain their capacity to participate, make decisions and give consent up to mild to moderate stage diseases (258). Excluding this significant population may impact outcomes, thereby casting doubt upon the applicability of the conclusions of such trials (257).

In light of this literature review, the psychocognitive factors including cognitive disorders, delirium during hospital care, post-hip fracture depressive mood and FoF seem to have an important role during recovery from hip fracture in geriatric patients. These symptoms share significant similarities in clinical presentation, co-occurrence and interactions, which calls for thorough appraisal. A CGA is warranted to accompany the patient from the initial hospital care through the recovery period to subsequent follow-up.

3 Aims

The aim of this study was to investigate new diagnoses of cognitive disorders emerging after hip fracture, related psychocognitive factors and their consequences during hospital care and recovery in older hip fracture patients. The specific aims of each part of the thesis were the following:

1) to identify the new diagnoses of cognitive disorders and associated factors in a two-year post-hip fracture follow-up
2) to evaluate the prognostic significance of in-hospital delirium on the development of new cognitive disorders in a one-year follow-up in older hip fracture patients in patients with no known diagnosis of cognitive disorder preoperatively
3) to examine the prevalence, severity and prognostic significance of post-hip fracture depressive mood and the clinical characteristics associated with it in a one-year follow-up
4) to investigate the factors associated with and one-year outcomes of post-hip fracture fear of falling.

4 Materials and Methods

4.1 Study population

The database from which the data for the present study was obtained was created at the beginning of orthogeriatric collaboration at Seinäjoki Central Hospital in September 2007. Data collection continued until January 2019.

Data were collected consecutively from patients aged 65 years or more suffering their first hip fracture (n=2,320). Pathological and periprosthetic fractures were excluded. All patients from a geographically defined area with a population of approximately 200,000 are treated in this same hospital providing acute surgical care.

4.2 Study design

In 2007, a care development programme was initiated in Seinäjoki Central Hospital for older hip fracture patients with the goal of improving the quality of care by standardized treatment guidelines. As a part of this development project, data collection was commenced for a database modified from the National Hip Fracture Database in the UK (259). Data collection was initiated on admission and continued throughout the hospital stay. The database includes demographic, surgical, medical, functional, social and outcome measures. Follow-up telephone interviews by a geriatric nurse at one-month, four months, one year and two years were scheduled. CGA at the geriatric outpatient clinic was scheduled four to six months after hip fracture. The properties of the care pathway and data collection have been constantly updated (9).

As a part of this care development project an interdisciplinary orthogeriatric committee was established including physicians from geriatric medicine, orthopaedic surgery and anaesthesia; nurses from the geriatric clinic and orthopaedic ward; and physiotherapists. The committee generated a written care programme with a standardized set of orders and instructions for hip fracture patients' hospital stay. Older hip fracture patients were moved from two different wards to one single ward. Each patient underwent a data collection interview with a geriatric nurse on admission. Geriatrician-led interdisciplinary rounds were commenced at first 1-3

times per week but later on all weekdays. The team included a geriatrician (or a resident), physiotherapist and a nurse from the orthopaedic ward. A nutritionist and other specialists were called upon if needed. The responsibility for the care was shared between an orthopaedic surgeon and a geriatrician. After the first postoperative day the main responsibility was transferred to the geriatrician. Discharge criteria and a recommendation for post discharge care were assigned. The principal objective was on individually tailored, multidisciplinary care throughout the hospital stay with a pre-planned follow-up (79).

4.3 Data collection

The present study utilized data collected on admission and on the orthopaedic ward, at the outpatient assessment 4-6 months post-hip fracture and the one-year and two-year follow-up interviews.

Eligible patients were identified by their diagnostic codes (ICD-10) of S72.0 (femoral neck fracture), S72.1 (pertrochanteric fracture) or S72.2 (subtrochanteric fracture) (260). Data collection was initiated by a structured interview conducted by a geriatric nurse with the patient, caregiver or next of kin. If needed, the patient's place of residence was contacted by telephone to obtain missing information. The interview was commonly conducted on the day of admission to hospital or the next prior to the surgical procedure. In some cases, the interview took place on the orthopaedic ward as soon as possible after the operation.

Patient-related data collected on admission included age, gender, fracture type, American Society of Anesthesiologists (ASA) score defining comorbidity, number of regularly taken medications, nutritional status according to the short form of the Mini-Nutritional Assessment (MNA-SF), presence of a prefracture diagnosis of cognitive disorder, prefracture mobility level and living arrangements (261,262). Delirium assessment was included in the treatment protocol in Semptember 2011. Nurses on the orthopaedic ward received training in assessing and detecting delirium episodes and in using CAM as a measuring tool (165).

All patients were invited to a CGA 4-6-months after hip fracture at the geriatric outpatient clinic. Caregivers or next of kin were invited to participate. The assessment included capabilities to diagnose cognitive disorders according to the national care guideline (105). A physiotherapist's assessment preceded the appointment, usually on the same day. If need for further examinations was noted during the hospital stay, these were conducted prior to the outpatient assessment according to the national care guideline (105).

Follow-up encounters at one and two years were conducted by telephone interview by the same experienced geriatric nurses who had met the patients during their ward care and at the outpatient assessment.

Information on dates of mortality was automatically updated to the electronic medical records from the National Population Register Centre.

4.4 Study participants and variables

The present thesis used the same database in all studies. The size of the patient samples and follow-up times varied between studies depending on the aim of each study. The content of each study is summarized in *Table 6*. Patients were included if complete documentation of the required data was available. Categorization of the variables is presented in *Table 7*.

Table 6. Patient sample in each study, follow-up period and outcomes.

	Patient sample	Number of patients eligible for analyses	Follow-up period	Outcomes
Study I	January 2010 to August 2015, n=1,165	831	2 years	New diagnoses of cognitive disorders - Alzheimer's Disease - Vascular Cognitive Impairment - Mixed Cognitive Impairment - Lewy Body Disease - Parkinson's disease-related dementia
Study II	October 2010 to August 2018, n=1,617	476	1 year	Delirium (positive CAM-test result) during hospital stay and new cognitive disorder (or strong suspicion of one)
Study III	September 2007 to December 2016, n=1,894	1,070	1 year	Depressive mood at the outpatient assessment and its association on change in mobility or living arrangements and mortality
Study IV	September 2007 to January 2019, n=2,320	916	1 year	Fear of falling at the outpatient assessment and its association on change in mobility or living arrangements and mortality

CAM=Confusion Assessment Method

4.4.1 Study I

Patients for Study I were collected between January 2010 and August 2015 (n=1,165). Of these, 334 (28.7%) had a diagnosed cognitive disorder at the time of the hip fracture and were therefore excluded. Ultimately, a sample of 831 patients was included in the follow-up. Baseline characteristics included age, gender, ASA score, MNA-SF, number of regularly taken medications, any known diagnosed cognitive disorder (yes/no), mobility level and living arrangements.

The diagnostic procedures for cognitive impairments were initiated if there was a clinical suspicion of a previously undiagnosed cognitive disorder either during

acute hip fracture care or at the outpatient CGA. Follow-up visits were scheduled if necessary. Medical history was extracted from the electronic patient files and by interviewing the patient and the next of kin or caregiver separately. Neuropsychological examinations carried out by a trained psychologist were also available at the outpatient clinic for purposes of differential diagnostics.

At the outpatient assessment MMSE, the Clock Drawing Test (CDT) and Clinical Dementia Rating (CDR) were used to assess cognition (263,264). In some cases, CERAD was completed before the outpatient assessment by the local memory nurse (265). Basic and instrumental activities of daily living (BADL, IADL) were assessed according to Katz and Lawton-Brody, respectively (266,267). Physiotherapist's assessment included Timed Up and Go (TUG) test and Elderly Mobility Scale (EMS) (268,269). Changes in mobility and living arrangements were scrutinized and compared to baseline. Basic laboratory tests were taken to exclude treatable causes of cognitive impairment. Computerized tomography brain scan or magnetic resonance imaging assessed by experts in neuroradiology was used as the imaging technique for the diagnostic evaluation in each patient. The diagnostic criteria for each type of cognitive disorder followed the currently valid care guideline for cognitive impairments (105). Diagnoses included AD, VCI, LBD, PD, and FTLD or a mixed aetiology of these. MCI was not included due to its position as a transitional phase between normal cognitive functions and specific diagnosis of a dementing disease (96). An experienced geriatrician or a resident in geriatric medicine under her supervision set the diagnoses of cognitive disorders.

Diagnoses of new cognitive disorders were extracted from the electronic patient files manually by the first author. Access was granted to scrutinize the electronic patient files of both the hospital and primary health care in the area. Prevalence of each diagnosis of cognitive disorder were calculated. Ultimately, domains of the outpatient assessment were crosstabulated according to having or not having an NDCD during the two-year follow-up.

4.4.2 Study II

Study II included patients from October 2010 to August 2018 (n=1,671). A group of 476 patients fulfilled the eligibility criteria and formed the final sample for analyses.

Age, gender, ASA-score, MNA-SF, mobility and living arrangements composed the baseline characteristics. At the follow-up outpatient assessment, information was included on whether there had been a documented episode of delirium during the hospital stay, i.e., a positive CAM test result during ward care.

Baseline characteristics accompanied by the CAM test result were analysed according to having or not having a newly diagnosed cognitive disorder at one-year time-point after hip fracture. Known diagnoses as set according to the national care

guideline by a specialist in geriatric medicine, a resident of geriatric medicine under her supervision, or a neurologist were obtained by a telephone interview with the patient, caregiver or nurse at the care facility in which the patient was accommodated (105). The diagnostic process was scrutinized from the medical records. In this study, exact diagnoses of known cognitive disorders were not further specified. Diagnostic investigations in some of the patients were incomplete at the one-year time-point signifying suspicion of a cognitive disorder but that not all the necessary diagnostic investigations had been completed. Therefore, for the purposes of analysis, they were pooled together with the established cognitive disorders.

4.4.3 Study III

Patients for Study III were collected between September 2007 and December 2016 (n=1,894). A total of 1,070 patients had complete documentation of the required data and formed the final sample.

At baseline, age, gender, ASA score, MNA-SF, known diagnosis of cognitive disorder, mobility level and living arrangements were documented. At the outpatient assessment, MMSE, TUG, EMS, BADL and IADL were included along with change in mobility level and living arrangements.

Depressive symptoms were measured at the outpatient assessment 4-6 months post-hip fracture by the GDS-15. The results were categorized into three groups: no depressive symptoms (0-5), mild depressive symptoms (6-9) or moderate/severe depressive symptoms (10-15).

4.4.4 Study IV

Study IV included patients treated from September 2007 to January 2019 (n=2,320). Ultimately, 916 patients had complete documentation of the required measures and formed the final sample.

In this study, baseline characteristics included age, gender, ASA score, scene of the accident, known diagnosis of a cognitive disorder pre-fracture, number of regularly taken medications, MNA-SF, mobility level, living arrangements and living modality (whether living alone or with company).

FoF was assessed for practicality and feasibility with a dichotomous single-item question (“Do you have a fear of falling?” yes/no). The interview was carried out at the outpatient assessment by geriatric nurses together with the patient and his/her escort.

Other domains of the outpatient assessment included whether there had been new falls since the hip fracture; whether the patient suffered from pain in the operated hip; if the patient suffered from urinary incontinence defined as any

involuntary leakage of urine. Orthostatic blood pressure was measured and defined as positive if blood pressure decreased according to the diagnostic standards (systolic: 20 mmHg or more, or diastolic: 10 mmHg or more respectively) (260). Fracture types were defined as femoral neck, intertrochanteric or subtrochanteric fractures according to the study protocol. Nutritional status was assessed using the MNA-SF by the same methods as before. BADL and IADL were documented as in the earlier studies. For cognition assessment, MMSE, CDT and CDR were used. Depressive mood was analysed with the GDS-15. Besides TUG and EMS, grip strength of the dominant arm measured by Jamar-dynamometer was included from the physiotherapist's assessment. Change in living modality and mobility level were elicited from the patient or, if necessary, from the next of kin, caregiver or care facility personnel. Information on mortality dates was obtained from the medical records to which they were automatically updated from the National Population Register Centre.

Table 7. Categorization of variables included in the studies.

Domain	Categorization	Included in study
Baseline characteristics		
Age	• 65-79 • 80-89 • >90	I-IV
Gender	• Female • Male	I-IV
ASA score[1]	• 1-3 • 4-5 or • 1-2 • 3 • 4-5	II-IV I
Scene of the accident	• Indoors • Outdoors	IV
Number of medications in regular use	• ≤4 • 5-10 • ≥10	I, IV
Prefracture diagnosis of a cognitive impairment	• Yes • No	IV
MNA-SF[2]	• ≤7 • 8-11 • 12-14	I-IV
Mobility level	• Independent • Non-independent	I-IV
Living arrangements	• Home, unassisted • Home, assisted • Assisted living arrangements	I-IV
Living modality	• Living alone • With company	IV

Domain	Categorization	Included in study
Outpatient assessment		
Fracture type[4]	• Femoral neck • Intertrochanteric • Subtrochanteric	IV
BADL[5]	• No difficulties, 6 • Difficulties at least in one area, ≤5	I, III, IV
IADL[6]	• No difficulties, 8 • Difficulties at least in one area, ≤7	I, III, IV
MMSE[7]	• Normal cognition, ≥25 • Mild cognitive impairment, 21-24 • Moderate cognitive impairment, 12-20 • Severe cognitive impairment, ≤11	I-IV
CDT[8]	• Normal 5-6 • 3-4 • ≤2	I, IV
CDR[9]	• No or possible dementia, 0-0.5 • Mild dementia, 1 • Moderate to severe dementia	I, IV
GDS-15[10]	• No depressive symptoms, 0-5 • Mild depressive symptoms, 6-9 • Moderate to severe depressive symptoms, ≥10	III, IV
TUG[11]	• Normal, 1-2 • Moderately abnormal, 3-4 • Markedly abnormal, 5	I, III, IV
EMS[12]	• Independent, >14 • Borderline independence, some assistance needed in daily activities, 6-13 • Dependent on assistance in daily activities, <5	I, II, IV
Grip strength of the dominant arm[13]	• Normal, >27kg in male and >16kg in female • Abnormal, ≤27kg in male and ≤16kg in female	IV

1) ASA=American Society of Anesthesiologists score, 2) MNA-SF=Mini-Nutritional Assessment-Short Form, 3) Definition of orthostatic hypotension: Decrease in systolic blood pressure ≥ 20 mmHg or in diastolic blood pressure ≥ 10 mmHg, 4) According to ICD-10 (S72.0-S72.2), 5) BADL=Basic Activities of Daily Living, 6) IADL=Instrumental Activities of Daily Living, 7) MMSE=Mini-Mental State Examination, 8) CDT=Clock Drawing Test, 9) CDR=Clinical Dementia Rating, 10) GDS-15=15-item Geriatric Depression Scale, 11) TUG=Timed Up and Go, 12) EMS=Elderly Mobility Scale, 13) Measured with Jamar-dynamometer

4.5 Statistical analyses

The statistical difference between groups was tested with Pearson's chi-square test, Fisher's exact test for categorical variables and t-test or Mann-Whitney test of continuous variables. Logistic regression analyses with adjusted models or Cox proportional hazard models for mortality were performed to examine the association of clinical features with the specific interests of each study

Study I. The distribution of baseline variables and CGA domains in accordance with receiving or not receiving an NDCD were described by number of patients with percentages for categorical variables. Continuous but skewed variables were

described by medians with interquartile ranges. Age and gender adjusted logistic regression analyses with odds ratios (OR) and 95% confidence intervals (CI) were conducted to examine the associations of each of the baseline variables and CGA domains with a NDCD.

Study II. The distribution of the baseline factors according to the CAM test result (negative or positive) in cross-tabulation were described in numbers of patients and percentages. Age- and multivariable-adjusted logistic regression analyses with ORs and 95% CIs were conducted to examine the association of CAM and the chosen baseline factors with a new cognitive disorder.

Study III. A cross-tabulation of the baseline variables and the outpatient control domains according to the depressive symptoms classified by the GDS-15 was performed. Logistic regression analyses with unadjusted, age- and gender-adjusted and multivariable-adjusted models were conducted to examine the association of mild and moderate to severe depressive symptoms with deterioration in mobility and need for more supported living arrangements from the outpatient assessment to one year post-hip fracture. Mortality was likewise analysed by Cox proportional hazard regression model. Model 1 was adjusted for age, gender, and baseline mobility and living arrangements. Model 2 was further adjusted for ASA, MMSE, TUG, EMS, BADL and IADL. Results were shown as ORs or hazard ratios (HR) with 95% CIs.

Study IV. Cross-tabulation of the baseline factors and the outpatient assessment domains according to FoF were analysed. Logistic regression analyses with age- and gender-adjusted and multivariable-adjusted models were conducted to examine the association of clinical attributes with post-fracture FoF. The multivariable models were adjusted for new falls before the outpatient assessment, pain in the operated hip, urinary incontinence, orthostatic hypotension, fracture type, nutritional status, functional and cognitive abilities, depressive mood, physical performance and living modality. The impact of FoF on the one-year follow-up outcomes was analysed by an age- and gender-adjusted logistic regression analysis for change in mobility or living arrangements. Results of the logistic regression analyses are shown using ORs and 95% CIs. One-year mortality was modelled using age- and gender-adjusted Cox proportional hazard regression analyses. Results are shown as HRs with 95% CIs. Risk-scoring for risk of having FoF was defined calculating the sum of statistically significant or nearly significant ($p<0.10$) variables in the multivariable-adjusted logistic regression analyses (female gender, having a cognitive disorder diagnosed pre-fracture, at least four medications, orthostatic hypotension, BADL≤5, IADL≤7, GDS-15 7-15, abnormal TUG and/or living alone). Each of these factors contributed one point. The theoretical maximum was nine points.

IBM SPSS Statistics version 26.0 (SPSS Inc. Chicago, Illinois) was used for statistical analyses. P-values under 0.05 were considered statistically significant.

4.6 Ethical considerations

The original study design was reviewed and approved in the meeting of the Ethics Committee of what was then the Hospital District of Southern Ostrobothnia on 1 November 2007. All participants or their representatives (legal guardian or next of kin) gave consent to participate the study.

5 Results

5.1 Study I

5.1.1 New diagnoses of cognitive disorders during two-year follow-up

From the initial patient sample of 831 patients, 26.7% (n=238) died during follow-up. NDCD was documented in 194 (23.3%) patients. AD was the most common diagnosis (n=79, 40.7%) followed by AD+VCI (n=73, 37.6%) and VCI alone (n=23, 11.8%). LBD, PD, alcohol-induced dementia and even rarer aetiologies such as dementia with amyotrophic lateral sclerosis and a case of Fahr's disease were diagnosed in altogether 19 (9.8%) patients. Dementia was deemed undefined in 10 (5.1%) patients.

5.1.2 Associated factors of the outpatient CGA

Of the baseline factors, higher age (>90 years, OR 3.13, 95% CI 1.74-5.64) and higher ASA score were associated with NDCDs (ASA 4-5, OR 2.61, 95% CI 1.37-4.95). Being at risk for malnutrition (MNA 8-11, OR 1.95, 95% CI 1.30-3.78), non-independent mobility (OR 2.05, 95% CI 1.36-3-07) or living in more supported living arrangements (OR 2.39. 95% CI 1.40-4.08) were also associated with NDCDs within the two-year follow-up.

All the results of tools used for cognition assessment at the outpatient clinic were associated with NDCDs. Patients with NDCDs had more difficulties in daily living according to the ADL tests and they performed more poorly in the physiotherapist's examinations. They were also more likely to have declined mobility level and need for more assisted living arrangements compared to the situation before the hip fracture. A detailed description of the study population is shown *Table 8*.

Table 8. Distribution of the domains of the post-hip fracture comprehensive geriatric assessment in relation with newly diagnosed cognitive disorders during follow-up (n = 541). From Original Publication I (270). Reproduced with permission from Springer Nature.

Domain	No cognitive disorder (n=347)		Cognitive disorder (n=194)			Age and sex adjusted cognitive disorder, yes vs. no	
	n	(%)	n	(%)	p	OR	95%CI
MMSE							
26-30	139	(40.1)	9	(4.6)		1.00	
21-25	119	(34.3)	46	(23.7)		5.56	(2.60-11.9)
12-20	42	(12.1)	96	(49.5)		32.2	(14.8-70.2)
<12	5	(1.4)	18	(9.3)		53.2	(15.7-180)
Unknown	42	(12.1)	25	(12.9)		8.42	(3.57-19.8)
Clock Drawing Test					<0.001		
5-6	139	(40.1)	17	(8.8)		1.00	
2-4	118	(34.0)	75	(38.7)		4.55	(2.52-8.23)
0-1	35	(10.1)	71	(36.6)		14.31	(7.41-27.6)
Unknown	55	(15.9)	31	(16.0)		3.58	(1.78-7.18)
CDR					<0.001		
0-0.5	127	(36.6)	10	(5.2)		1.00	
1	92	(26.5)	46	(23.7)		6.12	(2.91-12.9)
2-3	17	(4.9)	90	(46.4)		62.68	(27.2-14.5)
Unknown	111	(32.0)	48	(24.7)		5.44	(2.60-11.4)
BADL					<0.001		
No difficulties, 6	167	(48.1)	44	(22.7)		1.00	
Difficulties at least in one, ≤5	134	(38.6)	125	(64.4)		3.05	(2.00-4.66)
Unknown	46	(13.3)	25	(12.9)		1.61	(0.87-2.97)
IADL					<0.001		
No difficulties, 8	96	(27.7)	7	(3.6)		1.00	
Difficulties in at least one, ≤7	205	(59.1)	162	(83.5)		8.90	(3.98-19.9)
Unknown	46	(13.3)	25	(12.9)		5.54	(2.18-14.1)
TUG Time, Median (IQR)	18.9	(13.3-26.4)	25.0	(19.6-34.4)	<0.001		
Normal, 1-2	142	(40.9)	48	(24.7)		1.00	
Moderately abnormal, 3-4	133	(38.3)	82	(42.3)		1.59	(1.03-2.47)
Markedly abnormal, 5	8	(2.3)	14	(17.2)		4.52	(1.75-11.7)
Unknown	64	(18.4)	50	(25.8)		1.76	(1.05-2.96)

Domain	No cognitive disorder (n=347)		Cognitive disorder (n=194)			Age and sex adjusted cognitive disorder, yes vs. no	
	n	(%)	n	(%)	p	OR	95%CI
EMS					<0.001		
≥14	258	(74.4)	107	(55.2)		1.00	
6-13	34	(9.8)	44	(22.7)		2.61	(1.56-4.37)
≤5	10	(2.9)	7	(3.6)		1.52	(0.55-4.18)
Unknown	45	(13.0)	36	(18.6)		1.57	(0.94-2.62)
Living arrangements					<0.001		
Same or less supported	258	(74.4)	113	(58.2)		1.00	
More supported	74	(21.3)	76	(39.2)		2.06	(1.38-3.08)
Unknown	15	(4.3)	5	(2.6)		0.76	(0.26-2.14)
Mobility					<0.001		
Same or improved	247	(71.2)	94	(48.5)		1.00	
More impaired	89	(25.6)	94	(48.5)		2.38	(1.51-3.50)
Unknown	10	(2.9)	6	(3.1)		1.45	(0.50-4.17)
Nutritional status, MNA-SF					0.031		
Same or better	218	(62.8)	100	(51.5)		1.00	
Worse	77	(22.2)	60	(30.9)		1.63	(1.07-2.50)
Unknown	52	(15.0)	34	(17.5)		1.18	(0.70-1.96)

MMSE=Mini-Mental State Examination, CDR=Clinical Dementia Rating, BADL=Basic Activities of Daily Living, IADL=Instrumental Activities of Daily Living, TUG=Timed Up and Go, EMS=Elderly Mobility Scale, MNA-SF=Mini-Nutritional Assessment, short form

5.2 Study II

5.2.1 Incidence of postoperative delirium

Of the 1,617 patients treated for hip fracture during the selected time period, a CAM test result was documented from 981 (61%) patients. Of these, 285 (29%) patients had cognitive disorder diagnosed pre-fracture and 154 (16%) patients had died before completion of the follow-up. Of the 285 patients already having a diagnosed cognitive disorder pre-fracture, 111 (39%) had a positive CAM test result. Data was incomplete in 66 cases (7%). Therefore, data on 476 patients was included in the final analyses. Positive CAM test result, i.e., delirium, was observed in 87 (18%) patients.

5.2.2 Association of delirium with new diagnoses of cognitive disorders

After one-year follow-up, established NDCD (n=102) or a strong suspicion thereof (n=103) was documented in 205 (43%) patients. Distribution of baseline factors associated with NDCDs at one-year follow-up are shown in *Table 9*. In the multivariable analyses, where the CAM test result and all the control variables were simultaneously adjusted for, the positive CAM test result remained strongly associated with NDCD (OR 2.29; 95% CI 1.39-3.79). In addition, patients who were 80-89 years of age or with poor nutritional status showed a significant association with NDCD (OR 1.62, 95% CI 1.04-2.51 and OR 1.05, 95% CI 1.03-2.43 respectively).

Table 9. Distribution of baseline factors according to having or not having a cognitive disorder at one-year follow-up (n=476). From Original Publication II (271). Reproduced with permission from S. Karger AG, Basel.

Domain	**No cognitive disorder**, n=271 (57%)		**Cognitive disorder**, n=205 (43%)			**Age-adjusted model**		**Multivariable-adjusted model**	
	n	(%)	n	(%)	p	OR	(95% CI)	OR	(95% CI)
Age					0.022				
65-79	109	(40)	59	(29)		1.00			
80-89	120	(44)	115	(56)		1.77	(1.18-2.66)	1.62	(1.04-2.51)
>90	42	(16)	31	(43)		1.36	(0.78-2.39)	1.11	(0.59-2.12)
Gender					0.381				
Female	204	(75)	147	(72)		1.00			
Male	67	(25)	58	(28)		1.34	(0.87-2.06)	1.35	(0.86-2.09)
CAM test					<0.001				
Negative	239	(88)	150	(73)		1.00			
Positive	32	(12)	55	(27)		2.59	(1.60-4.22)	2.29	(1.39-3.79)
ASA score					0.713				
1-3	235	(87)	176	(86)		1.00			
4-5	33	(12)	28	(14)		1.13	(0.65-1.95)	1.05	(0.59-1.85)
MNA-SF					0.005				
12-14	200	(74)	127	(62)		1.00			
<11	71	(26)	76	(37)		1.65	(1.10-2.45)	1.58	(1.03-2.43)
Mobility					0.098				
Independent	216	(80)	148	(72)		1.00			
Non-independent	54	(20)	56	(27)		1.39	(0.89-2.17)	1.00	(0.60-1.68)
Living arrangements					0.027				
Home, independent	184	(68)	119	(58)		1.00			
Supported accommodation	87	(32)	86	(42)		1.46	(0.98-2.19)	1.19	(0.76-1.87)

Differences between groups of patients with or without cognitive disorder were determined using logistic regression analysis with odds ratios (OR) and 95% confidence intervals (CI). Multivariable-adjusted analysis included age, gender, Confusion Assessment Method (CAM), American Society of Anesthesiologists score (ASA), Mini-Nutritional Assessment - short form (MNA-SF), mobility and living arrangements. Results for unknown data (ASA n=2, MNA-SF n=1, and mobility n=2) not shown

5.3 Study III

5.3.1 Prevalence of post-hip fracture depressive mood

A total of 1,070 patients fulfilled the inclusion criteria and formed the final sample. Of these, 22% (n=238) were documented to have mild depressive symptoms, while 6% (n=67) had moderate to severe depressive symptoms at the outpatient assessment.

5.3.2 Factors associated with depressive mood

Descriptive figures of the data are collected in *Table 10.* There were no significant differences in the distribution of gender or ASA score in patients with or without depressive symptoms, but patients with depressive symptoms were more likely to be older, to have a pre-fracture diagnosis of cognitive disorder, poor nutritional status, non-independent mobility level or to have more supported living arrangements than the patients without depressive symptoms. Patients with depressive symptoms were also significantly more likely to have more often decline in mobility from baseline to outpatient assessment than patients with no depressive symptoms. No statistically significant difference was observed between patients with or without depressive symptoms in moving to more supported living accommodation from the time of the fracture to the outpatient assessment.

Table 10. Distribution of baseline characteristics and domains of the outpatient assessment according to severity of depressive symptoms at the follow-up visit 4-6 months after hip fracture (n=1,070). From Original Publication III (272). Reprinted by permission of Infoma UK Limited, trading as Taylor & Francis Group © 2021.

Domain	**No depressive symptoms**, (GDS-15 0-5, n=765, 72%)		**Mild depressive symptoms**, (GDS-15 6-9, n=238, 22%)		**Moderate to severe depressive symptoms**, (GDS-15 10-15, n=67, 6%)		
	n	(%)	n	(%)	n	(%)	p
Baseline							
Gender							0.614
Female	569	(74)	181	(76)	47	(70)	
Male	196	(26)	57	(24)	20	(30)	
Age							0.014
65-79	265	(39)	65	(27)	22	(33)	
80-89	383	(50)	143	(60)	33	(49)	
≥90	87	(11)	30	(13)	12	(18)	
ASA score							0.452
1-3	642	(84)	189	(79)	56	(84)	
4-5	114	(15)	45	(19)	11	(16)	
Unknown	9	(1)	4	(2)	0	(0)	
Diagnosed cognitive disorder							<0.001
Yes	154	(20)	56	(23)	21	(31)	
No	610	(80)	182	(77)	45	(67)	
Unknown	0	(0)	0	(0)	1	(2)	
MNA-SF							0.014
12-14	376	(49)	97	(41)	23	(34)	
8-11	173	(23)	69	(29)	27	(40)	
0-7	24	(3)	10	(4)	1	(2)	
Unknown	192	(25)	62	(26)	16	(4)	
Mobility							<0.001
Independent	557	(73)	125	(52)	36	(54)	
Non-independent	208	(27)	113	(48)	31	(46)	
Living arrangements							<0.001
Home, independent	437	(57)	94	(39)	22	(33)	
Supported accommodation	328	(43)	144	(61)	45	(67)	

Domain	**No depressive symptoms**, (GDS-15 0-5, n=765, 72%)		**Mild depressive symptoms**, (GDS-15 6-9, n=238, 22%)		**Moderate to severe depressive symptoms**, (GDS-15 10-15, n=67, 6%)		
	n	(%)	n	(%)	n	(%)	p
Outpatient assessment							
MMSE							<0.001
26-30	207	(27)	40	(17)	9	(13)	
21-25	234	(31)	65	(27)	17	(25)	
12-20	248	(32)	93	(39)	29	(43)	
<12	75	(10)	39	(16)	12	(18)	
Unknown	1	(0)	1	(0)	0	(0)	
TUG							<0.001
Normal (1-2)	256	(34)	43	(18)	15	(22)	
Moderately abnormal (3-4)	345	(46)	116	(49)	28	(42)	
Markedly abnormal (5)	35	(5)	29	(12)	7	(10)	
Unknown	120	(16)	50	(21)	17	(26)	
EMS							<0.001
>14	566	(74)	123	(52)	37	(55)	
6-13	118	(15)	81	(34)	19	(28)	
<5	39	(5)	18	(8)	4	(6)	
Unknown	42	(6)	16	(7)	7	(10)	
BADL							<0.001
No difficulties, 6	329	(43)	39	(16)	16	(24)	
Difficulties in at least in one area, ≤5	419	(55)	197	(83)	49	(73)	
Unknown	17	(2)	2	(1)	2	(3)	
IADL							<0.001
No difficulties, 8	160	(21)	10	(4)	2	(3)	
Difficulties in at least in one area, ≤7	586	(77)	226	(95)	63	(94)	
Unknown	19	(3)	2	(1)	2	(3)	
Mobility							<0.001
Independent	367	(48)	65	(27)	13	(19)	
Non-independent	393	(51)	171	(72)	52	(78)	
Unknown	5	(1)	2	(1)	2	(3)	

Domain	**No depressive symptoms**, (GDS-15 0-5, n=765, 72%)		**Mild depressive symptoms**, (GDS-15 6-9, n=238, 22%)		**Moderate to severe depressive symptoms**, (GDS-15 10-15, n=67, 6%)		
	n	(%)	n	(%)	n	(%)	p
Living arrangements							<0.001
Home, independent	312	(41)	54	(23)	11	(16)	
Supported accommodation	443	(58)	182	(77)	55	(82)	
Unknown	9	(1)	2	(1)	1	(2)	
Change in mobility							0.001
Same or better	495	(65)	136	(57)	29	(43)	
Declined	265	(35)	100	(42)	36	(54)	
Unknown	5	(1)	2	(1)	2	(3)	
Change in living arrangements							0.072
Same or better	532	(70)	148	(62)	39	(58)	
Declined	223	(29)	88	(37)	27	(40)	
Unknown	10	(1)	2	(1)	1	(2)	

ASA=American Society of Anesthesiologists score, MNA-SF=Mini-Nutritional Assessment-Short Form, MMSE=Mini-Mental State Examination, TUG=Timed Up and Go, EMS=Elderly Mobility Scale, BADL=Basic Activities of Daily Living, IADL=Instrumental Activities of Daily Living

5.3.3 Association of depressive mood with follow-up outcomes

In the unadjusted logistic regression analysis, neither mild nor moderate to severe depressive symptoms showed any significant association with decline in mobility level from the outpatient assessment to one-year post-hip fracture (OR 1.35; 95% CI 0.88-2.08 and OR 1.25; 95% CI 0.60-2.63 respectively). No associations were observed in the further adjusted models. Depressive symptoms were not significantly associated with moving to more supported living accommodation in any of the analyses. Mild or moderate to severe depressive symptoms were likewise not associated with one-year mortality.

5.4 Study IV

5.4.1 Prevalence of post-hip fracture fear of falling

From the sample including 2,320 patients 475 (20%) had died before the outpatient assessment. A total of 345 (15%) patients had not attended the outpatient clinic within the desired time period. Data on FoF were missing from 580 (25%) patients. Ultimately, the final sample comprised 916 (39%) patients. Almost half of the patients reported FoF at the outpatient assessment (n=452, 49%).

5.4.2 Factors associated with fear of falling

Of the baseline characteristics, FoF was more common in women (OR 1.46, 95% CI 1.08-1.98) and in patients taking four to ten medications regularly (OR 1.56, 95% CI 1.07-2.2.26). Cognitive disorder diagnosed pre-fracture remained inversely associated with FoF (OR 0.51, 95% CI 0.36-0.73) in the multivariable-adjusted model

In the age and gender adjusted analyses of domains documented at the outpatient assessment, orthostatic hypotension (OR 1.59, 95% CI 1.12-2.26), difficulties in daily activities (BADL OR 1.57, 95% CI 1.18-2.09 and IADL OR 1.79, 95% CI 1.23-2.60), CDR-score of 0.5 (OR 1.51, 95% CI 1.00-2.28), depressive mood (OR 2.28, 95% CI 1.59-3.26) and poorer physical performance were more common in patients with FoF than in those without. In the multivariable model including all variables, EMS lost its significance. FoF was more common in patients living alone (OR 1.45, 95% CI 1.05-2.00) than in those living with company. Patients with mild to severe dementia as indicated by the CDR score reported less FoF than did those with normal cognition or only mild dementia. However, different levels of cognition as measured with the MMSE, or the CDT were not associated with FoF. Domains of

the outpatient assessment according to having or not having FoF are shown in *Table 11*.

The overall rate of having FoF at the geriatric assessment grew steadily as the number of concurrent risk factors increased

5.4.3 Association of fear of falling with follow-up outcomes

FoF was not significantly associated with the follow-up outcomes between outpatient assessment and one-year post-fracture after adjusting for age and gender: change in living arrangements OR 0.81, 95% CI 0.53-1.23, change in mobility OR 1.15, 95% CI 0.75-1.76 and mortality hazard ratio (HR) 1.25, 95% CI 0.66-2.3.

Table 11. Distribution of domains of the outpatient assessment according to having or not having fear of falling (n=916). From Original Publication IV (273). Reproduced with permission from Springer Nature.

Domain	YES (n=452, 49%)	NO (n=464, 51%)		Adjusted for age and gender	Multivariable adjusted
	n (%)	n (%)	p	OR (95% CI)	OR (95% CI)
New fall before outpatient assessment			0.010		
No	361 (81)	395 (88)		1.00	1.00
Yes	83 (19)	56 (12)		1.61 (1.11-2.33)	1.33 (0.89-1.99)
Pain in operated hip			0.291		
No	301 (67)	324 (70)		1.00	1.00
Yes	147 (33)	136 (30)		1.15 (0.87-1.52)	1.02 (0.75-1.38)
Urinary incontinence			0.057		
No	161 (36)	194 (42)		1.00	1.00
Yes	285 (64)	265 (58)		1.19 (0.91-1.57)	1.04 (0.74-1.45)
Orthostatic hypotension[1]			0.034		
No	318 (70)	347 (75)		1.00	1.00
Yes	94 (21)	67 (14)		1.59 (1.12-2.26)	1.42 (0.97-2.07)
Unknown	40 (9)	50 (11)		0.86 (0.55-1.34)	0.48 (0.26-0.88)
Fracture type			0.154		
Femoral neck fracture	271 (60)	283 (61)		1.00	1.00
Pertrochanteric fracture	140 (31)	154 (33)		0.92 (0.69-1.23)	0.86 (0.63-1.16)
Subtrochanteric fracture	40 (9)	26 (6)		1.55 (0.92-2.63)	1.54 (0.88-2.72)
MNA-SF			0.088		
12-14	186 (41)	215 (46)		1.00	1.00
8-11	214 (47)	206 (44)		1.16 (0.88-1.53)	1.00 (0.72-1.38)
≤7	50 (11)	41 (9)		1.33 (0.84-2.10)	1.11 (0.64-1.90)
BADL			0.002		
No difficulties, 6	129 (29)	183 (39)		1.00	1.00
Difficulties in at least one area, ≤5	315 (70)	274 (59)		1.57 (1.18-2.09)	1.57 (1.04-2.36)
IADL			0.008		
No difficulties, 8	57 (13)	94 (20)		1.00	1.00
Difficulties in at least one area, ≤7	387 (86)	363 (78)		1.79 (1.23-2.60)	1.38 (0.87-2.17)
MMSE			0.953		
26-30	112 (25)	112 (24)		1.00	1.00
21-25	121 (27)	121 (26)		0.96 (0.66-1.39)	0.67 (0.44-1.02)
13-20	150 (33)	151 (33)		0.91 (0.63-1.30)	0.67 (0.41-1.11)
≤12	56 (12)	64 (14)		0.78 (0.49-1.23)	0.69 (0.34-1.37)

Domain	YES (n=452, 49%)	NO (n=464, 51%)		Adjusted for age and gender	Multivariable adjusted
	n (%)	n (%)	p	OR (95% CI)	OR (95% CI)
Clock drawing test			0.256		
5-6	97 (22)	121 (26)		1.00	1.00
2-4	179 (40)	158 (34)		1.31 (0.92-1.87)	1.24 (0.83-1.86)
<2	144 (32)	150 (32)		1.09 (0.76-1.58)	1.15 (0.68-1.92)
CDR			0.005		
0	77 (17)	81 (18)		1.00	1.00
0.5	136 (30)	97 (21)		1.51 (1.00-2.28)	1.05 (0.66-1.66)
1-3	138 (31)	183 (39)		0.72 (0.49-1.07)	0.41 (0.24-0.68)
Unknown	101 (22)	103 (22)		1.12 (0.73-1.70)	0.78 (0.49-1.23)
GDS-15			0.001		
0-6	324 (72)	386 (83)		1.00	1.00
7-15	105 (23)	56 (12)		2.28 (1.59-3.26)	1.97 (1.32-2.94)
Unknown	23 (5)	22 (5)		1.19 (0.65-2.17)	2.40 (0.91-6.33)
TUG			0.001		
Normal (1-2)	143 (32)	200 (43)		1.00	1.00
Moderately abnormal (3-4)	200 (44)	188 (41)		1.46 (1.08-1.97)	1.39 (0.97-1.98)
Markedly abnormal (5)	35 (8)	21 (5)		2.45 (1.36-4.42)	3.14 (1.49-6.63)
Unknown	74 (16)	55 (12)		1.84 (1.21-2.78)	3.38 (1.76-6.47)
EMS			0.021		
>14	281 (62)	328 (71)		1.00	1.00
<14	147 (33)	114 (25)		1.48 (1.10-2.00)	1.05 (0.69-1.59)
Grip strength decreased[2]			0.469		
No	100 (22)	118 (25)		1.00	1.00
Yes	330 (73)	322 (69)		1.32 (0.98-1.79)	1.14 (0.81-1.60)
Unknown	22 (5)	24 (5)		1.09 (0.58-2.05)	0.69 (0.30-1.66)
Living modality			0.167		
With company	283 (63)	310 (67)		1.00	1.00
Alone	166 (37)	150 (33)		1.15 (0.87-1.51)	1.45 (1.05-2.00)

Multivariable model was simultaneously adjusted for all the variables included in the table. ASA=American Society of Anesthesiologists score, MNA-SF=Mini-Nutritional Assessment-Short Form, MMSE=Mini-Mental State Examination, CDR=Clinical Dementia Rating, TUG=Timed Up and Go, EMS=Elderly Mobility Scale, BADL=Basic Activities of Daily Living, IADL=Instrumental Activities of Daily Living, GDS-15=15-item Geriatric Depression Scale. Differences between fear of falling groups were tested using Pearson chi-square test or Fisher's exact test and logistic regression analysis showing results by odds ratios (OR) with 95% confidence intervals (CI). Results for unknown data were shown if results were statistically significant ($p<0.05$) or nearly significant ($0.05>p<0.10$), or if number of unknown data was over 20%. Statistically significant results were expressed in bold.

1) Definition of orthostatic hypotension: Decrease in systolic blood pressure ≥ 20 mmHg or in diastolic blood pressure ≥ 10 mmHg (260)

2) Grip strength of the dominant arm less than 27 kg in men and less than 16 kg in women (179)

6 Discussion

This real-life follow-up study of older patients revealed clinically relevant psychocognitive factors associated with hip fracture recovery. We implemented a systematic approach from initial hospital admission to ward care, comprehensive outpatient clinical assessment and follow-up interviews to study these complicated conditions. Psychocognitive factors seemed to have an important role in hip fracture recovery offering new routes for interventions and treatment.

Cognitive disorders are globally underdiagnosed even though they are among the major geriatric syndromes with substantial impact on patients' care. As far as we know, this was the first study to report the most reliable diagnoses of different cognitive disorders after hip fracture. Cognitive disorders can affect gait and stability control, which may partly explain the falls causing hip fracture. Symptoms of cognitive decline may be exacerbated by acute trauma or they are detected during the postoperative follow-up period.

Delirium during hospital care was associated with malnutrition and subsequent cognitive decline. Therefore, it deserves to be noted and addressed accordingly as an important indication of reduced cognitive reserves in this frail patient population. Systematic follow-up with capabilities to diagnose cognitive disorders is warranted for geriatric hip fracture patients.

Postoperative depressive mood seemed to be mostly a reactive symptom to the traumatic injury, impaired mobility and loss of independence. Furthermore, it was associated with malnutrition and lower scores on cognitive and physical performances at the outpatient assessment, which corroborates earlier studies linking depressive mood with dementia and frailty: these conditions have been detected to have significant overlap, co-occurrence and interaction (195). FoF is a multifactorial condition affecting both the physical performance and mood of hip fracture patients. Interestingly, patients with known cognitive disorders reported less FoF than those without cognitive impairments. Neither depressive mood nor FoF were decisive factors in the recovery outcomes of mortality, change in living arrangements or mobility level.

Our pragmatic approach aimed to further underline the importance of CGA in clinical practice and the care of older patients aligning treatment targets with the patients' priorities.

6.1 New cognitive disorders after hip fracture (Study I)

Previously undiagnosed or imperceptibly developing cognitive disorders were common in older hip fracture patients, as might have been presumed according to earlier observations (9). The severity of new cognitive disorders had often reached a moderate or severe stage before diagnosis. This emphasizes the need for earlier detection of cognitive disorders and neurodegenerative processes. Moreover, falls risk assessment deserves to be included in the diagnostic investigations of cognitive disorders as a preventive measure of fall-related injuries such as hip fractures. Systematic follow-up and cognitive screening a few months after the hip fracture for older patients suffering their first hip fracture are strongly recommended.

Cognitive trajectories after hip fracture have been studied but there seems to be a gap in what is known about the specific diagnoses of cognitive disorders even though a growing body of literature has described an association between critical illness and cognitive impairment (194,274–276). In a real-life study of Swedish hip fracture patients by Samuelsson and co-workers, cognitive dysfunction was observed in 55% of the cases (276). The method for cognitive assessment was the Short Portable Mental Status Questionnaire, which is a valid screening tool for organic brain syndromes but is not sufficient for definitive diagnoses (105,277,278). A more elaborate instrument, the MMSE, was used by Beishuizen and colleagues in their study: from a sample of 209 patients, 127 patients (61%) received a score lower than 26/30 on admission (275). Screening tools are important to detect patients in need for further examinations, not to reach a definite diagnosis or label the patient (279,280).

Since the decline in cognitive abilities may affect motor behaviour, a multidisciplinary assessment including domains conducted by a physiotherapist is strongly recommended (143–145). In Study I, the domains of motor functionality were associated with NDCD which accords these earlier observations. In pathological studies, AD has been observed to affect brainstem nuclei at an early stage (281). By means of their widespread afferent projections these may modulate diverse brain regions, causing impairment in motor and cognitive responses (39). Gait abnormalities become more common later on, when brain degeneration reaches the frontal areas (135). Poor gait performance, regardless of how it is defined, can be observed years before the dementia diagnosis (137). Studies have shown a direct association with cognitive impairment severity and increased gait abnormalities (37,137). Therefore, measures of gait and motor performance could help in the early detection of dementing diseases.

Moreover, both malnutrition on hospital admission or development of poorer nutritional status to follow-up were associated with NDCDs. These results are supported by previous research (182,183). Multiple cellular and molecular level mechanisms, such as deficiencies in essential nutrients, decreased levels of important

hormonal substances, oxidative stress and increased levels of free radicals, explain the association of malnutrition and cognitive decline. Additionally, in this frail patient population, malnutrition in associated with sarcopenia and osteoporosis (182). When combined, these findings are descriptive examples of factors demanding urgently a geriatric intervention.

In our study, AD was the most common diagnosis followed by mixed cognitive disorder and VCI alone. Unlike in earlier studies, our post-hip fracture care pathway with systematic follow-up and comprehensive assessment enabled well-founded differential diagnosis of cognitive disorders. The spectrum of diagnoses did not differ from that observed in general population, suggesting that the hip fracture itself has no causative association with the impairment, but merely accelerates the development of such a condition or exacerbates its symptoms (82,282). The finding supports the significance of providing a standardized post-hip fracture care pathway which enables diagnostic investigations of previously undiagnosed cognitive disorders.

Recently, a study by Arieli and co-workers reported the benefits of functional cognitive assessment over traditional screening tests during acute hospitalization. A closer analysis of patients' capability to perform in IADL and social leisure activities (e.g. dining in a restaurant, meeting friends and family, travelling) may give a better insight into crucial cognitive components, which may be overlooked by traditional tests (283). However, these domains may be more relevant in higher functioning older adults (283,284).

6.2 Incidence and significance of in-hospital delirium (Study II)

Delirium is a common complication in older hip fracture patients (285). Delirium and dementia share a tangled relationship: each acts as a risk factor, cause and coincidence for the other (162,174,184,189). In our data, a positive CAM test result was more than twice as common in patients with a known prefracture cognitive disorder as in those without. Reviews by Bruce and Kagansky report the incidence of preoperative delirium in hip fracture patients to range from 4 to 36% and postoperative delirium from 5 to 53% (176,286). Higher incidences has commonly been observed in studies including patients with known cognitive impairment (176,287).

Earlier studies report the incidence of delirium to vary depending on the tool selected for delirium assessment, timing of the assessment and the patients included in the analyses (149,162,176,286,287). Methodological variation is vast in these studies, explaining the differences in results. First, systematic assessment of delirium symptoms may be hindered by the lack of an established assessment protocol (288). Given the fluctuating course of symptoms, a single assessment may be insufficient to detect delirium (167). Second, the wide variety of tools available reflect the heterogeneity of the condition and the characteristics of settings in which they are

applied (167,289). The selected tool should be tailored according to the circumstances, patient population and utilization of the results.

In our study, delirium during hospital care was an independent risk factor for the development of NDCD, which corroborates earlier studies (175,184,189,288). In a comprehensive meta-analysis by Pereira and colleagues in which dementia was not further subcategorized, delirium was observed to carry substantially higher odds for subsequent dementia (OR 11.9, 95% CI 7.3-19.6), compared to ours (OR 2.59, 95% CI 1.60-4.22) (148). Our lower odds for NDCD may be explained by the possibly more reliable diagnosis of cognitive disorder.

Earlier studies have debated whether delirium is solely a sign of underlying brain pathology or whether there is a potentially causal relationship to subsequent dementia (90,159). A recent hypothesis identifies delirium as a neurobehavioural syndrome that is mediated by the disturbance of the neural networks and alterations in the neurotransmitter functions secondary to systemic insults (90). The more substrate elements are affected, the more likely it is that the patient will suffer further deterioration of CNS functions. These findings suggest that the pathological processes associated with delirium can cause direct neuronal injury, leading to persistent cognitive impairment (90,159). The manifestation of behavioural and cognitive changes seen in delirium is constructed by the precipitant (patient/circumstances/situation-related characteristics) and substrate (the mechanism) factors according to the subjective characteristics (90). These findings emphasize the importance of a delirium episode as an indicator of diminished cognitive reserves. It is of major importance to prevent, identify and manage delirium with all methods available. Systematic follow-up and more elaborate cognitive examinations should be arranged for these patients.

6.3 Prevalence and significance of post-hip fracture depressive mood (Study III)

Depressive mood is among the most common neuropsychiatric comorbidities in older hip fracture patients (193,194,196,290). In our data, slightly over a quarter of patients suffered from depressive mood at the outpatient assessment, a result which concurs with those of earlier studies, where prevalence has been reported to range from 9 to 47% (193,196,291). In studies using the same tool for assessment as in our study, the GDS-15, prevalence has been observed to range from 24 to 46% (202,219).

Post-hip fracture depressive mood has been repeatedly associated with poor outcomes after hip fracture although not all studies have made this observation (202,290,292–295). In a study by Kelly-Pettersson and co-workers comprising 162 patients (35 in the depression group, 127 in control group), baseline depressive mood assessed with HADS was not associated with poorer functional outcomes one year after hip fracture (295). Another study by Rathbun and colleagues assessed post-hip

fracture depressive mood with CES-D two months after hip fracture in a patient sample of 209 patients and found no statistically significant association with changes in physical performance (296). The lack of unequivocal data connecting functional recovery and depressive symptoms may be explained by methodological issues. For example, the timing of the assessment and the tools used vary, producing diverse results (202,203,297). Some studies may use diagnostic criteria for depression assessment whereas others use a screening tool for depressive symptoms (298). The bidirectional relationship between disability and depression may complicate the distinction between somatic and psychological problems, especially during the acute phase of trauma and recovery (54,226,299).

Depressive mood in hip fracture patients has been associated with decline in physical activity because of the changes in behaviour that may result in reduced participation in physiotherapy sessions (218,295,296). Moreover, it has been observed to aggravate the experience of pain, with decreased compliance with medical care during the recovery process and with an increase in sedentary lifestyle, all of which may be among the factors linking depressive mood to frailty (296,300). The harmful effect of depressive mood on exercise should be noted.

Hip fracture is a sudden, unexpected misfortune with a dire impact on subsequent functional capacity. Understandably, there is an effect on the patient's mood. However, in our data, post-hip fracture depressive mood was not associated with the change in mobility level, living arrangements or mortality as the follow-up reached one year. Based on our findings, depressive symptoms appear not to be the mediating factor for poor outcomes. A study by Chang and co-workers supports this hypothesis, suggesting that the disability may have a greater impact on depressive symptoms than depressive symptoms have on disability (299). In our data, depressive symptoms at the outpatient assessment were more common in patients with impaired prefracture mobility level, thereby supporting this assumption. Burns and co-workers report in their review that although depressive symptoms can be improved with interventions, they have only a slight positive effect on non-psychiatric outcomes. Ultimately, the outcomes are explained by factors other than depressive mood (301). It has been assumed that depressive symptoms in the presence of physical illness are reactive and therefore less responsive to interventions (302).

Depressive mood is a condition with a negative impact on subjective daily living (303,304). Depression and depressive mood have been associated with decreased bone mineral density and gait disturbances, both of which increase the risk for falls and fractures (220). Moreover, they have been associated with increased sensation of fear, anxiety, frailty and cognitive impairment signifying major overlap in symptoms and manifestations between these conditions (195,199,201). From the clinical point of view, depressive symptoms after hip fracture seem to manifest as a part of the declining functional status and cognitive reserves.

6.4 Prevalence and significance of post-hip fracture fear of falling (Study IV)

After hip fracture, FoF is a very common consequence: in our data, nearly every other patient reported FoF at the outpatient assessment four to six months after the index fracture. The frequency is within the wide range of 21-85% reported in a systematic review by Scheffer and colleagues and similar to follow-up studies with comparable methods (32,234,305).

The course of fear develops during recovery, as pointed out by Bower and co-workers (234). Fear during the acute phase or immediately after a surgical procedure may be understood as a reactive response to the distress of hospitalization rather than indicating actual fear of falls (231,232,247). The appropriate time point to assess fear is months after the primary accident because at this point the rehabilitation may have improved to a point where mobility has been regained at least to some measure and normal life has been resumed. Researchers have agreed that fear measured not immediately but after a few weeks or months better predicted the one-year outcomes (12,234). The time point at which fear was assessed in our study (4-6 months post hip fracture), may thus strengthen the significance of this factor.

In our data, however, FoF was not associated with the one-year follow-up outcomes. Decline in mobility, change to more supported living arrangements or mortality one-year post-fracture are explained by factors other than FoF. Petrella and co-workers report results similar to ours: physical function and FoF had no correlation after hip fracture rehabilitation (233). This may be partly due to similar reasons as with depressive mood: the aetiology of FoF is multifaceted as are its consequences, thereby reducing the effect of a single factor (237,239,306). FoF has been associated with activity restriction, social isolation, worse balance and psychological distress (231,237). Moreover, fear of future falls may also be a psychological symptom of developing cognitive disorder (142). A study by Bower and colleagues observed that the effect of FoF on one-year outcomes was influenced by baseline functionality: greater FoF was associated with poorer outcomes in those with high premorbid functionality whereas in patients with low baseline functionality, FoF was not predictive of functional outcomes (234).

The consequences of FoF may be more disabling than the fall itself (47,230). Patients experiencing FoF may avoid participating in rehabilitation programmes, thereby jeopardizing the regaining of functional capacity and ultimately resulting in poorer physical and mental health (229). Fear may manifest in different ways: as incapacity to perform daily tasks, fear of social embarrassment, loss of independence or as fear of pain and suffering (231). Hence, FoF seems to have a similar influence on the decline in functional and cognitive abilities to that of depressive mood.

Interventions targeting mobility after hip fracture seem to help restore mobility and may reduce FoF: exercise focusing on improving strength, balance, walking and

functionality in daily tasks can help patients get back on their feet and walk safely after hip fracture (307). Therefore, the post-hip fracture follow-up should include a comprehensive assessment of patients' physical performance, such as a physiotherapists' assessment as in our post-fracture pathway, and thus, an exercise program can be tailored to the patients needs.

6.5 Domains associated with psychocognitive factors (Studies I-IV)

Of the baseline characteristics, female gender was associated with post-hip fracture FoF (Study IV), which corroborates earlier studies (237,240). Gender was not associated with any of the other psychocognitive factors included in our data although in previous studies female gender has been associated with more frequent post-hip fracture psychological symptoms (294,308). Men tend to be underrepresented in studies, which likely explains the higher prevalence observed in women (174,251,300).

Higher age was associated with NDCDs after two-year follow-up. This serves to confirm that age is the most common risk factor for cognitive disorders (115). Prevalence of cognitive dysfunction after hip fracture has been observed equally in male and female patients (226,276,309). Age alone is known to contribute to the degeneration of tissues and decline of organ function lowering the threshold to withstand stressors (57,149). Higher age also contributes to higher probability of predisposing and precipitating factors for perioperative delirium as observed in earlier studies (162,310). Our results (Study II) are in line with these findings, in which an association of higher age with higher incidence of delirium has been observed (162,174,311). However, the opposite has also been reported (286). In this study, Kagansky and co-workers noted that the difference in the risk of postoperative delirium was insignificant between old and very old age groups. The result was explained by the significant contrast between biological and chronological age. Age alone as an indicator of survival, functional capacity or disease development is inaccurate because deficits do not accumulate linearly during our lifetime (3,312). In earlier studies, age seems to have been assumed rather than substantiated (313,314). Chronological age is still a strong predictor of functional decline but simultaneous utilization of observable measures of health domains, such as cognitive or physical performance, may provide clinically beneficial targets for interventions (312).

In our data, higher age was associated with post-hip fracture depressive mood but not with FoF (Studies III and IV). Earlier studies have reported results both corroborating and contradicting ours (206,297,315,316). It has been assumed that these symptoms are more likely to be associated with health-related functional impairment than patient-related characteristics such as age (302,315). In a review by Djernes and co-workers a strong association was reported between the onset of

depressive symptoms and chronic somatic diseases, cognitive impairment and other health-related functional impairments (315). The association between higher age and FoF has been explained by a similar context (32,316). We observed less reported FoF in higher age group; a group in which cognitive impairment was also more prevalent. Thus, a possible explanation for this might be symptom unawareness, as mentioned before (241,242).

Preoperative ASA score as a measure of multimorbidity showed an association with NDCDs (Study I) but not with delirium (Study II), depressive mood (Study III) or FoF (Study IV). ASA score was not included in the analyses of the domains of the outpatient CGA because we had multiple other modalities to describe patients' overall health status, as presented in *Table 6*. An association between higher preoperative ASA score and subsequent cognitive decline has been observed in an American study on 674 patients aged 65 years and over with a follow-up of 12 months (178). Moreover, higher ASA score has been associated with psychocognitive disorders (delirium and depressive mood) in hip fracture patients but these results should be interpreted with caution: acute hospital care is not the optimal situation to assess cognition or define characteristics of mental health (192,317). In a study by Kelly-Petterson and colleagues on 162 older hip fracture patients and with a longer follow-up (one year vs. one month), ASA score was not associated with post-hip fracture depressive mood (295). ASA is not a detailed measure of multimorbidity but it has a strong association with length of hospital stay and care costs, according to a Swiss study by Cavalli and co-workers (318). More elaborate instruments of comorbidity, such as the Charlson Comorbidity Index or Hospital Frailty Risk Score, could provide better detection and prevention of complications and introduce treatment options (319).

Poor nutritional status on admission as measured by the MNA-SF was associated with NDCDs, delirium during hospitalization and depressive symptoms at the outpatient CGA (Studies I-III). Nutritional status was not associated with FoF (Study IV). These findings are well in line with those of earlier studies linking poor nutritional status to sarcopenia, osteoporosis and physical inactivity (320,321). Furthermore, these conditions are associated with frailty due to extensive overlap in clinical characteristics (253,321). It is essential to assess nutritional status during hospital care and subsequent encounters. Malnutrition is among the key indicators of poor prognosis, yet feasible for intervention (14,322,323). A recent randomized study of 168 primary care patients aged 65 years or more with a three-month follow-up, reported significant reduction in frailty and improved self-reported health status with printed leaflets of information targeting protein-rich diet (1.2g/kg) and providing a weekly exercise regime (324). Such easy-to-apply manoeuvres are much needed to combat the gradual decline of functional, psychological and cognitive capacities of ageing population.

Known diagnosed cognitive disorder at the time of the hip fracture was a risk factor for delirium during hospital care (Study II), as observed in earlier studies (174,194). Juliebø and co-workers observed that patients with cognitive impairment prior to hip fracture were almost three times more likely to suffer a postoperative delirium episode (174). In our data, a known cognitive disorder was also associated with depressive mood at the outpatient assessment (Study III) but not with FoF (Study IV). Depressive mood and cognitive disorders have commonly been observed in combination in hip fracture patients and are both factors for poor functional outcomes (217,226). Lack of an association between cognitive disorders and FoF is in accordance with earlier studies: Uemura and co-workers have observed that lack of self-reported FoF is associated with cognitive decline (325). Lower baseline mobility level was associated with NDCDs, delirium and depression (Studies I-III) but not with FoF (Study IV). These findings reflect the effect of possible unawareness of symptoms among patients with lower baseline functioning and/or cognitive capabilities (241,242).

Patients living in supported living arrangements were more likely to be diagnosed with cognitive disorder during the two-year follow-up (Study I), more likely to suffer a delirium episode during hospital care (Study II) and more likely to report depressive mood at the outpatient assessment than were those living independently (Study III). FoF was associated with living alone with organized home care in age- and gender-adjusted analysis. However, the significance was lost after further adjusting for other parameters (Study IV). Our findings are in line with those of earlier studies: patients living in supported living arrangements tend to have lower prefracture function, disability and characteristics of frailty, which increases the risk of post-hip fracture physical and psychological complications (326–329). Recovery from hip fracture should include screening and proper management of psychological factors during the process. These factors may represent opportunities to intervene and improve health outcomes in this vulnerable group of patients.

In Studies I and III, measures of activities of daily living (BADL and IADL), nutritional status (MNA-SF), physical performance (EMS and TUG) as well as measures of cognitive capability were associated with new cognitive disorders and with depressive mood. The results of the MMSE, CDT and CDR revealed that the new cognitive disorders had often progressed to moderate to severe stage before diagnosis. Changes in mobility and living arrangements were associated with NDCDs, but in Study III, change in living arrangements only came close to reaching statistical significance ($p=0.072$). There is no curative treatment for cognitive disorders but as the FINGER study showed, multi-domain lifestyle intervention has a beneficial effect on cognition regardless of age, gender or baseline cognitive performance level (127).

Study IV included the widest range of domains in the analyses. Interestingly, many of the significant factors in the age- and gender-adjusted analysis lost their association with FoF after further adjusting for other parameters. The psychological

characteristic of FoF has been observed in studies by Painter and Yardley (237,330). They observed that even though the majority of older adults are well aware of methods for fall prevention, they may not engage in preventive actions, such as exercise or physical activity because they do not believe or want to admit that they are at risk of falling (237,330). Factors that retained their association with FoF in the multivariable analyses are supported by findings of earlier studies. Difficulties in basic daily activities may signify a state of objective or subjective disability increasing the sensation of FoF (32,229,331). Moderate to severe depressive mood and markedly abnormal TUG test result have been associated with FoF, supporting the view of FoF as a complex symptom with physical and psychological components (32,316). Living alone may induce a sense of loneliness or helplessness, increasing the probability of FoF (306,316). A CDR score of 1-3 was negatively associated with FoF, which may be explained by symptom unawareness as mentioned earlier in chapter *2.7.1* (241,325).

6.6 Strengths and limitations

The patients included in this study were drawn from a geographically defined area of what at the time was the Hospital District of Southern Ostrobothnia in Finland with a population of approximately 200,000 inhabitants. All patients of 65 years of age or more, regardless of socioeconomic status, medical history, pre-fracture cognitive status, living arrangements or mobility, were enrolled in the study and treated according to the same treatment protocol in the same hospital. Only patients with pathological or periprosthetic fractures were excluded. Therefore, the results represent well the actual effects in real-life circumstances. The population of Southern Ostrobothnia amounts to 3.5% of the total population of Finland which, however, limits the generalizability of the results.

Our hip fracture patients' care pathway used standardized methods with a comprehensive and systematic approach. Several clinical characteristics were systematically documented to thoroughly investigate the clinical factors associated with each selected topic. The outpatient assessment included all the necessary capabilities to diagnose cognitive disorders including laboratory tests, neuropsychiatric assessment, brain imaging analysed by a specialist in neuroradiology and cerebro-spinal fluid assessment. Patients were accompanied by a close relative, a caregiver or staff member from the patient's place of residence to acquire information from the perspective of a close associate. Data were collected by face-to-face interview and/or telephone interviews. If necessary, follow-up visits were scheduled. The participation rate at the outpatient assessment was high (69%, Study I).

Data were collected by a few specialized individuals whose meticulous approach improved the quality of the data. The dates of death were provided by the National

Population Register Centre and confirmed from the electronic patient files of the hospital. There were no losses to mortality follow-up.

Data collection was prospective, being initiated on 1 September 2007 and completed on 1 January 2019. Updates were made to the treatment protocol during that time, therefore, not all measures were available throughout the entire data collection period. Data collection was initiated on admission, thus there were no data on prefracture status. For example, prefracture level of cognition was unknown. Due to real-life hospital circumstances with staff turnover and inadequately trained personnel, there was a notable amount of missing data on different variables. For example, delirium assessment with CAM was not systematic, which excluded a substantial patient population. In addition, some of the domains of the outpatient assessment were not feasible in some cases, such as the TUG test or measure of orthostatic blood pressure for bedridden patient, which increased the number of undocumented values. Missing data has been observed as a special challenge of geriatric research due to the susceptibility of this population to physical and cognitive decline, sudden complications and death (332,333). Okpara and co-workers have reported that an average of 14% of missing data is observed in studies on older patient population (333). Our results are in concordance with these findings.

In Study III, we only focused on depressive symptoms occurring during rehabilitation. Prefracture depressive symptoms were not documented. Additionally, depressive mood was assessed at only one time-point so the evolution or plausible changes of symptom severity could not be examined. The same limitation also occurred in Study IV. Both fear and depressive mood are dynamic phenomena: the impact of the symptoms is connected to the progress of recovery and rehabilitation (12,234). These symptoms should be assessed repeatedly to obtain a precise understanding of their impact on rehabilitation outcomes.

In Study IV, we used a single dichotomous question to assess FoF. A more elaborate instrument might have produced a more detailed picture of the symptom. We consider, however, that our approach was better suited to the patient population and the study design. In our understanding, a single-item instrument enabled a maximal and most reliable response rate. Furthermore, the large amount of missing data on the elicitation of FoF deserves to be noted. This may have introduced a risk of bias and the prevalence figures must therefore be interpreted with caution.

After discharge from hospital the patients were transferred to the wards of the local public health care centres, all of which possessed different resources for hip fracture patients' care and rehabilitation. We did not measure the effect on our study outcomes of the care received at the post-discharge facilities.

Lastly, the influence of CGA on the follow-up outcomes was not evaluated. Our study design lacked a reference population since the data was collected on a real-life patient population prospectively. Therefore, we can make no claims about the benefits of our care pathway. However, from the high attendance rate and the feedback

received from our patients, close relatives and other health care professionals, the benefits of our comprehensive approach look promising. Moreover, our earlier study indicated the effect on quality indicators and mortality of the orthogeriatric collaboration (79,334).

6.7 Interpretation of the results

> "*It takes a child one year to acquire independent movement and ten years to acquire independent mobility. An old person can lose both in a day*". - Professor Bernard Isaacs.

The risk factors for hip fracture seem to be multidimensional. Recovery from such an event can also be multifactorial. The importance of geriatric input and CGA is highlighted by this study. Falling seems not only to break bones but also to damage the mind: these both affect the recovery process and the regaining of daily functionality. Orthogeriatric collaboration and a multidisciplinary approach, together with systematic follow-up with sufficient resources for a comprehensive assessment, are key components of beneficial care.

To the best of our knowledge, this is the first study to document the NDCDs, specified by clinically assessed diagnoses, in a systematic follow-up of older hip fracture patients. We moreover identified other noteworthy psychocognitive determinants and associated factors affecting the rehabilitation outcomes.

The human is a biopsychosocial creature. Who we are depends on where we have been, what we have done and what has happened to us (87). Ageing alone increases the impact of physiological, environmental and social factors on the change in cognitive and functional capabilities. Remarkable events, such as falls and hip fractures, are unexpected additions to these series. They may modify the course of life by impairing independent mobility or forcing a change in living arrangements (335). Pain and loss of autonomy can affect identity and behaviour and ultimately our social environment (203). Lack of physical and social incentives accelerates the vicious cycle of declining cognitive and physical capabilities (123,315).

A recent journal article discussed the dynamic properties of symptoms in multimorbidity in relation to the concepts of disease, illness and sickness (336). Clinical reasoning relies to a large extent on diagnosing the specific underlying pathogenesis which, according to a conventional approach, is the root cause of ill health. In old age and multimorbid patients the causal relations are multifactorial, which needs to be assessed simultaneously, questioning the reliability of the single disease paradigm. Similar complex associations between symptoms and causes have been reported in various circumstances from dental health to dizziness and falls risk assessment (337–340). The observations of this dissertation concur with this

hypothesis: symptoms interact and overlap, each affecting the other. To determine the intervention from which the patient benefits the most requires understanding the complexity of symptoms and diseases in relation to the prognosis, while keeping in mind the preferences of the patient. This combined context is conceptualized in *Figure 5*. According to this thesis and earlier literature, gait and cognitive disturbances, psychological symptoms and malnutrition seem to be part of the same dynamic symptom network (DSN), highlighting the importance of geriatric expertise to intervene most productively on such occasions.

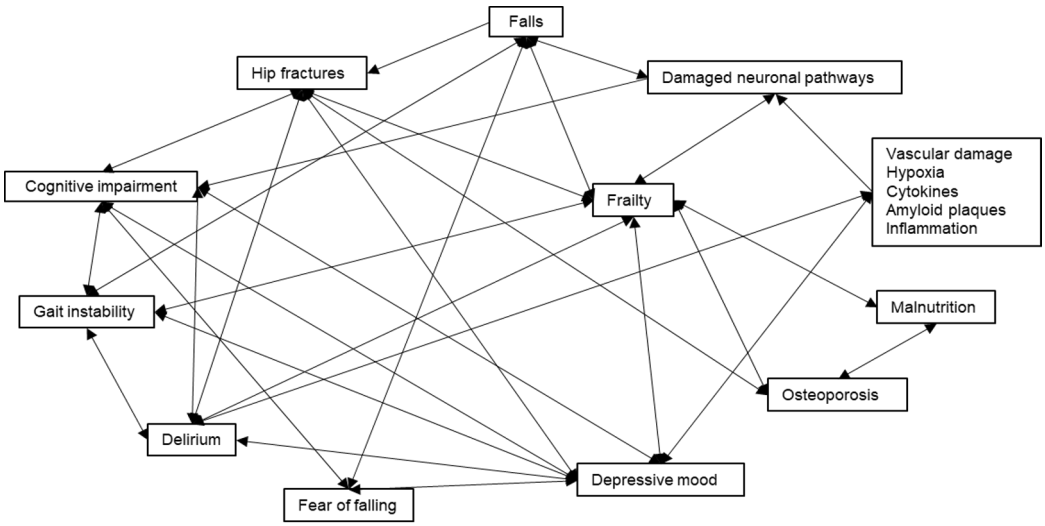

Figure 5. Author's draft of the interactions between geriatric conditions related to recovery from hip fracture according to the literature and the findings of this thesis.

7 Conclusion

Cognitive disorders were common in hip fracture patients aged 65 years or more. Previously undiagnosed or imperceptibly developing conditions were frequently encountered during hospital care and subsequent recovery period. The severity had often reached a moderate or severe stage before diagnosis. NDCDs were associated with higher age, malnutrition and impaired physical capabilities. The distribution of diagnoses did not differ from that observed in general population. Suggesting that the hip fracture itself has no causative association with cognitive impairment but merely accelerates the development of such condition, a systematic care pathway with resources to detect cognitive disorders is warranted post hip-fracture.

An episode of delirium was associated with the development of cognitive disorders during one-year post-hip fracture follow-up. Delirium during hospital care is a warning signal of diminished reserve capacities, susceptibility to subsequent cognitive decline and low resources for rehabilitation. Delirium prevention is therefore extremely important, likewise the diligent treatment of acute episodes and systematic follow-up thereafter. Malnutrition may be one of the first signs of cognitive disorder; it is associated with in-hospital delirium and with subsequent cognitive decline. Therefore, poor nutritional status deserves considerable attention.

Post-hip fracture depressive mood was common but mostly mild. Patients with depressive mood at the post-hip fracture assessment performed more poorly in tests of physical performance, functioning and cognition than those without depressive mood. However, depressive mood alone seems to have no effect on the outcomes of change in mobility level or living arrangements, or on mortality during one-year follow-up. Nevertheless, it may have a profound effect on quality of life and neurocognitive well-being and thus demands recognition during the recovery period.

Almost every other older hip fracture patient suffered from FoF at the outpatient assessment. Patients with pre-fracture cognitive disorder or those with mild to severe dementia documented at the outpatient assessment reported less FoF than did those with better cognitive capabilities. As with depressive mood, the decline in one-year follow-up outcomes seems not to be explained by FoF alone. Nevertheless, it requires attention during hip fracture care and recovery.

8 Implications for health care development and future research

Mental health disturbances merit interventions before they have an impact on physical or cognitive abilities. The comprehensive approach to patients' rehabilitation is not only meant to benefit the patient but also their next of kin and the health care system. CGA has been acknowledged as a cost-effective modality with significant benefits for the patient's quality of life. Hip fracture in older patients may mark the beginning of a downward spiral of cognitive, physical and psychological degradation. These conditions interact, collectively complicating the recovery process. A comprehensive geriatric approach can be recommended to predict, prevent and intervene in treatable issues. The idea of DSN and complexity science methods calls for more research to increase the understanding and improve the treatment of geriatric syndromes.

CGA should be implemented as a standard protocol in older hip fracture patients' care and rehabilitation. Cognitive examinations are suggested to be incorporated from the first falls risk assessment. Interventions should focus on physical, cognitive, mental and social aspects of the individual. The recovery process deserves to be tailored to the patient's specific needs with routine follow-up assessments. Follow-up needs to be organized in multidisciplinary fashion with the capability to accurately diagnose cognitive disorders. The long-term effects and subjective benefits of comprehensive geriatric assessment call for more research. Healthcare service pathways should be investigated and optimized.

As a society, we are facing a veritable tsunami of age-related issues, such as fragility fractures and cognitive decline, as in the coming years the most rapid population growth is predicted to be in the oldest age-groups. A diminishing dependency ratio, increasing costs of energy and commodities, burden occasioned by the pandemic and counterproductive choices of the health care system paint a bleak picture of ageing. Geriatric expertise should be highlighted and given the appreciation it so richly deserves to manage the approaching turmoil. Political actions should urgently increase proactive efforts for dignified ageing.

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Roope Jaatinen

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