ANNALES UNIVERSITATIS TURKUENSIS

SARJA - SER. D OSA - TOM. 907

MEDICA - ODONTOLOGICA

SURGICALLY TREATED HIP FRACTURE IN OLDER PEOPLE

With Special Emphasis on Mortality Analysis

by

Jorma Panula

TURUN YLIOPISTO
UNIVERSITY OF TURKU
Turku 2010

From the Department of Surgery, University of Turku, Turku University Hospital, Turku, Finland
and the Departments of Surgery, Satakunta Central Hospital and Pori City Hospital, Pori, Finland

Supervised by

Professor Pertti Aarnio MD, PhD
Department of Surgery, Turku University Hospital
Department of Surgery, Satakunta Central Hospital
University of Turku, Turku
Finland

Professor Sirkka-Liisa Kivelä MD, PhD
Unit of Family Medicine, Turku University Hospital
Satakunta Central Hospital
Institute of Clinical Medicine, Family Medicine
University of Turku, Turku
Finland

Reviewed by

Docent Jari Parkkari MD, PhD
University of Tampere, Tampere
Finland

Docent Tuomo Visuri MD, PhD
University of Helsinki, Helsinki
Finland

Dissertation Opponent

Professor Heikki Kröger MD, PhD
Department of Orthopaedics, Traumatology and Hand Surgery
Kuopio University Hospital
University of Kuopio, Kuopio
Finland

ISBN 978-951-29-4309-8 (PRINT)
ISBN 978-951-29-4310-4 (PDF)
ISSN 0355-9483
Painosalama Oy – Turku, Finland 2010

To the generations who made this possible

ABSTRACT

Jorma Panula

Surgically treated hip fracture in older people with special emphasis on mortality analysis

Department of Surgery, University of Turku, Turku University Hospital, Turku, Finland
Departments of Surgery, Satakunta Central Hospital and Pori City Hospital, Pori, Finland
Annales Universitatis Turkuensis
Painosalama Oy – Turku, Finland 2010

Hip fractures are associated with significant morbidity and mortality. Cervical and trochanteric fractures have a different morphometry, surgical treatment, and outcome. Polypharmacy, common in older people, is associated with increased mortality. The risk factors for mortality can be identified based on cause-of-death analysis.

In this population-based study, 461 older, surgically in 1999-2000 treated hip fracture patients were enrolled. Incidence, morphometry, medication, mortality, and cause-of-death were analysed.

Hip fractures were most commonly sustained by women, occurred mostly indoors, and often in institutions. One in four patients had sustained a previous fracture. Routine clinical radiographs revealed no differences in the hip geometry between hip fracture types. Age-adjusted mortality was higher in men than in women during the follow-up. Chronic lung disease and male sex were predictors of mortality after cervical fracture. In men, potent anticholinergics were associated with excess age-adjusted mortality. Men were more likely to die from circulatory disease and dementia after hip fracture than women. Mortality after hip fracture was 3-fold higher than that of the general population, including every cause-of-death class.

Fracture prevention in institutions and homes, indoor safety measures, and treatment of chronic lung diseases should be encouraged. Hip morphometry analyses require more accurate measures than that provided by routine radiographs. Careful use of potent anticholinergics may reduce mortality. Compared to the general population, excess mortality after hip fracture was evident up to 9 years after hip fracture. Cause-of-death analysis indicates that all major comorbidities require optimal treatment after hip fracture surgery.

KEY WORDS: Hip fracture, older people, aged, population-based, incidence, bone geometry, radiography, sex distribution, cervical, mortality, medication, anticholinergics, cause-of-death

TIIVISTELMÄ

Jorma Panula

Vanhusten kirurgisesti hoidettu lonkkamurtuma, erityisesti kuolleisuuden tarkastelu

Kirurgia, Turun yliopisto, Turku
Kirurgia, Satakunnan keskussairaala ja Porin kaupunginsairaala, Pori
Annales Universitatis Turkuensis
Painosalama Oy – Turku 2010

Suuri ilmaantuvuus ja korkea kuolleisuus ovat tunnusomaisia lonkkamurtumalle. Vanhuksilla monien lääkkeiden yhtäaikainen käyttö on yleistä, ja siihen liittyy kohonnut kuolleisuuden riski. Kuolemansyyanalyysistä on hyötyä arvioitaessa kuolleisuuden riskitekijöitä. Reisiluunkaulan ja sarvennoisalueen murtumatyyppien geometrinen muoto, kirurginen hoito ja sen tulokset eroavat toisistaan.

Tähän väestöpohjaiseen tutkimukseen kuului 461 iäkästä lonkkamurtumapotilasta, jotka hoidettiin leikkauksella vuosina 1999-2000. Ilmaantuvuus, lonkan geometrinen muoto, lääkitys, kuolleisuus ja kuolemansyyt selvitettiin.

Naiset saivat lonkkamurtuman miehiä useammin, ja murtumat sattuivat useimmin sisätiloissa ja usein laitoksissa. Joka neljännellä potilaalla oli aiemmin ollut murtuma. Tavanomaisten kliinisten röntgenkuvien perusteella lonkkamurtumatyyppien välillä ei todettu lonkan geometrian eroja. Miesten ikävakioitu kuolleisuus oli korkeampi kuin naisilla seurannan aikana. Pitkäaikainen keuhkosairaus ja miessukupuoli ennustivat reisiluunkaulan murtuman jälkeistä kuolleisuutta. Miehillä vahvojen antikolinergien käytöllä oli yhteys ikävakioituun kohonneeseen kuolleisuuteen. Miesten kuolleisuus verenkiertosairauksiin ja dementiaan oli korkeampi kuin naisilla. Lonkkamurtumapotilailla ikä- ja sukupuolistandardisoitu kuolleisuus oli kolme kertaa suurempi kuin väestöllä, ja samansuuntainen ero todettiin kaikissa kuolemansyyryhmissä.

Murtumien ehkäisyä laitoksissa ja kotona, sisätilojen turvallisuutta ja pitkäaikaisten keuhkosairauksien hoitoa tulisi tehostaa. Rutiiniröntgenkuvausta tarkempia menetelmiä tarvitaan lonkan geometrian arviointiin. Varovaisuus voimakkaiden antikolinergien käytössä saattaa alentaa kuolleisuutta etenkin miehillä. Väestöön verrattuna lonkkamurtuman jälkeinen kuolleisuus pysyi koholla jopa yhdeksän vuoden ajan leikkauksesta. Kuolemansyyanalyysin perusteella kaikkien tärkeimpien tautiryhmien mahdollisimman hyvä hoito on tärkeää lonkkamurtuman jälkeen.

AVAINSANAT: Lonkkamurtuma, vanhus, iäkäs, väestöpohjainen, ilmaantuvuus, luun geometria, röntgenkuvaus, sukupuolijakauma, reisiluunkaula, kuolleisuus, lääkitys, antikolinergit, kuolemansyy

TABLE OF CONTENTS

ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
DXA	Dual-energy X-ray absorptiometry
FNAL	Femoral neck axis length
FNW	Femoral neck width
HAL	Hip axis length
HFx	Hip fracture
HR	Hazard ratio
ICD10	International Statistical Classification of Diseases and Related Health Problems, 10th edition
NSA	Femoral neck shaft angle
OR	Odds ratio
PY	Person-year
RR	Relative risk, risk ratio
SAS	Statistical Analysis System
SD	Standard deviation
SPSS	Statistical Package for Social Sciences
SSRI	Selective serotonin reuptake inhibitor

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, which are referred to in the text by the Roman numerals I-V:

I Jaatinen PT, Panula J, Aarnio P, Kivelä SL. Incidence of hip fractures among the elderly in Satakunta, Finland. Scand J Surg 96: 256-260, 2007.

II Panula J, Sävelä M, Jaatinen PT, Aarnio P, Kivelä SL. The impact of proximal femur geometry on fracture type – a comparison between cervical and trochanteric fractures with two parameters. Scand J Surg 97: 266-271, 2008.

III Panula J, Pihlajamäki H, Sävelä M, Jaatinen PT, Vahlberg T, Aarnio P, Kivelä SL. Cervical hip fracture in a Finnish population: incidence and mortality. Scand J Surg 98: 180-188, 2009.

IV Panula J, Puustinen J, Jaatinen PT, Vahlberg T, Aarnio P, Kivelä SL. Effects of potent anticholinergics, sedatives and antipsychotics on postoperative mortality in elderly patients with hip fracture: a retrospective, population-based study. Drugs Aging. 26: 963-971, 2009.

V Panula J, Pihlajamäki H, Mattila VM, Jaatinen PT, Vahlberg T, Aarnio P, Kivelä SL. Mortality and cause of death of hip fracture patients aged 65 years or older. Submitted.

1. INTRODUCTION

Among all bone fractures, hip fractures in older people are associated with the highest degree of morbidity and mortality. In addition, the cost burden of hip fractures is substantial. Hip fracture patients usually require hospitalisation and surgery. After surgery, patients require additional support through the rehabilitation and recovery. One in three hip fracture patients dies within the first year after hip fracture;[1] and one in three is admitted to a nursing home for the first time within 1 year of the hip fracture.[2] Effective strategies are needed to reduce the burden on healthcare providers and to improve patient quality of life and outcome after hip fracture. For this purpose, guidelines for hip fracture treatment were published in Finland in 2006.[3]

Hip fractures commonly affect an already frail population. Most patients are women and the mean age at first presentation of hip fracture is 80 years.[4] Osteoporosis is considered an important contributory factor to the incidence of bone fractures. Some studies report a levelling off and even a decrease in the incidence of hip fracture.[5-8]

Assessment of the risk of hip fracture is essential toward preventing the fracture event. Most people with hip fracture have osteoporosis[9] and more than 90% of all hip fractures are attributed to falls.[10] Bone densitometry does not provide reliable estimates of a person's true bone mineral density (BMD).[11] The majority of hip fractures occur among people who are not classified as having osteoporosis based on the bone densitometry threshold values for osteoporosis.[12] Therefore, new strategies for identifying individuals at increased risk of hip fracture are currently being investigated. Some evidence suggests that assessing hip geometry parameters can significantly improve the ability to identify people at risk for fracture. Cervical and trochanteric hip fractures differ from each other in their morphometric parameters, surgical treatments, and outcomes.

Older people with hip fractures are at considerable risk for subsequent osteoporotic fractures and premature death. Much of this mortality is related to underlying medical conditions that predate the fracture, rather than to the fracture itself. The hip fracture event, however, may increase the likelihood of dying from these comorbidities.[13] In addition, polypharmacy, which is common in older people, is associated with an increased risk of mortality.[14]

In the present study, the incidence of surgically treated hip fractures was examined in Satakunta, Finland. Geometrical differences assessed by measuring femoral neck shaft angle (NSA) and femoral neck axis length (FNAL) between cervical and trochanteric hip fractures were also evaluated. In addition, the incidence and mortality

of cervical hip fractures were studied. The relationships between the use of sedatives, antipsychotics, and potent anticholinergics and mortality after hip fracture surgery were assessed. Both short-term and long-term mortality after hip fracture were analysed and compared with that in the general population, and cause-of-death was analysed.

2. REVIEW OF THE LITERATURE

This thesis focuses on hip fracture patients aged 65 years or older. In 1999, the Human Rights Commission of the United Nations proposed using the term 'older people' instead of the word 'elderly' as a more respectful way to reference this rapidly growing segment of the population.[15] Following the recommendations of the European Summit on Age-Related Disease in September 2008, the term 'older' is used throughout the summary of this thesis. This was a retrospective population-based study that included an observational analysis of mortality.

Older people usually sustain hip fractures with 'low-energy trauma' as a consequence of a fall to the floor from standing height or less,[10 16] which is distinguishable from the fractures of younger people who usually sustain hip fracture in traffic accidents or falls from a greater height.[17] In older people, these traumas are high-impact injuries to the specific injury site, often creating forces that clearly exceed the breaking strength of bone.[10 16] Hence, fractures in older people should be termed 'fall-induced high-impact injuries'.[18]

2.1 Short historical overview of hip fracture

The modern sedentary lifestyle relying on automation and mechanisation is associated with fall-induced fractures.[19] Osteoporosis and its complications, however, have been present in human populations for thousands of years.[20] Probably one of the oldest cases of hip fracture is described in a report of osteoporosis complicated by a femoral neck fracture in a female skeleton from Lisht, ancient Upper Egypt (1990-1786 B.C.).[20] Until the 19th century, hip fracture was considered to be untreatable and surgeons followed the directive of Sir Astley Cooper, one of Britain's surgical authorities, to 'treat the patient and let the fracture go'.[21] The era of surgical hip fracture treatment became popular in the 20th century: in 1902, Murphy began using nails to stabilize the femoral head[22] and in 1940, Austin T. Moore, in collaboration with Harold Bohlman, inserted the first Vitallium prosthesis to replace the upper portion of a femur.[23]

2.2 Epidemiology of hip fracture

Hip fracture is associated with significant morbidity, loss of independence, and diminished quality of life.[24] Hip fractures rarely occur in those under the age of 50 years, with fractures below this age constituting only 2% of the total.[25] In older people, even the mere fear of the consequences of hip fracture can cause significant mental suffering and psychological burden.[26] Of women aged 75 years or older, 80% would rather be dead

than experience the loss of independence and quality of life that results from a 'bad' hip fracture with subsequent admission to a nursing home.[26] Furthermore, hip fracture often triggers a series of problems and treatments at different levels of care.

Worldwide, the number of hip fractures is predicted to increase from 1.7 million in 1990 to 6.26 million by the year 2050, mainly as a result of an increase in life expectancy and an increase in the population of older people in nearly all countries.[27] Considerable geographic variations in hip fracture rates have been reported; rates are lowest in Africa, Asia, and Latin America, and in Europe, rates are higher in northern countries than in southern countries.[28] The average age of hip fracture patients is 80 years, and nearly 80% are women.[29] The life-time risk of suffering a hip fracture among women is estimated to be 20% in Sweden.[30]

The three major components of a hip fracture event are falling and osteoporosis, alone or more frequently combined,[31] and direct impact on the greater trochanter of the proximal femur.[10] Approximately 30% of community-living people aged 65 years or older fall at least once a year.[32] In older people, approximately 5% of falls result in fractures; nearly half of them are hip fractures.[32 33] This is due mainly to the orientation of the fall; most hip fractures result from individuals falling sideways, failing to break their fall with an outstretched hand, and directly impacting on the greater trochanter.[10]

The identification of risk factors for hip fracture has potential value. Treatable risk factors, such as impaired visual acuity, smoking, and low bone mass, are useful guides to interventions that can substantially reduce an individual's risk of hip fracture.[34] Recognition of untreatable risk factors, such as maternal history of hip fracture, patient's past history of hip or other fractures, and his/her age or height, can be useful in making treatment decisions, because these factors identify people who are likely to derive benefit from interventional treatment, for example, drugs that maintain or increase bone mass.[34] From an individual's point of view, the effect of eliminating or modifying solitary risk factors may be substantial, but the same interventions may have only modest effects on the fracture rates in a population.[34]

Hip fracture is the main source of osteoporosis-related health care costs.[24] In 2000, the cost of treating hip, spine, and wrist fractures in Europe was 32 billion Euros, with hip fractures accounting for 890,000 (23%) of fracture cases.[35] In the United States, adjusted first-year costs associated with hip fracture for patients aged 65 years or older were US $ 15,196, compared with the costs of US $ 6701 for vertebral fracture at the beginning of this millennium.[36]

Almost every hip fracture patient requires hospitalisation; furthermore, the majority of hip fracture patients are treated surgically, which is documented in hospital records. Although approximately 15% of femoral neck fractures may be impacted there is no consensus on

their treatment whether it should be conservative or operative.[37] In general, conservative treatment of hip fracture is rare due to the potential complications, poor outcomes, and prolonged hospital stays. The occurrence of hip fracture is used as an international index of the frequency of osteoporosis[38] and it reflects the efficacy of preventive efforts in the population.[5] Because of its burden on mortality, morbidity, and socioeconomic costs, hip fracture is among the most thoroughly investigated consequence of osteoporosis.[13]

2.3 Circumstances and risk factors of hip fracture

Hip fracture is a general description for several different fracture types of fracture in the proximal part of the femur.[30] The two main types are fractures of the femoral neck (cervical, intracapsular) and fractures through the muscle insertions distal to the femoral neck (pertrochanteric or intertrochanteric, together referred to as trochanteric or extracapsular) (Figure 1).

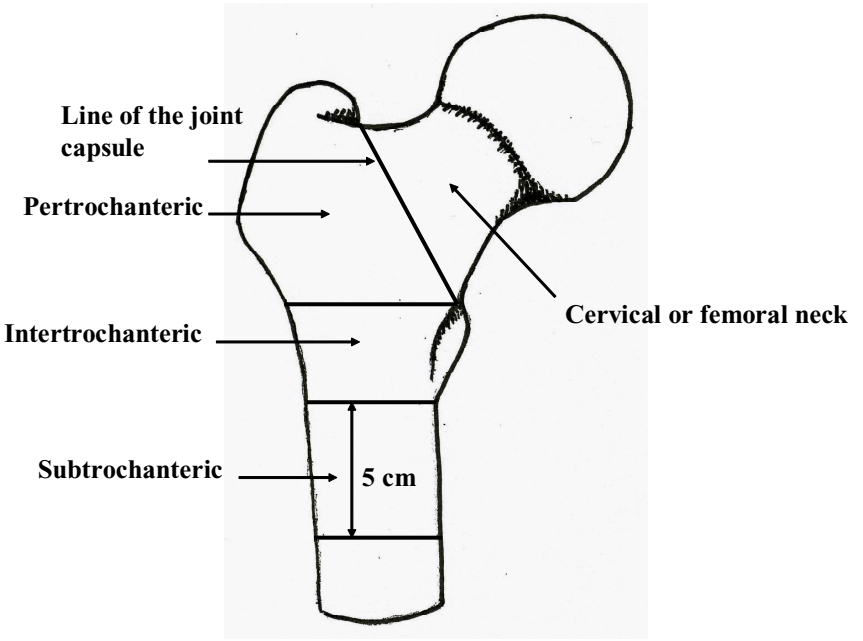


Figure 1. Classification of hip fractures into intracapsular (cervical or femoral neck) and extracapsular (trochanteric and subtrochanteric) fractures.

2.3.1 Incidence of hip fractures

For primary treatment, 7083 hip fracture patients aged 50 years or older were admitted to hospitals in Finland in 2004.[8] Several recent studies report a trend-break in the incidence of hip fracture. In Canada, nationwide hospitalisation data of all hip fracture patients for 1985 to 2005 were analysed.[5] Age-adjusted hip fracture rates decreased by 31.8% in women and by 25.0% in men. A change in the decrease in linear slope was identified around 1996; prior to 1996, the average annual percentage decrease was 1.2%, and after 1996, it was 2.4%. Interestingly, the hip fracture incidence in Finland began to decline almost simultaneously from 1997.[8] In the United States, the age-adjusted hip fracture incidence of both sexes increased from 1986 to 1995 and then steadily decreased from 1995 to 2005.[6] At the same time, however, comorbidities of hip fracture patients increased. In Denmark, the incidence of hip fractures decreased by approximately 20% from 1997 to 2006 in both men and women aged 60 years or older.[7] This decrease in hip fractures was much too large to be explained by an increase in the use of anti-osteoporotic medication.

The reasons for the decreasing hip fracture rates are not clear. In Canada, trends toward decreasing fracture rates became evident before widespread BMD assessments and modern pharmacotherapy.[5] A similar decreasing pattern in both sexes argues against the effects of hormone replacement therapy or oral contraception. In women, an increased number of reproductive years and exposure to circulating endogenous hormones are proposed as explanations.[5] Lifestyle changes, such as calcium and vitamin D supplementation, avoidance of smoking, regular weight-bearing exercise, an awareness of falls, and moderating alcohol intake, may have also contributed to the decreased incidence of hip fractures.[6] The nationwide decline in the incidence of hip fracture observed in Finland from 1997 to 2004 is assumed to be due to a cohort effect toward a healthier ageing population, increased average body weight, and improved functional ability among older people.[8]

A decrease in hip fracture rates is not reported in all countries. In Germany, a population-based study observed an increased hip fracture incidence from 1995 to 2004, although the increase was not as large as in previous years.[39] The decreasing trend of the hip fracture incidence is also not obvious throughout the whole population studied. In Finland, a nationwide decrease in the incidence of hip fractures was observed in both sexes aged 50 years or older from 1997 to 2004 (in men, from 238/100,000 persons to 223/100,000 persons; in women, from 494/100,000 persons to 412/100,000 persons).[8] A population-based study in Central Finland from 1992-1993 to 2002-2003, comprising patients aged 50 years or older, showed an increase in the age-adjusted incidence in both sexes (in men, from 2.0/1000 person year [PY] to 2.8/1000 PY; in women, from 3.9/1000 PY to 5.6/1000 PY).[40] In the Umeå area of Sweden, the age-adjusted incidence decreased in

the population older than 50 years, but absolute fracture rates and incidence increased in women older than 90 years.[41]

There is a substantial geographic variation in the hip fracture incidence.[28] Hip fracture probabilities were assessed for 29 countries and the probabilities were expressed as a proportion of the probability in Sweden (defined as a probability of 1).[42] Norway, Iceland, Sweden, Denmark, and the United States were classified as countries with a 'very high risk' (probability range 1.24-0.78, respectively). Germany, Finland, the United Kingdom, and Australia were defined as 'high risk' countries (0.72-0.57); Japan and China as 'medium risk' countries (0.39 and 0.29); and Turkey, Korea, and Chile as 'low risk' countries (0.18-0.08). The reasons for the geographic variation are not clear; possible explanations include geometrical parameters,[43] hereditary factors, body stature, physical activity, and nutrition.[30] The variation in the incidence of fractures between countries suggests a large heterogeneity in fracture risk.[44] In addition to differences between countries, some studies report considerable variability within countries, with higher rates in urban than in rural areas.[45]

Latitude and seasonal variation are also potential reasons for the high fracture incidence in Scandinavian countries.[46] In the northern countries, there are slippery conditions during winter months with snow and ice; in addition, there are fewer hours of daylight, which may diminish outdoor activities and formation of vitamin D in older people. A seasonal variation in the hip fracture incidence, however, has also been found in countries with a subtropical climate.[47] Although there is evidence for a seasonal effect on hip fracture incidence, this has not been a universal finding.[44 46]

Understanding the variations in the hip fracture incidence is a vital step in planning health resources for older people. Despite the decrease in the hip fracture incidence rates, large age cohorts of those vulnerable to fracture will override the lower incidence trend and result in an overall increase of the number of hip fractures in the coming decades.[30] The most rapidly growing segment of the United States population is persons 85 years of age or older, and life expectancy of both men and women is projected to continually increase during the next several decades.[13] In Central Finland, patients of both sexes aged 85 years or older were the fastest growing age group from 1992-1993 to 2002-2003.[40] Better health among the oldest of the old may also delay the age at which fractures occur.[41]

2.3.2 Falling

The principal causal components of an osteoporotic fracture are a fall and a fragile skeleton. Both falling and osteoporosis are independent risk factors of older people's fractures,[18] but falling rather than osteoporosis is the strongest single risk factor.[31 48 49] In

older people, approximately 5% to 10% of falls result in a major injury such as a fracture, serious soft tissue injury, or traumatic brain injury.[32 50] Falls are major contributors to functional decline and health care utilisation; falling without serious injury increases the risk of admission to a nursing facility by 3-fold, and a serious fall injury increases the risk 10-fold.[51] The consequences of falling are not only physical; diminished self-confidence may explain functional losses following falls without serious injury.[52] The risk of falling in residential care populations is reported to be 2- to 3-fold higher than in community-living older people.[53 54] The prevalence of falls increases with advancing age, but it is generally higher in women than in men.[55]

In older people, falling is strongly associated with sustaining a hip fracture. Although only about 1% of all falls results in a hip fracture,[32] over 90% of hip fractures are due to a fall.[10] There is also a clear relationship between the number of falls and hip fracture risk.[56] The aetiology of falling is complex and multifactorial, and over 400 potential risk factors for falling have been identified.[57] A number of factors identified as risk factors for falls are also associated with hip fracture.[58]

There is no consistent classification of risk factors for falling, but they can be divided into intrinsic, extrinsic, or combined.[59] Intrinsic factors are those related to neurosensorial impairment (e.g., visual or balance deficit, cognitive disorder), use of drugs known to facilitate falls (short- and long-acting benzodiazepines, neuroleptics, tricyclic antidepressants, selective serotonin reuptake inhibitors, diuretics, and other antihypertensives), or diseases associated with an increased risk of falling (e.g., depression, diabetes, osteoarthritis, and stroke). Extrinsic factors are unrelated to diseases or medication, but include environmental risks of slipping or tripping (e.g., slippery surfaces, poor lighting or weather conditions, loose carpets, or doorsteps). Combined risk factors include both intrinsic and extrinsic components. Medications are particularly complex risk factors of falling; diseases such as hypertension may increase the fall risk, but so do the drugs taken to treat these diseases.[52]

According to a recent systematic review, in community-living older people, the strongest risk factors for falling include previous falls; strength, gait, and balance impairments; and use of specific medications.[52] The risk of falling increases with the number of risk factors present.[32] The independent risk factors for falling in community-living circumstances, identified in a systematic review, are listed in Table 1.

Table 1. Independent risk factors for falling among community-living older adults according to a systematic review of 33 studies. Adapted from Tinetti et al.[52]

Risk factor	N	RR	OR
Previous falls	16	1.9-6.6	1.5-6.7
Balance impairment	15	1.2-2.4	1.8-3.5
Decreased muscle strength	9	2.2-2.6	1.2-1.9
Visual impairment	8	1.5-2.3	1.7-2.3
Medications (>4 or psychoactive medication)	8	1.1-2.4	1.7-2.7
Gait impairment or walking difficulty	7	1.2-2.2	2.7
Depression	6	1.5-2.8	1.4-2.2
Dizziness or orthostasis	5	2.0	1.6-2.6
Functional limitations, ADL disabilities	5	1.5-6.2	1.3
Age >80 years	4	1.1-1.3	1.1
Female	3	2.1-3.9	2.3
Low body mass index	3	1.5-1.8	3.1
Urinary incontinence	3		1.3-1.8
Cognitive impairment	3	2.8	1.9-2.1
Arthritis	2	1.2-1.9	
Diabetes	2	3.8	2.8
Pain	2		1.7

N=number of studies in which risk factor was significant, RR=relative risk, OR=odds ratio (ORs presented separately because they may overestimate the risk of the factor with a common outcome such as falling), ADL=activities of daily living

Although numerous studies show that, among older people, falling, not osteoporosis, is the strongest risk factor for fracture, the risk of falling remains overlooked in clinical practice.[11] Proposed clinical measures include systematic assessment of the falling risk, strength and balance training, intake of vitamin D and calcium, prescribed medications, and smoking cessation, and referral of people with high falling risks for professional environmental assessment.[11] Systematic reviews and meta-analyses of randomised trials show that at least 15% of falls in older people can be prevented, with individual trials reporting reductions of up to 50%.[60 61] To emphasise the fatality of falling, the focus in fracture prevention should be shifted from osteoporosis and treating low BMD to preventing falls.[11] In clinical practice, this is a question of resources as the multifactorial aetiology of falling necessitates multifactorial interventions.

2.3.3 Osteoporosis

In 1842, Sir Astley Cooper described the original classical epidemiologic hallmarks of osteoporotic fractures: incidence rates that increase with age; rates that are higher among women than men; and fractures that are associated with only moderate trauma at sites containing large amounts of trabecular bone.[62] The term ‘osteoporosis’ describes the porosity of the histological appearance of aged human bone.[62]

Osteoporosis is defined as a systematic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fractures.[63] According to the definition of the World Health Organization, BMD values (T score) lower than 2.5 standard deviations (SD) below the mean for young adults represent osteoporosis.[64] Cut-off values of the definition were intended for epidemiologic studies and not as the clinical treatment thresholds they are being used for today.[65] Classic osteoporotic fractures are hip, vertebral, and wrist fractures (Table 2). Although the characteristics of typical osteoporotic fractures were already described in the 19th century, there are problems in defining an osteoporotic fracture;[66] i.e., the definition of 'falling from the same level' may not be adequate.

Table 2. Impact of osteoporosis-related fractures. Adapted from Holroyd et al.[62]

	Hip	**Vertebral**	**Wrist**
Lifetime risk (%)			
Women	14	28	13
Men	3	12	2
Hospitalisation (%)	100	2-10	5
Relative survival	0.83	0.82	1.00

Osteoporosis is classified as primary (idiopathic) or secondary. Predictors of primary osteoporosis are female sex, increased age, oestrogen deficiency, white race, low weight, and body mass index (BMI), family history of osteoporosis, smoking, and history of prior fracture.[67] Secondary osteoporosis can be a result of medications, diseases, or other factors.[67] The clinical presentation of osteoporosis varies between men and women.[68] Osteoporosis tends to develop about a decade later in men than in women. The incidence of osteoporosis-related fractures in men is lower than in women; osteoporotic fractures, however, are associated with greater morbidity and mortality in men.[68] In addition, secondary causes of osteoporosis, such as alcoholism, glucocorticoid excess, and hypogonadism, are more frequently identified in men than in women and cause approximately 50% of cases.[68 69]

There is a strong inverse relationship between bone density and fracture risk, with a 2- to 3-fold increase in the fracture incidence for each SD reduction in BMD.[70] In routine clinical use, measuring BMD is currently the best available non-invasive assessment of bone strength.[38] Unfortunately, however, bone densitometry does not provide reliable estimates of the true BMD: more than 80% of low trauma fractures occur in people who do not have osteoporosis defined as a T score of -2.5 or less.[11] Hence, a simple risk assessment tool based on clinical risk factors (age, previous fracture, maternal hip fracture, weight, smoking, and ability to rise from a chair without hands) can predict fractures in postmenopausal women as well as BMD.[71] Even simpler, a Swedish twin study reported that asking the question 'Do you have impaired balance?' identified

individuals aged ≥55 years at substantially increased risk of fracture, with approximately 40% of hip fractures attributable to self-reported impaired balance.[72] Furthermore, low calcaneal ultrasound measurement predicted early postmenopausal fractures as well as or even better than axial BMD.[73]

Management of osteoporosis is pharmaceutical and non-pharmaceutical. An adequate supply of vitamin D and calcium is essential for maintaining bone strength and, according to recent studies, for skeletal muscle function.[74 75] A recent meta-analysis of randomised controlled trials showed that vitamin D given alone in doses of 10 to 20 μg is not effective for preventing fractures; in contrast, calcium and vitamin D given together reduce hip fractures, irrespective of age, sex, or previous fractures.[76] The evidence of benefits of specific anti-osteoporotic drugs (such as alendronate, risedronate, clodronate, teriparatide, and strontium ranelate) for reducing the risk of hip fracture remains scarce and is less consistent than that for their efficacy in reducing the risk of vertebral fractures.[77] Oral dosing of biphosphonates is inconvenient (fasting before and after intake, taking with a full glass of water, remaining upright for 30-60 minutes after intake) and leads to generally poor compliance to anti-osteoporotic treatment.[78] Nevertheless, anti-osteoporotic medication is most effective in patients with reduced BMD and previous fractures; subsequently, the presence of specially educated personnel is suggested for hospitals that treat fractures to improve the secondary prevention of fractures.[79]

2.3.4 Impact of falls

The great majority of hip fractures are caused by a sideways fall with a direct impact on the greater trochanter of the proximal femur.[10] The proximal part of the femur, with a more horizontal than vertical position, is the weakest part; moreover, primary bone loss is also greatest at this unusual loading direction.[80] Hence, in addition to preventing osteoporosis and falling, prevention of fractures despite osteoporosis and falling is essential.[18] For this purpose, external hip protectors incorporated into underwear have been designed to weaken and divert the impacting force and energy away from the greater trochanter at the time of the fall.[18] The results of the first randomised controlled trials performed to evaluate the efficacy of padded, shield-type hip protectors were promising; the risk of hip fracture was 60% less in the protected group than in the control group, and the risk reduction was more than 80% if the protectors were actually worn at the time of falling.[81] Recent systematic reviews, however, have revealed that hip protectors are not effective in community-dwelling people.[58 82] In institutions with high rates of hip fracture, the use of hip protectors may reduce hip fractures by 23% to 60% according to some meta-analyses and systematic reviews.[60 61] The most common problems with the use of hip

protectors are compliance deficits, mechanically insufficient and weak protectors, and lack of caregiver motivation.[18]

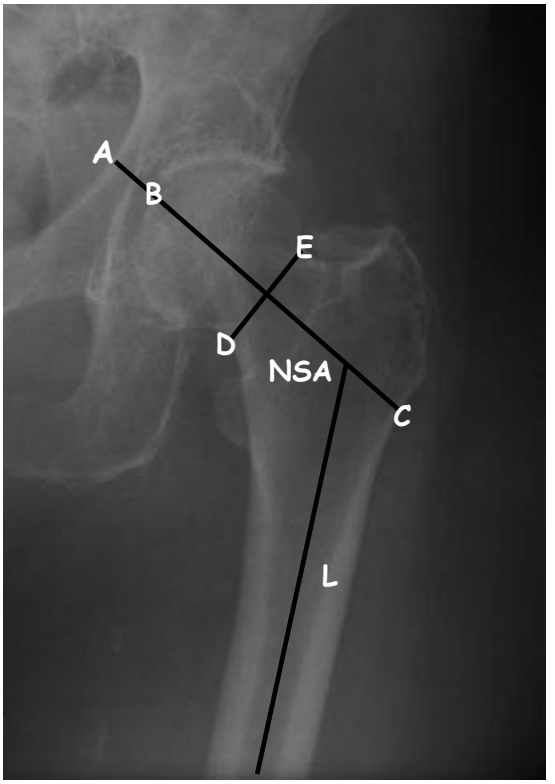
2.4 Impact of hip geometry on the fracture type

The structure of the hip serves at least two remarkable functions; the angulated neck must carry the superimposed body and permit freedom of motion in the hip joint.[22] The strength of an object is a function of its geometry.[83] Other issues are the mechanical properties of the material, and the location and direction of the forces to which the structure is subjected. In addition to BMD, many other skeletal characteristics contribute to bone strength. These include bone macroarchitecture (shape and geometry), bone microarchitecture (trabecular and cortical), matrix and mineral composition, and the degree of microdamage accumulation and the rate of bone turnover.[84] Together these measures are referred to as bone quality.[38] Normal bone remodelling occurs when osteoblastic resorption and osteoclastic reconstruction are in balance with each other.[85] Under abnormal loading, the process of resorption, however, becomes dominant and may lead to microfractures in the bone and with continuing abnormal loading resulting in complete stress fractures.

The bone mass of an individual in later life is a result of the peak bone mass developing during intrauterine life, childhood, and puberty, as well as the subsequent rate of bone loss.[38 86] For individuals of normal body weight, total skeletal mass peaks a few years after fusion of the long bone epiphyses.[86] Thus, the amount and quality of an individual's skeleton reflect everything that has happened from intrauterine life through the years of growth into young adulthood.[86] Based on this continuum, encouraging to physical activity and adequate dietary calcium intake is essential during childhood and adolescence. Chronologically, preventive strategies against osteoporotic fractures should even include optimisation of maternal nutrition and intrauterine growth.[86]

2.4.1 Measures of hip geometry

Several measures of hip geometry have been studied as possible risk factors for hip fracture.[87] Mechanical strength of the proximal femur depends on the size of the bone and the distribution of mass within the bone.[13] Hip axis length (HAL), the distance between the inner pelvic brim and the greater trochanter, is a measure of the length of the 'lever arm' of the femur.[13] Femoral neck axis length (FNAL) is determined as HAL minus the pelvic portion (Figure 2).[87]



AC = HAL (hip axis length) = length along the femoral neck axis from below the lateral aspect of the greater trochanter through the femoral neck to the inner pelvic brim

BC = FNAL (femoral neck axis length) = length between the lateral border of the base of the greater trochanter and the femoral head

DE = FNW (femoral neck width) = shortest distance within the femoral neck

NSA (neck shaft angle) = angle between the femoral neck and the femoral shaft (angle between lines AC and L)

Figure 2. Geometrical parameters of the proximal femur.

The simplified mechanism of cervical fracture is bending of the femoral neck by the body weight. The bending moment that breaks the neck is the product of the FNAL and the bending component of the body weight. The bending component of the body weight is perpendicular to the femoral neck axis and is higher if the femoral neck shaft angle (NSA) is larger (Figure 3).[88] The larger the NSA and the longer the FNAL, the higher is the bending moment applied to the femoral neck, which increases the risk of cervical fracture.

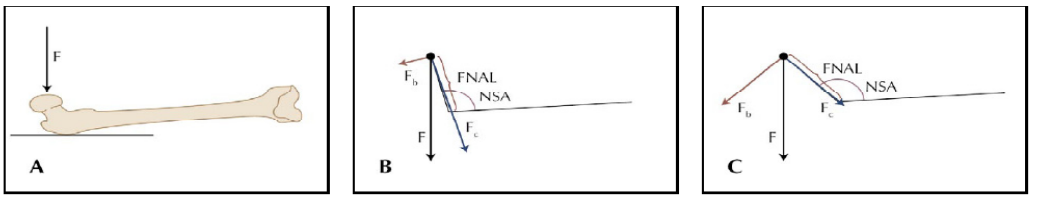


Figure 3. Role of geometry of the upper part of the femur in the risk of cervical hip fracture. **A**, Cervical fracture usually results from a fall on the side, when body weight (F) bends the femoral neck. **B**, The bending moment is the product of the bending component of body weight (F_b) and the femoral neck axis length (FNAL). F_b is lower when the neck shaft angle (NSA) is less open. **C**, F_b is higher when the NSA is larger. The femoral neck is also subject to F_c, the compressive component of F. With kind permission from Springer Science+Business Media.[88]

The FNAL and the femoral neck width (FNW) are strongly positively correlated.[89] Thus, subjects with cervical fracture may have longer femoral necks and, by chance, wider femoral necks. The distribution of mass within the proximal femur is described by FNW, NSA, cortical thickness, the cross-sectional moment of inertia of the femoral neck (a measure of bone's resistance to bending), and femoral neck section modulus.[90] Of these parameters, HAL has the greatest promise for enhancing the assessment of fracture risk and can be used to predict hip fractures independently of age and BMD in older women.[91] The mean HAL is reported to be 10.5 cm in women of mainly European decent and is positively related to height.[92]

The risk of hip fracture in white women is twice that of black women; the greater hip strength in black women than in white women is attributed to more favourable geometrical parameters, such as shorter HAL and greater cortical thickness of the femoral neck.[43] In Japan, women have a lower incidence of hip fracture, about half that of white women; they also have a shorter HAL and a smaller NSA.[93] Each centimeter increase in HAL increases the risk of hip fracture by 50% to 80% in older white women.[87] HAL is a proposed marker for the ability of the femur and/or pelvis to absorb the impact of a fall.[87] A longer HAL causes the greater trochanter to extend beyond the pelvis to a larger degree, which increases the risk of fracture on impact.[91] Overall evidence suggests that assessing and measuring hip geometry can significantly improve the ability to identify people at risk for hip fracture. Although several studies in older women suggest that a longer HAL, a larger NSA, and a wider FNW all increase the risk of hip fracture, there are inconsistencies in the literature.[87]

2.4.2 Measuring hip geometry

Prior to the launch of dual-energy X-ray absorptiometry (DXA) in the 1980s, radiographs were used to estimate the effects of hip geometry on fracture risk.[87] Since then, several techniques for in vivo assessment have been developed, including ultrasound, high resolution computed tomography, and magnetic resonance imaging. There are, however, some limitations to each method; inaccuracy (DXA, ultrasound), radiation dose (computed tomography), availability (DXA, computed tomography, magnetic resonance imaging), or cost (computed tomography, magnetic resonance imaging).[94]

2.4.3 Hip geometry and hip fracture type

The aetiologies of cervical and trochanteric hip fractures are likely different.[95] Cortical thickness, trabecular structure, and bone size in the proximal femur and pelvis are important in the pathogenesis of these fracture types.[96] Trochanteric fractures are related to severe osteoporosis mainly in the trabecular compartment, whereas cervical

fractures are related to pelvic and hip geometry.[95] Hip geometry of the two fracture types varies, although the measures and patient materials studied have differed between reports.[97] In a study setting with a standardised patient position and calibrated dimension measurements, NSA was larger in patients with a cervical hip fracture than in those with a trochanteric fracture.[97] Decreased femoral shaft cortical thickness is predictive of trochanteric fractures, whereas increased acetabular width and decreased femoral neck cortical thickness are predictive of femoral neck fractures.[96]

2.5 Incidence of cervical hip fractures and mortality of cervical hip fracture patients

There are several classifications of hip fractures. Cervical fractures are regarded as intracapsular and trochanteric fractures as extracapsular. The blood supply to the fractured fragment is more critical in intracapsular fractures, especially displaced fractures.[98] Consequently, alterations in blood supply to the femoral head and tamponade effect may result in the femoral head aseptic necrosis.[99] In trochanteric fractures, the circulation is good and healing complications are unusual.[100] In the beginning of the 19th century, Sir Astley Cooper classified hip fractures as those that healed and those that did not; he was convinced that intracapsular hip fractures were incapable of healing.[21] The best treatment for femoral neck (intracapsular) fractures remains under debate[101] and the various treatment methods include a hip compression screw, percutaneous pinning, two or three parallel screws, or arthroplasty;[102] or, in rare cases, no surgery.[103]

Many studies have ignored the two subtypes of hip fracture. Hip fracture patients, however, are not a homogeneous group; people who sustain a trochanteric fracture are older, smaller, and have a lower BMD than those who sustain a cervical fracture.[104] As the BMD of the trochanteric region is lower in patients with trochanteric fractures than in those with cervical hip fractures,[105] even a low-energy impact on the hip region caused by an indoor fall may result in a trochanteric fracture.[106] Moreover, trochanteric fractures are associated with increased mortality compared with cervical fractures, and are related to more complications, poorer outcomes, and higher cost.[107]

The trochanteric region has a greater proportion of trabecular bone (50%) than the femoral neck (25%);[108] hence, the aetiology of each fracture type may also differ due to the differences in bone composition.[109] Falling indoors is related to the occurrence of trochanteric fractures.[106] The fall mechanisms may differ between falls occurring indoors and outdoors;[106] although the potential energies of falls resulting in cervical and trochanteric fractures may be similar,[105] associated kinetic energies may differ with regard to the type of fall.[110] It has been proposed that the fall characteristics of older people may have changed during recent decades resulting in increasing numbers of

trochanteric fractures because the type of hip fracture also depends on the impact angle of the greater trochanter at the moment of contact with the floor.[107]

2.5.1 Incidence of cervical hip fractures

In women, the ratio of cervical to trochanteric fractures differs across three periods: before the age of 50 years, the incidence of both fractures is almost equal; between the ages of 50 and 60 years, cervical fractures increase markedly; and after 60, this imbalance progressively diminishes due to an increase in trochanteric fractures.[111] In men, cervical fractures are progressively more common with increasing age, with the ratio cervical/trochanteric exceeding unity after 70 years of age. Hence, the incidence of cervical fractures is greater than that of trochanteric in both sexes during a limited period of time.[111] Some geographic variation in the incidences also exists: in Sweden and Norway, the ratio is approximately 1:1; in Finland and Iceland, the proportion of cervical fractures is higher.[100]

2.5.2 Mortality of cervical hip fracture patients

Several studies have investigated the factors associated with high rates of morbidity and mortality following surgery for a displaced cervical hip fracture.[112] According to a recent systematic literature review, 1-year mortality after hip fracture, in general, varies from 6% to 50%.[113] Most survival studies in hip fracture patients, however, have not distinguished between different fracture types.[114] In a 1-year prospective cohort study of women, the mortality risk after intertrochanteric (extracapsular) hip fracture was 2.5-fold higher than that after femoral neck (intracapsular) fracture, despite a similar long-term functional outcome in both groups.[114] The study also found that differences in mortality between hip fracture types could not be entirely explained by differences in age or comorbidities; hence, the conclusion was that fracture type is an independent predictor of mortality in hip fracture patients.

2.6 Use of potent anticholinergics, sedatives, and antipsychotics in hip fracture patients

In older people, lean body mass and total body water decrease, whereas total body fat relatively increases.[115] These changes lead to a decreased volume of distribution for hydrophilic drugs, such as digoxin.[116] Hepatic mass and blood flow are reduced with ageing; drugs such as tricyclic depressants, which have a first-pass effect in liver, may have a higher bioavailability in older people and thus, may be effective at lower doses.[116] Furthermore, renal excretion is altered as a result of age-related changes in kidney structure and reduced renal blood flow, which affects the clearance of many drugs.[115]

Ageing is also associated with changes in the end-organ responsiveness to drugs at the receptor or postreceptor level.[116] In addition to distribution, metabolism, and excretion, drug absorption may be altered in older people.[117] Serum albumin concentrations are 15% to 25% lower in individuals aged 65 years or older than in young adults.[118] Therefore, protein-bound drugs, such as warfarin and digoxin, have greater physiological effects at smaller doses in older people.

Medication use increases with age; polypharmacy, the use of multiple medications and/or the administration of more medications than are clinically indicated, is common among older people.[119] In the United States, 12% of uninstitutionalised women aged 65 years or older took 10 or more medications and 23% took at least 5 prescription drugs.[120] For certain diseases, such as tuberculosis and hypertension, a polypharmacological approach improves the therapeutic response; on the other hand, polypharmacy may induce iatrogenic complications.[117] Furthermore, polypharmacy is a risk factor for falling[52] and, overall, inappropriate prescribing in older people is associated with significant morbidity, mortality, and financial costs.[116]

2.6.1 Potent anticholinergics

Cholinergic dysfunction is involved in the pathogenesis of many delirious states.[121] Anticholinergic drugs are frequently prescribed in older people.[122] Drugs such as tricyclic antidepressants, antipsychotics, antispasmodics, anti-Parkinson agents, and antiarrythmics possess anticholinergic activity and produce adverse central nervous system (CNS) effects.[123] Their use in older people should be carefully considered and monitored.

The cumulative burden of several drugs with mild to moderate anticholinergic activity has the potential to induce anticholinergic toxicity. Hence, ranitidine, codeine, warfarin, isosorbide dinitrate, digoxin, and prednisolone possess anticholinergic activity sufficient to cause significant impairment of recent memory and attention in healthy older people.[122] Avoiding adverse drug effects is not always achieved by replacing a previous medication with a new one. Tricyclic antidepressants were first introduced in the late 1950s; at present, selective serotonin reuptake inhibitors (SSRI) are preferentially prescribed for older people instead because of an assumed reduction in the potential for adverse effects.[124] The increased risk for hip fracture, however, is similar for both drug types.[125] In addition, SSRIs are associated with lower BMD.[126]

Drugs possessing anticholinergic activity present a risk for cognitive impairment, which is a risk factor for falling.[52] High anticholinergic burden is also associated with reduced physical function and even low anticholinergic serum levels cause mild but measurable cognitive impairment in older people.[127] The CNS effects of medications

depend on dosage, pharmacokinetics (including possible differences in distribution into the CNS), and pharmacodynamics.[123] Moreover, blood-brain barrier permeability can increase with age,[128] illness, stress, and specific drugs, which may further affect the risk for developing adverse CNS effects following anticholinergic drug exposure.[129] Older people are particularly vulnerable to anticholinergic drug intoxication, even from the therapeutic doses of medications.[121]

2.6.2 Sedatives

Ageing increases sensitivity to the CNS effects of benzodiazepines and sedation is subsequently induced by diazepam at lower doses and lower plasma concentrations in older adults than in young adults.[130] Due to a relative increase in total body fat with ageing, benzodiazepines, which are lipid-soluble drugs, have an increased distribution volume, thereby their maximal effects are delayed resulting in accumulation with continued use.[116] Data regarding the relationship between benzodiazepine use and the incidence of hip fracture are conflicting. Benzodiazepine use may directly increase the risk of hip fracture in older people by increasing susceptibility to falls.[131] On the other hand, benzodiazepine use among older people may be a marker of conditions that substantially increase fracture risk, such as poor health, frailty, impaired cognition, weight loss, and low BMD.[125]

A cohort study of more than 125,000 enrollees aged 65 years or older reported an association between benzodiazepine use and the incidence of hip fracture.[132] The results also suggested that the short half-life benzodiazepines, which are often considered the best choice for older patients among this class of drugs, carry a significant risk of hip fracture. Hip fracture risk was highest during the first few weeks after the start of benzodiazepine use.[132] A prospective study of more than 8000 community-living women aged 65 years or older, however, reported that benzodiazepine use was not independently associated with an increased risk of hip fracture.[125] Early studies noted that zolpidem, a nonbenzodiazepine hypnotic, might have potential advantages compared to benzodiazepines and therefore promoted zolpidem as having a favorable safety profile.[133] The use of zolpidem by older people, however, was associated with nearly twice the risk for hip fracture in a case-control study compared with non-use.[133]

2.6.3 Antipsychotics

Chlorpromazine, thioridazine, and haloperidol are conventional or typical antipsychotics. These drugs have significant anticholinergic activity at therapeutic doses administered to older adults.[123] Before the introduction of atypical antipsychotics, such as olanzapine and risperidone, conventional antipsychotics were commonly used for behavioural and psychological symptoms of dementia.[134] In recent years, there has been a shift in the

recommendations to treat this difficult syndrome in favour of the atypical antipsychotics, largely due to the positive efficacy and apparent safety.[135] A critical review, however, stated that an increased risk of anticholinergic adverse effects and falls must be considered with both typical and atypical antipsychotics.[134]

Osteoporosis affects individuals with schizophrenia, but the relationship is complex and is attributed to both antipsychotic medications and the illness itself.[136] Schizophrenia patients often have comorbidities and take multiple medications resulting in an increased risk of falling. Decreased BMD has been noted among patients with schizophrenia,[137] and may be mediated by elevated homocysteine levels disturbing collagen cross-linkage.[138] In a case-control study of more than 16,000 hip fractures, use of typical prolactin-raising antipsychotics was an independent risk factor for hip fracture, but schizophrenia was not.[139] Long-term antipsychotic-induced hyperprolactinaemia is associated with BMD loss, which may be mediated by secondary hypogonadism.[140]

2.7 Mortality and causes of death of hip fracture patients

An association between hip fracture and mortality was shown as early as 1959, in the era after which surgery became the standard of care.[141] There is, however, debate about the magnitude of the increased mortality and the length of its duration. The community mortality rates associated with hip fracture are higher than for other, better known life-threatening conditions such as pancreatic or stomach cancer and myocardial infarction.[142 143] In addition, survival after stroke and myocardial infarction, for example, has improved without any obvious improvement in survival after hip fracture.[144]

The excess mortality after hip fracture can be attributed to comorbid conditions, the acute effect of the trauma, or their combination.[145] Short-term high mortality may be explained by a combination of comorbid conditions and the acute effects of the injury.[146] Nonetheless, there is an increased early mortality even among patients with no apparent comorbidity suggesting that at least some of the excess mortality is due to the immediate consequences of the fracture, i.e., results of trauma and surgery.[147] Long-term excess mortality after hip fracture, on the other hand, may be due to comorbid conditions.[148] Because of the excess mortality in patients with hip fracture and the high incidence of hip fractures in older people,[149] hip fractures may contribute to a relatively large proportion of deaths in the population. Any change in mortality after a hip fracture may thus have a significant effect on a population level.[144]

2.7.1 Mortality studies

A review of all published articles on the mortality after hip fracture in 1959-1998 showed that the mean age of people sustaining hip fracture steadily increased at a rate of 1 year of age for every 5-year time period.[1] The incidence of intracapsular fractures showed a definite downward trend. Although the mean age of hip fracture patients increased, the mortality at 6 months (11%-23%) and 12 months (22%-29%) after hip fracture remained essentially unchanged over the four decades.[1] The reasons for this may be improved medical and surgical treatment, awareness of need for early surgery, better nursing and community care, and an older population more medically fit and not as frail as in earlier years.[1] Geographical variations in mortality after hip fracture were also observed; mortality at 6 months and 1 year were higher in the United Kingdom (23% and 28%) than in the United States and Scandinavia (18% and 24%). In the United States and Scandinavia, patients were 3 years younger and the proportion of men was lower than in the United Kingdom, which may explain the differences.[1]

A recent systematic epidemiological review of 63 studies reported that both excess and unadjusted mortality rates among hip fracture patients indicated that the greatest risk of death was within the first 6 months after the fracture.[113] Older patients had higher mortality following hip fracture in absolute terms, but the RR of death was greater in younger age groups where the expected risk of all-cause-death was lower.[113] The review did not determine whether hip fracture-related mortality had increased or decreased in recent years. Even with a stable rate of death following hip fracture, however, the actual number of deaths after hip fracture can be expected to increase consistent with a growing and increasingly older global population.[113]

Summaries of the mortality studies with their main results, published between January 1, 2005 and December 31, 2009, are presented in Tables 3 and 4.

Table 3. Summary of studies published in 2005-2009 and reporting mortality after hip fracture in short-term and long-term.

Reference, year, country Study design	Demography of material	Duration of follow-up (Fu) or catchment period	Mortality		Other results
Studies on mortality at 0-2 years after HFx					
Penrod JD [150], 2008, USA Prospective	2692 HFx, ≥50y (95% ≥65y), ♀ 79%	Fu 6 mo	6 mo Men Women	 19% 9%	Whites and women more likely to survive 6 months after HFx than nonwhites and men.
Pioli G [151], 2006, Italy Prospective, cohort	252 HFx, ≥70y, ♀ 85.5%	Fu 1 y	In-hospital 3 mo 6 mo 1 y	4.8% 12.5% 18.9% 24%	Low serum albumin level (<3g/dL) a strong predictor of early and late mortality.
Vestergaard P [144], 2007, Denmark Retrospective, register-based, cohort	163,313 HFx, 87% ≥65y, ♀ 72.1%	HFx sustained 1981-2001	1-y survival compared to the general population 1981-2001: Men Women	 72%-68% 82%-78%	Mortality increased in HFx patients, whereas it decreased among controls. Mortality RR of 1.05 for arthroplasty compared to osteosynthesis.
Bass E [152], 2007, USA Retrospective, cohort	43,165 HFx, ≥65y, ♂ 87%	Fu 1 y	1 mo 3 mo 6 mo 1 y 1 y men 1 y women	8.9% 15.6% 21.8% 29.9% 32% 18%	Predominantly male sample
de Luise C [153], 2008, Denmark Population-based, cohort, population controls	11,985 HFx, 90% ≥65y, ♀ 71%	Fu 22 mo	Mortality risk by age: 1 mo 3 mo 1 y	 3.02-7.15 2.50-5.97 2.26-4.93	COPD, cardiac failure, dementia, tumor, and malignancy were significantly associated with mortality after HFx.
Hindmarsh DM [154], 2009, Australia Population-based	16,836 Hfx, ≥65y, ♀ 75%	Fu 3 y	1-y survival Men 65-74y ≥85y Women 65-74y ≥85y	 82% 65% 90% 80%	For patients ≥85y excess mortality persisted for only 3 months.
Brauer CA [6], 2009, USA Observational, register-based	786,717 Hfx, ≥65y, ♀ 77.2%	HFx sustained 1986-2005	Decrease of mortality between 1986 and 2005: Men 1 mo 6 mo 1 y Women 1 mo 6 mo 1 y	 21.8% 25.4% 20.0% 11.9% 14.9% 8.8%	Mortality after HFx among patients ≥65y was declining.
Bentler SE [155], 2009, USA Prospective	495 Hfx, ≥69y, white ♀ 73%	1993-2005	In-hospital 6 mo 1 y	2.7% 19% 26%	Sex, age, dementia, and frailty were significantly associated with mortality. Declines in functional status after HFx prospectively captured.
Söderqvist A [156], 2009, Sweden Prospective cohort	1944 HFx, ≥66y, ♀ 75%	Fu 2 y	In-hospital 4 mo 2 y	4% 16% 38%	Predictive model assessing physical health and cognitive function identified HFx patients with an increased mortality risk.
Studies on mortality at more than 2 years after HFx					
Vestergaard P [157], 2009, Denmark Retrospective, population-based, register-based, cohort	169,145 Hfx, ≥64 y, ♀ 72%	1977-2001	Loss of life years Men ≤50y >80y Women ≤50y >80y	 18% 58% 27% 38%	A large proportion of the excess mortality occurred within the first year after HFx.

Reference, year, country Study design	Demography of material	Duration of follow-up (Fu) or catchment period	Mortality		Other results
Tosteson AN [158], 2007, USA Prospective, register-based	730 HFx (25,178 enrollees), ≥65y, ♀ 74%	Median fu 1.5 y			Mortality risk for HFx 6.28 compared to controls at 6 months after HFx. No increased mortality for HFx after 6 months after adjustment for demographic and health variables.
Robbins JA [141], 2006, USA Prospective, cohort	379 HFx (5888 enrollees), ≥65 y, ♀ 74%	Mean fu 3.7 y	Excess mortality Men 1 y 5 y Women 1 y 5 y	 24% 26% 9% 24%	Risk of mortality was highest in the first 6 months after HFx. In men, the risk of death approximated that of men without HFx after 6 months. In women, a moderately greater risk persisted through the fourth year.
Farahmand BY [147], 2005, Sweden Population-based, case-control	2245 HFx, ≥50 y, ♀ 100%	Mean fu 5 y	Hfx Controls	40% 13%	Mortality risk highest in the first 6 months after HFx. Mortality risk increased for at least 6 years independently of HFx risk factors.
Tsuboi M [159], 2007, Japan Prospective	753 HFx, ≥50 y, ♀ 75%	10 y	1 y 2 y 5 y 10 y	19% 33% 51% 74%	The survival rate decreased dramatically for 2 years after HFx and mortality risk remained higher for 10 years compared to the general population.
Paksima N [160], 2008, USA Prospective	1109 HFx (ambulatory, cognitive intact, living in their own homes), ≥65 y, ♀ 79%	>16 y	In-hospital 1 y 2 y 5 y 10 y	2.7% 11.9% 18.5% 41.2% 75.3%	The increased mortality risk was highest during the first year after HFx and returned to the risk of the standard population 3 years postoperatively.
von Friesendorff M [161], 2008, Sweden Retrospective, observational	766 HFx, >20 y (91%≥65y), ♀ 100%	22 y	Survival Overall 22-y 1 y 5 y 10 y	 6% 79% 48% 33%	The residual lifetime risk for any fracture was 45%. Age and survival were the most important factors for future fracture risk.

HFx=hip fracture, Fu=follow-up, y=year, mo=month, RR=risk ratio, COPD=chronic obstructive pulmonary disease

Table 4. Summary of studies published in 2005-2009 and reporting effects of enhanced cocare on mortality.

Reference, year, country Study design	Demography of material	Duration of follow-up or catchment period	Mortality	Other results
Thwaites JH [162], 2005, New Zealand Retrospective	150 HFx, ≥65 y, ♀ 77%	23 days (median of length of stay in hospital)	In-hospital 0.7%	Shared care between geriatricians and orthopaedic surgeons was associated with a low in-hospital mortality.
Fisher AA [163], 2006, Australia Prospective cohort observational with a retrospective control	951 HFx, ≥60 y, ♀ 75%		In-hospital mortality: Without geriatric consultation 7.7% With geriatric consultation 4.7% ($p<0.01$)	Shared care between geriatricians and orthopaedic surgeons was associated with a significant reduction in in-hospital mortality.
McGinn T [164], 2005, USA Prospective cohorts prior to corrective treatment protocol and after the implementation of the protocol.	185 HFx (preprotocol group), ≥65y, ♀ 72% 644 HFx (postprotocol group), ≥65y, ♀ 77%	2000-2003	30-day mortality Preprotocol group 4.9% Postprotocol group 0.8%	Mortality rates can be reduced by systematic application of comprehensive preoperative assessment when implemented by specially trained and privileged staff.

HFx=hip fracture

2.7.1.1 Sex differences in mortality

Several studies have reported higher mortality in men than in women after hip fracture.[141] [144] [150] [152] [154] The reasons for this are not clear. In a recent registery-based Danish study of more than 41,000 hip fracture patients, excess mortality among men compared to women could not be explained by controlling comorbidities and medications.[165] It has been suggested, however, that the difference in mortality risk is due to poorer health in men with hip fractures than in women with hip fractures and, in addition, the increased mortality in men is secondary to increased infections, such as septicemia and pneumonia.[166]

It is possible that to develop weak bones, other disease processes may be operating in men than in women, who lose bone naturally throughout their adult life and at an accelerated rate after menopause. These disease processes may increase comorbidity, promote falls, and lead to fractures and a poorer survival rate in men.[9] The excess mortality in men may be explained by the interaction of the fracture with the underlying comorbidity status because survival is poorer among male hip fracture patients compared with age-matched controls with any level of comorbidity.[145] One study reported that male sex was associated with an increased risk of postoperative complications, including pneumonia, arrhythmia, delirium, and pulmonary embolism, even after controlling for age and surgical risk.[167]

2.7.1.2 Operative delay and mortality

The Royal College of Physicians' guidelines recommend that hip fracture surgery be performed within 24 hours after admission because early versus late surgical repair is believed to be associated with increased survival; decreased risk of infection, venous tromboembolism or decubitus ulceration; shorter hospital stay; and lower cost.[168] Conflicting results however, have been reported.[168] To estimate the current evidence of effects of delayed surgery on mortality after hip fracture, a systematic review, meta-analysis, and metaregression of 16 studies was performed.[168] According to the study, surgery delayed beyond 48 hours after admission may increase the odds of 30-day all-cause mortality by 41% and of 1-year all-cause mortality by 32%. In addition, an undue delay may be harmful to hip fracture patients with a relatively low mortality risk and to those who are young.[168]

The reasons for delayed surgery can be classified as medical-related or system-related including several factors, such as waiting for routine medical consultation or clearance, unavailability of an operating room or surgeon, waiting for family discussion or laboratory results, waiting for stabilisation of a medical problem, admission too late in the day, and others.[169] It has also been argued that delayed surgery itself is not responsible for mortality; patients for whom surgery was delayed could have been sicker on admission than those for whom surgery was not delayed.[168]

2.7.1.3 Postoperative medication and mortality

In a randomised double-blinded placebo-controlled study, all patients received vitamin D and calcium and, in addition, the treatment group received intravenous infusion of zoledronic acid within 90 days after hip fracture surgery.[170] During median follow-up of 1.9 years, mortality was lower in the treatment group than in the placebo group (9.6% and 13.3%, p=0.01). A Finnish prospective study of 221 hip fracture patients also showed a potential relationship between reduced mortality and daily post-fracture administration of prescribed dose of 500-1000 mg calcium and 400-800 IU vitamin D.[171]

2.7.1.4 Hip fracture types and mortality

The effects of hip fracture type on mortality are controversial. A prospective Greek study of 499 hip fracture patients (33% cervical and 67% trochanteric fractures) reported excess mortality at 5 and 10 years after surgery in patients with trochanteric fracture compared to patients with cervical hip fracture.[172] The conclusion was that hip fracture type was an independent predictor of long-term mortality after hip fracture. In contrast, a retrospective Danish register study of 2674 hip fractures (64% cervical and 30% pertrochanteric fractures) showed no differences in mortality between hip fracture types during a mean follow-up of 2.6 years.[173]

2.7.1.5 Complications after hip fracture and mortality

According to a prospective observational study of 2448 hip fracture patients, the most common postoperative complications were chest infection and heart failure. Both complications were associated with substantial mortality risk: one-year mortality was 71% after chest infection and 92% after heart failure.[174] A prospective Finnish survey of 2276 hip fracture patients observed deep infection rate of 1.3% [175]. One-year mortality was slightly increased after deep infection.

2.7.2 Causes of death

Sex differences in the predisposing factors and causes of death have not been systematically studied. Analysis of mortality and cause-of-death, however, is an important procedure for identifying risk factors for death following trauma and for anticipating complications.[176]

In a longitudinal study with a 2-year follow-up of 173 men and 631 women with hip fracture, men were twice as likely as women to die, but prefracture medical comorbidity, type of fracture, type of surgical procedure, and postoperative complications did not explain the observed difference.[166] Although increases in cause-of-death were comparable for both sexes for most major causes, such as cardiovascular diseases and cancer, the greatest

increases in mortality after hip fracture for men versus women were due to infectious causes of death (e.g., septicaemia, influenza, and pneumonia). This finding suggests that after a hip facture, a new process, which differs in men and women, is set in motion.[9] The role of infection was also highlighted in a report indicating that 39% of inpatient deaths among patients with isolated limb and pelvic fractures were due to bronchopneumonia.[176]

In Denmark, a cohort study of 163,313 hip fracture patients and 505,960 controls showed that within the first year after hip fracture cancer, cerebrovascular, and cardiovascular deaths were the most common causes of death in both fracture patients and controls, but these causes were rarer in fracture patients than in controls.[144] Moreover, the proportion of deaths due to lung diseases and psychiatric causes increased in patients and controls from 1981 to 2001, which calls for measures to improve the treatment of these diseases. Cause-of-death related to the trauma that caused the fracture explained most of the deaths (68%-76%) within the first 30 days after the fracture. Complications, such as pulmonary embolism, fat embolism, lung infections, and other infections increase mortality after hip fracture.[174]

According to an Australian population-based study, the underlying causes of death after hip fracture are diseases of the circulatory system in nearly 45%, diseases of the respiratory system in 10.8%, and neoplasms in 10.7%.[154] Based on death certificates, mortality due to hip fracture can be underestimated: hip fracture was mentioned as a contributing cause of death in 21% of deaths and as an underlying cause of death in fewer than 2% of deaths.[154]

3. AIMS OF THE PRESENT STUDY

1. To define the incidence of surgically treated hip fractures in patients aged 65 years or older in Satakunta, Finland, and the circumstances related to these fractures.

2. To evaluate the geometrical differences between cervical and trochanteric hip fractures by measuring the NSA and the FNAL, and to compare the distributions of these parameters and the distributions of fracture type by sex.

3. To describe the incidence of cervical hip fractures and the relationships between selected background variables and mortality at 30 days, 6 months, and 3 years postoperatively.

4. To describe the relationships between use of potent anticholinergics, sedatives, and antipsychotics and postoperative mortality in patients with hip fracture.

5. To evaluate mortality and cause-of-death over both the short- and long-term in patients sustaining hip fracture and to evaluate mortality after hip fracture compared to the general population with a special focus on cause-of-death.

4. THE PRESENT STUDY

4.1 Patients and methods

In 1999-2000, the Satakunta Hospital District comprised 25 municipalities and approximately 4.6% (December 31, 2000; population of 237,661) of the Finnish population lived in the area.[177] People aged 65 years or older comprised 17.4% (41,408 persons) of the population.[177] Hip fracture patients were referred to three hospitals in the Satakunta Hospital District (Satakunta Central Hospital, Rauma Hospital, and Pori City Hospital) and to two hospitals related to the Satakunta Hospital District (Vammala Hospital and Loimaa Hospital).

Study I. Hip fracture patients aged 65 years or older were identified based on the Hospital Discharge Register in Finland. This register was screened using the codes of the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD10)[178] for proximal femur fractures (S72.0-S72.2) as search terms. All hip fractures that were sustained and surgically treated from January 1, 1999, to December 31, 2000, were enrolled in the study. All patients living in Satakunta and surgically treated for hip fracture in the five local hospitals were included in the study. Patients not residing in Satakunta were excluded. A total of 461 patients were identified (Table 5). Age-specific incidences were calculated based on the population of Satakunta in December 31, 2000, retrieved from Statistics Finland.[177] The distributions of hip fracture subjects in Studies I-V are shown in Figure 4. Original medical records of the identified patients were reviewed and information was collected on 18 variables that were not included in the Finnish Hospital Discharge Register. Of these variables, data on patient age, sex, month of sustaining the hip fracture, prefracture residential status and information on previous fractures were included in Study I.

Table 5. Sex and age distributions of hip fracture patients surgically treated in Satakunta in 1999-2000.

	Number of patients		
Age (years)	**Men**	**Women**	**Total**
65-69	10	14	24
70-74	22	32	54
75-79	32	61	93
80-84	17	83	100
85-89	27	98	125
≥90	5	60	65
	113 (24.5%)	348 (75.5%)	461 (100%)

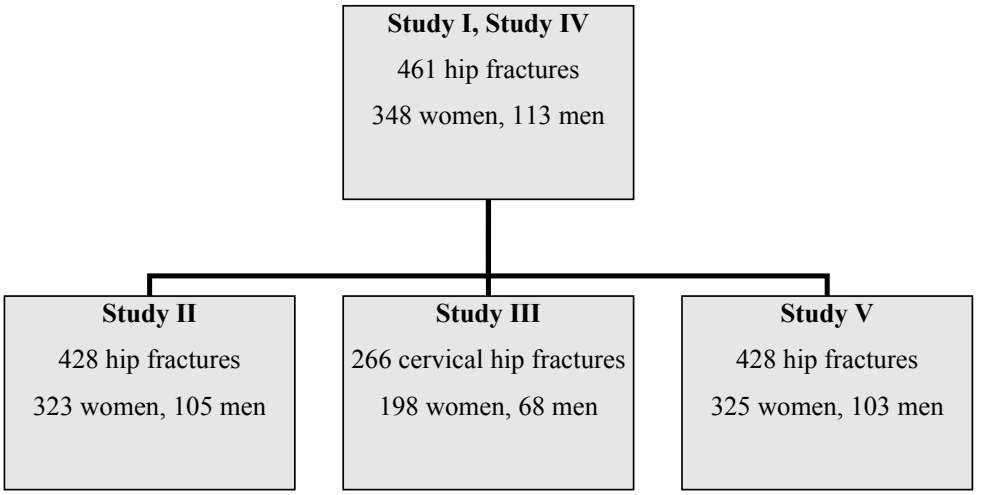


Figure 4. The distributions of the hip fracture subjects in Studies I-V.

Study II. For the analysis of hip geometry in Study II, valid information was collected for 428 of the 461 patients described in Study I (Figure 4). Of these, 323 patients (75.5%) were female and 105 patients (24.5%) were male. In routine clinical settings, anteroposterior plain pelvic radiographs were obtained prior to surgical treatment with two perpendicular radiographs from the injured hip; and postoperatively, two perpendicular radiographs of the operated hip were taken. Hip fractures were classified as cervical and trochanteric (including pertrochanteric, intertrochanteric, and subtrochanteric fractures). Measurements of NSA and FNAL were made manually by one observer with a plastic ruler (precision: 1 mm) and a goniometer (precision: 1°) as shown in Figure 2, and the fracture type was determined at that time. Fracture type could be assessed in 428 patients, NSA in 407 patients, and FNAL in 404 patients. The magnification error was corrected based on the actual size of the implant as filed in the medical records and by measuring the implant in postoperative radiographs. Mean magnification was 15.2%.

Study III. Of the 461 patients described in Study I, 266 sustained a cervical hip fracture (Figure 4). In Study II, cervical hip fractures were classified according to Garden (I, II, III, and IV).[179] Data on 20 baseline characteristics of cervical fracture patients were identified from the original medical records. Some essential variables were as follows: medical comorbidities (cardiovascular and neurological diseases, chronic lung diseases, diabetes, and dementia); types of surgical treatment (internal fixation methods including cannulated screws and dynamic hip screws, and arthroplasties including cemented unipolar or bipolar hemiarthroplasties and total hip arthroplasties); and delay to surgical treatment.

Data on population numbers for Satakunta and Finland were retrieved from Statistics Finland,[177] and age-adjusted and age-standardised incidences were calculated. Data on

deaths of cervical hip fracture patients were obtained from the Official Cause-of-Death Statistics of Finland.[177] The mortality of cervical hip fracture patients over the short-term (30 days and 6 months postoperatively) and long-term (3 years postoperatively) was analysed. The Finnish Official Cause-of-Death Register is an extensive medico-legal death investigation system that is in practice 100% complete, because each death, its certificate, and the corresponding personal information are cross-checked.[180]

Study IV. Among the 461 patients identified in Study I, use of psychotropic medications and potent anticholinergics during the occurrence of hip fracture was analysed in Study IV (Figure 4). Data on medications, patient pre-injury ability to ambulate, and comorbidities (with the same classification as in Study III) were collected from the original medical records. The Anatomical Therapeutic Chemical (ATC) classification system[181] was applied to define the main groups of medications including sedatives (benzodiazepines and related drugs, meprobamate, and barbiturates), antipsychotics, and potent anticholinergics. Potent anticholinergics were further divided into drugs for chronic obstructive pulmonary disease (COPD), drugs for urinary incontinence, typical antipsychotics (chlorpromazine, levomepromazine, perfenazine, prochlorperazine, periciazine, thioridazine, flupentixol, melperone, zuclopenthixol), tricyclic antidepressants, and 'other anticholinergics' (e.g., metoclopramide, antiparkinson biperiden, and hydroxyzine).

Mortality was evaluated over both the short-term (30 days, 3 months, and 6 months after surgery) and long-term (3 years after surgery). Data on deaths of hip fracture patients were obtained from the Official Cause-of-Death Statistics of Finland.[177]

Study V. For the mortality and cause-of-death analysis in Study V, a cohort of 428 patients with available death information was identified among the hip fracture patients described in Study I (Figure 4). Mortality and cause-of-death in hip fracture patients were compared with the general population which comprised people who resided in Finland in 1999-2000 and were 65 years of age or older during this period. The hip fracture patients and the general population were stratified by sex and age (65-74, 75-84, and ≥85 years). Hip fractures were classified as cervical or trochanteric by examining the original radiographs. Data on deaths of hip fracture patients were obtained from the Official Cause-of-Death Statistics of Finland.[177]

Mortality of the hip fracture patients was evaluated at 30 days, 6 months, 1 year, 3 years, and 7 years after hip fracture surgery and at the end of 2007; and mortality of the general population was assessed at the end of each year from 1999 through 2007. Cause-of-death for the patients and population was classified according to ICD10 diagnostic main classes[178] (Table 6). For the patients, preoperative comorbidities were similarly classified.

Table 6. Cause-of-death classification according to ICD10.

Disease class	Code
Malignant neoplasms	C00-C97
Dementia (including Alzheimer's disease)	F01, F03, G30, R54
Diseases of the circulatory system (cerebrovascular diseases included)	I00-I42.5, I42.7-I99
Diseases of the respiratory system	J00-J64, J66-J99
Diseases of the digestive system (alcohol-related diseases excluded)	K00-K93, excluding K70, K86.0, K86.01, K86.08
Others	Codes not before-mentioned

4.2 Statistical analysis

Study I. Hip fracture patients were stratified by sex and age (65-69, 70-74, 75-79, 80-84, 85-89, and ≥90 years). Data on population numbers for Satakunta were retrieved from Statistics Finland[177] and age-specific incidences were calculated. Data on variables obtained from the hospital discharge register and original medical records were entered into a matrix file of the Statistical Package for Social Sciences (SPSS). Statistical significances of linear distributions and cross-tabulations of the selected variables were evaluated using chi-square and Fisher's exact tests.

Study II. Hip fracture patients were stratified by sex and age into 5-year age groups or into two age groups (65-79 years and ≥80 years). A t-test was used to compare mean values of continuous variables and their differences of these were also assessed with Pearson's correlation coefficient or a linear regression coefficient. A chi-square test and Fisher's exact test were used for assessing p-values of nominal and ordinal variables.

Study III. Cervical hip fracture patients were stratified by sex and age (65-69, 70-74, 75-79, 80-84, 85-89, and ≥90 years). Cervical hip fracture incidences were calculated using population data for the hospital district and Finland retrieved from databases of Statistics Finland.[177] Age-standardised incidences were calculated using a direct method; 95% confidence intervals (95% CI) for sex- and age-specific incidences were calculated based on the Poisson distribution. Results are presented as hazard ratios (HR) with 95% CIs. Baseline characteristics between sexes were compared using a two-sample t-test and chi-square test. The Kaplan-Meier method was used to calculate and illustrate the cumulative probability of survival. Age-adjusted proportional hazards regression models (Cox regression model) were first used to analyze the associations of 20 selected background variables with mortality. Variables significantly associated with mortality were further entered into the multivariate models. Statistical analyses were performed using the Statistical Analysis System (SAS) for Windows®.

Study IV. Baseline characteristics between sexes were evaluated using a chi-square test to assess the significance of categorical variables and a two-sample t-test for continuous variables. The associations between taking psychotropic medicines and potent anticholinergics, comorbidities or functional variables with mortality were first analysed using an age-adjusted Cox proportional hazards model. Variables that were significantly associated with increased mortality were subsequently entered into the multivariate models. Results are presented as HR with 95% CIs.

Study V. The hip fracture patients and the general population were stratified by sex and age (65-74, 75-84, and ≥85 years). Baseline characteristics between sexes were evaluated using a chi-square test to assess the significance of categorical variables and two-sample t-test for continuous variables. Between sexes, the age-adjusted differences in mortality were evaluated with a Cox proportional hazards regression model. Between hip fracture types, the age- and sex-adjusted differences of mortality were analysed with a Cox proportional hazards regression model. Results are presented as HRs with 95% CIs. Annual age- and sex-standardised mortality of hip fracture patients was calculated for the three age groups with a direct method based on the general population in Finland.

Data in Studies I-II were analysed with SPSS for Windows® and data in Studies III-V were analysed with SAS for Windows®. P-values less than 0.05 were considered significant.

4.3 Ethical considerations

Studies I-V were approved by the Ethics Committee of the Satakunta Hospital District.

5. RESULTS

5.1 Incidence of hip fractures in Satakunta in 1999-2000 (Study I)

5.1.1 Incidence of hip fractures in patients aged 65 years or older

A total of 461 surgically treated hip fractures (348 women, 113 men) were identified in Satakunta in 1999-2000. The age-specific incidence was higher in women (688/100,000) than in men (350/100,000) and it steadily increased with age (Figure 5). In women, the age-specific incidence of hip fractures was highest in the oldest patients (≥90 years). In men, the highest occurrence was slightly earlier (85-89 years).

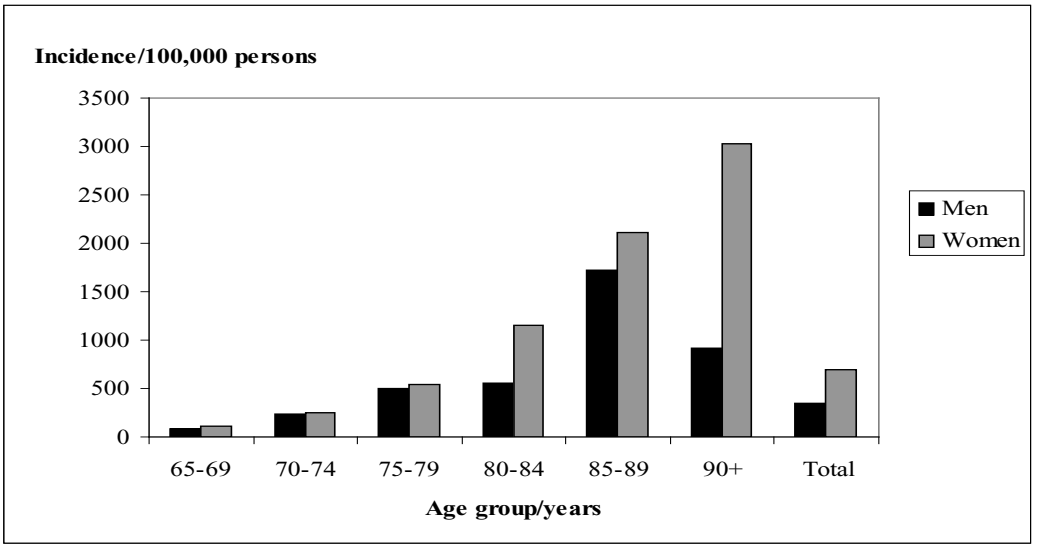


Figure 5. Age-specific incidences of hip fractures by sex in 1999-2000 in Satakunta.

5.1.2 Circumstances related to hip fractures

Residential status (living alone or with a companion) of 300 (65.1%) patients prior to hip fracture was verified. The majority of them (n=174, 58.0%) lived alone and one-third (n=98, 32.7%) lived with a spouse. The majority of men lived with a spouse (n=70, 62.0%), whereas the majority of women lived alone (n=228, 65.5%). Most of the hip fracture patients were home-dwelling (n=292, 63.3%); with the remaining living in retirement homes (n=129, 28.0%) and in service homes or hospitals (n=40, 8.7%). Of the hip fracture patients, approximately 1 in 10 (n=51, 11.1%) had been granted long-

term care compensation, which they are entitled to after 3 months institutional care in Finland.

Women were more likely to sustain hip fracture indoors than men (91.1% vs. 75.7%, p<0.001). Of hip fractures, 49.1% (n=225) occurred in homes and 41.9% (n=192) in institutions. Older people living alone at home were more likely to sustain a hip fracture at home (72.3%) than in institutions (14.5%) compared with those living with another person (35.1% and 58.6% respectively, p<0.001). Prior to hip fracture, the majority of patients (n=300, 65.1%) did not need a walking aid and 90.7% (n=418) managed activities of daily living independently. According to the medical records, more than one-fourth of hip fracture patients (n=124, 26.9%) had sustained a previous fracture. The most common fracture sites were an upper extremity (n=49) and hip or pelvis (n=42). No obvious seasonal variation was detected; 46.6% of fractures (n=215) were sustained during the months with slippery conditions (November-March), whereas 40.1% of fractures (n=185) were sustained from May to September.

5.2 Impact of hip geometry on the fracture type (Study II)

In fracture type analyses, NSA and FNAL were similar between cervical and trochanteric hip fractures. Mean NSA was larger in men (136°) than in women (133°, p<0.001); mean FNAL was longer in men (101 mm) than in women (93 mm, p<0.001; Figures 6 and 7).

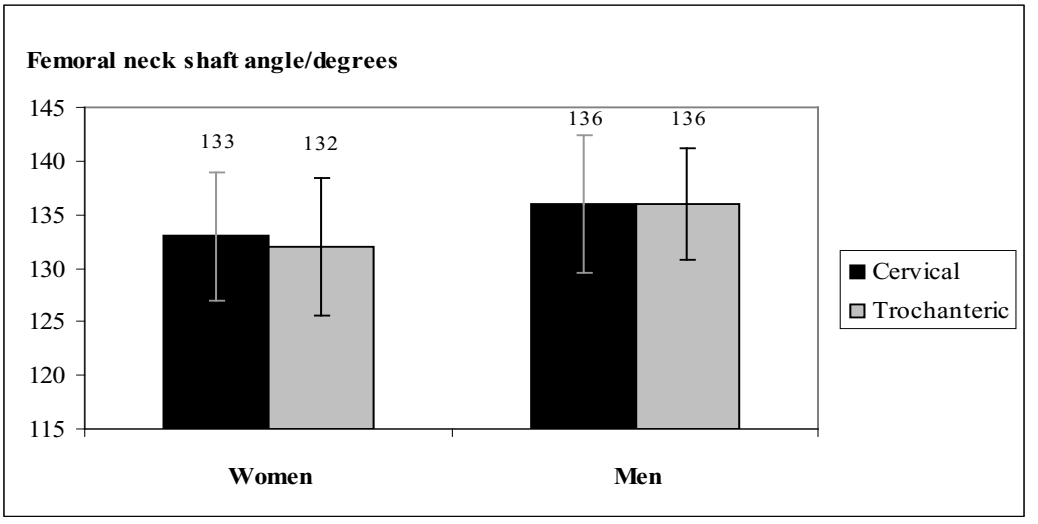


Figure 6. Femoral neck shaft angle (NSA) with standard deviations in hip fracture patients stratified by fracture type.

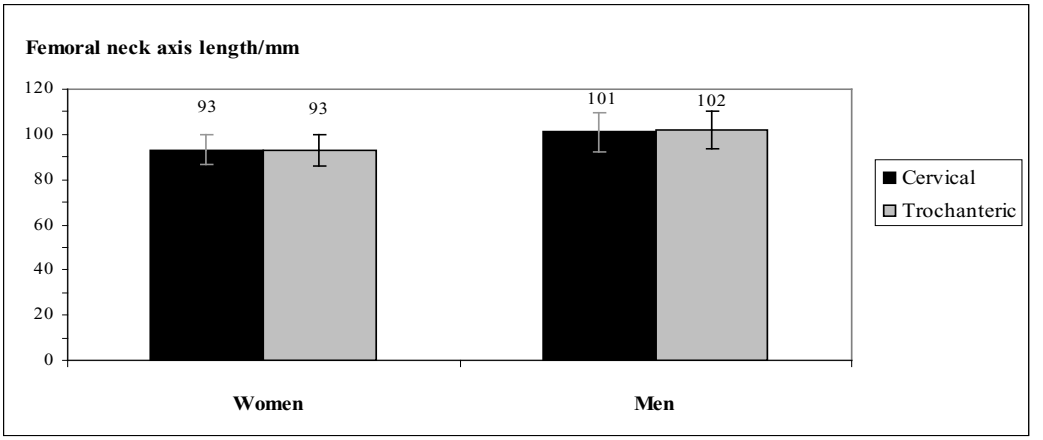


Figure 7. Femoral neck axis length (FNAL) with standard deviations in hip fracture patients stratified by fracture type.

The proportions of cervical (women 61.3%, men 64.8%) and trochanteric (women 38.7%, men 35.2%) hip fractures were similar between both sexes. In women, patients with trochanteric hip fracture were older than patients with cervical hip fracture (mean age 84.2 and 82.0 years, p=0.003). In men, patients with cervical hip fracture were older than patients with trochanteric hip fracture (mean age 79.6 and 76.8 years, p=0.048). In both sexes, the parameters of hip geometry remained unchanged with increasing age.

5.3 Incidence of cervical hip fractures and mortality of cervical hip fracture patients (Study III)

5.3.1 Baseline characteristics of cervical hip fracture patients

Of the 266 surgically treated cervical hip fracture patients, the majority were women (n=198, 74.4%), and the women were older than the men (mean ages 82.0 vs 79.6 years, p=0.018). The majority of the patients (n=179, 67.3%) were able to walk without walking aid and the majority of the patients (n=144, 58.1%) had only 0-1 comorbidity. One-year mortality was 22.6% (n=60 patients). The proportion of Garden type I-II fractures was 5.3% (n=14) and that of Garden type III-IV fractures was 94.7% (n=252). Hip fractures were treated with arthroplasty in 215 patients (80.8%) and with open reduction and internal fixation in 51 patients (19.2%). Surgery was performed a mean of 2 days after admission to the hospital and the mean hospital stay was 9.1 days (SD 6.1).

Men were more likely to have chronic lung disease (n=12, 19.4%) than women (n=14, 7.5%; p=0.008). Of women, 44.4% (n=88) lived alone, whereas only 16.2% of men (n=11) lived alone (p<0.001). In addition, there was a seasonal difference in the hip

fracture occurrence between sexes; 63.3% of men (n=38) sustained a hip fracture during slippery season (November-March) and 52.0% of women (n=91) during the non-slippery season (May-September, p=0.04). No seasonal variation was detected among home-dwelling people, but a seasonal variation was observed among institutionalised patients, 72.2% of men (n=13) and 37.7% of women (n=20) sustained a hip fracture during the slippery months (p=0.011).

5.3.2 Incidence of cervical hip fractures

The crude incidence of cervical hip fractures in women (404/100,000) was higher than that in men (223/100,000). Age-adjusted incidence of cervical hip fractures in women (364/100,000) was 1.3-fold (95% CI: 1.0-1.8; p=0.04) higher than that of men (271/100,000). After standardisation according to the entire Finnish population, the incidences were 359/100,000 in women and 267/100,000 in men.

5.3.3 Mortality of cervical hip fracture patients

Short-term mortality of cervical hip fracture patients after surgery was 9.4% at 30 days and 19.9% at 6 months. In age-adjusted analysis at 30 days, chronic lung disease, male sex, and presence of 2 to 5 comorbidities were associated with increased mortality, but only chronic lung disease and male sex remained independent risk factors for increased mortality after multivariate analysis. In age-adjusted analysis at 6 months, cardiovascular disease, chronic lung disease, presence of 2 to 5 comorbidities, male sex, and the need for postoperative mobility assistance were associated with increased mortality. After multivariate analysis, all these factors except for the number of comorbidities remained significant predictors for increased mortality.

Long-term mortality at 3 years was 39.5%. In age-adjusted analysis at 3 years, chronic lung disease, presence of 2 to 5 comorbidities, male sex, need for postoperative mobility assistance, and poor postoperative ambulation were predictors of excess mortality. Except for the number of comorbidities, these factors remained independent predictors of mortality after multivariate analysis.

In conclusion, chronic lung disease and male sex were independent predictors for increased mortality during the entire follow-up.

5.4 Effects of potent anticholinergics, sedatives, and antipsychotics on mortality after hip fracture surgery (Study IV)

5.4.1 Patient characteristics and use of medications

As in Study I, 461 patients (348 women, 76% and 113 men, 24%) were identified. At the time of sustaining the hip fracture, the women were older than the men (mean age 82.9 and 79.0 years, respectively, $p<0.001$). Regarding comorbidities, two significant differences between sexes were noted: women were more likely to have dementia (n=102, 29%) than men (n=17, 15%; $p=0.003$) but men were more likely to have chronic lung disease (n=23, 20% vs n=29, 8%; $p<0.001$). Regarding the use of the main groups of medications (potent anticholinergics, sedatives, and antipsychotics), the only significant difference between sexes was that women took more sedatives (n=144, 41%) than men (n=35, 31%; $p=0.049$). Regarding the use of potent anticholinergics, the only significant difference between sexes was that men were less likely to use 'other anticholinergics' than women (n=3, 14% vs n=28, 36%; $p=0.046$).

5.4.2 Relationships between medications and mortality

Cumulative mortality was higher in men than in women over both the short-term (30 days, 3 months, and 6 months) and long-term (3 years). Based on age-adjusted univariate analysis, mortality in women was not associated with the use of any of the main groups of medications, whereas in men, taking potent anticholinergics was associated with excess mortality at every timepoint (Table 7). Furthermore, age-adjusted univariate analysis revealed that the presence of cardiovascular disease and the presence of chronic lung disease were predictors of excess mortality (Table 7). Predictors of excess mortality identified in the age-adjusted univariate analysis were further entered into the multivariate models. The use of potent anticholinergics emerged as an independent predictor of excess mortality in men at 3 months and 3 years (Table 7). In addition, the presence of cardiovascular disease and chronic lung disease were independent risk factors for excess mortality after hip fracture surgery in men (Table 7).

Table 7. Relationship between mortality after hip fracture surgery and use of potent anticholinergics and comorbidities in men (n=113)

Variable	30 days		3 months		6 months		3 years	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age-adjusted univariate analysis								
Potent anticholinergic vs no potent anticholinergic	3.37 (1.28-8.88)	**0.014**	3.14 (1.38-7.15)	**0.007**	2.91 (1.35-6.26)	**0.006**	2.50 (1.41-4.41)	**0.002**
Cardiovascular disease	2.71 (0.88-8.34)	0.082	2.22 (0.93-5.33)	0.073	2.46 (1.10-5.54)	**0.029**	2.07 (1.23-3.47)	**0.006**
Chronic lung disease	3.67 (1.35-10.00)	**0.011**	2.27 (0.92-5.60)	0.075	2.54 (1.13-5.68)	**0.024**	2.18 (1.24-3.82)	**0.007**
Multivariate Cox proportional hazards regression analysis								
Potent anticholinergic vs no potent anticholinergic	2.19 (0.76-6.29)	0.145	2.52 (1.05-6.03)	**0.038**	2.22 (0.99-5.01)	0.053	1.99 (1.09-3.63)	**0.025**
Cardiovascular disease	2.63 (0.84-8.18)	0.096	2.25 (0.92-5.46)	0.074	2.65 (1.16-6.06)	**0.021**	2.13 (1.25-3.63)	**0.006**
Chronic lung disease	3.07 (1.02-9.26)	**0.046**	1.98 (0.75-5.24)	0.168	2.46 (1.02-5.93)	**0.044**	2.35 (1.30-4.23)	**0.005**

n=number, HR=hazard ratio, CI=confidence interval

5.5 Mortality and cause-of-death of hip fracture patients (Study V)

5.5.1 Patient characteristics

Of the baseline population of 461 surgically treated hip fracture patients, 428 hip fracture patients were identified for Study V. The majority of patients were women (n=325, 75.9%). Women were older (mean age 82.7 years) than men (79.0, $p<0.001$). In both sexes, the proportion of cervical to trochanteric hip fractures was approximately 3:2. The mean follow-up period was 3.7 years (range 0-9 years). Cumulative numbers of deaths after surgery were as follows: 30 days, n=45 (10.5%); 6 months, n=92 (21.5%); 1 year, n=117 (27.3%); 3 years, n=209 (48.8%); 7 years, n=315 (73.6%); and on December 31, 2007 (end of follow-up), n=338 (79.0%).

5.5.2 Mortality and cause-of-death of hip fracture patients: differences between sexes

In age-adjusted models, the HR of death for men was significantly higher than that in women at each timepoint (Figure 8).

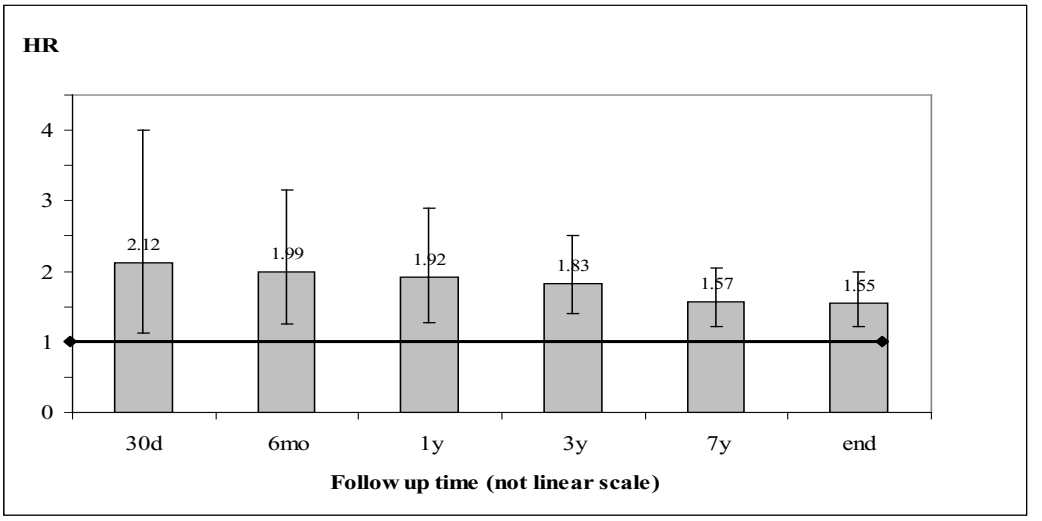


Figure 8. Age-adjusted risk of mortality in men after hip fracture surgery compared to women as hazard ratios (HR) and 95% confidence intervals. d=day, mo=month, y=year, end=December 31, 2007

In cause-of-death analyses, circulatory system disease was more commonly a cause of death in men than in women at 30 days (HR 3.35, 95% CI 1.12-9.98, p=0.030), 6 months (HR 3.14, 95% CI 1.47-6.70, p=0.003), 1 year (HR 2.58, 95% CI 1.31-5.07, p=0.006), and 3 years (HR 2.34, 95% CI 1.41-3.88, p=0.001). The risk of men dying from dementia and Alzheimer's disease was higher than that of women at 3 years (HR 2.67, 95% CI 1.07-6.65, p=0.035), 7 years (HR 3.41, 95% CI 1.54-7.54, p=0.003), and at the end of the follow-up (HR 3.43, 1.55-7.56, p=0.002).

5.5.3 Mortality and cause-of-death of hip fracture patients: differences between fracture types

In age- and sex-adjusted analyses, the mortality risk for cervical hip fracture patients was higher than that for trochanteric hip fracture patients at 6 months (HR 1.89, 95% CI 1.11-3.09, p=0.018) and mortality tended to increase in cervical hip fracture patients at 30 days (HR 2.09, 95% CI 0.95-4.60, p=0.067). In age- and sex-adjusted analyses of cause-of-death, circulatory system disease was less likely the cause of death in cervical hip fracture patients compared to trochanteric hip fracture patients at the end of the follow-up (HR 0.70, 95% CI 0.49-0.99, p=0.005) and the trend was similar at 7 years (HR 0.73, 95% CI 0.51-1.04, p=0.080).

5.5.4 Mortality and cause-of-death: comparisons between hip fracture patients and the general population

Age- and sex-standardised mortality in hip fracture patients was approximately 3-fold higher than that in the general population during the follow-up in 1999-2007. Cause-of-death analyses showed that age- and sex-standardised mortality of hip fracture patients was 2.5 to 8.4-fold higher than that in the general population in each cause-of-death category (Figure 9).

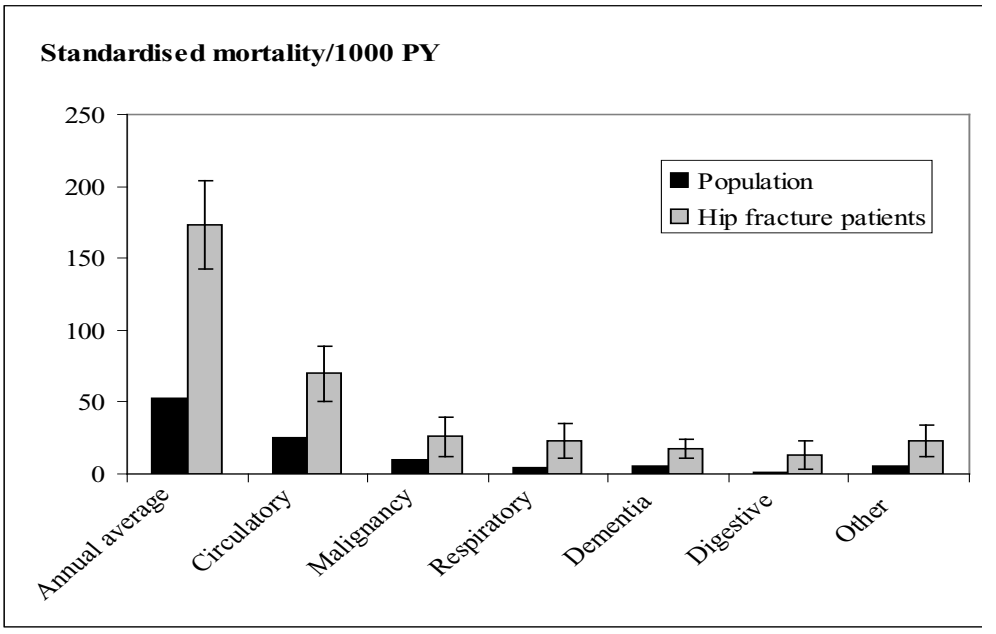


Figure 9. Age- and sex-standardised annual mortality and cause of death in hip fracture patients and the general population in 1999-2007 per 1000 person-years (with 95% confidence intervals in patients).

6. DISCUSSION

6.1 General considerations

The present population-based study describes the incidence of surgically treated hip fractures in patients aged 65 years or older and circumstances related to these fractures. In addition, the geometrical differences between cervical and trochanteric hip fractures and sexes were evaluated. The incidence of cervical hip fractures – the most common hip fracture type – was also determined. Finally, mortality was analysed from various points of view: by describing the relationships between selected background variables and mortality after cervical hip fracture; by describing the relationships between the use of psychoactive medications and mortality after hip fracture; and by evaluating mortality and cause of death after hip fracture compared to the general population.

From 1999 to 2000, 461 surgically treated hip fracture patients (348 women, 113 men) were identified in Satakunta. The age-specific incidence was higher in women (688/100,000) than in men (350/100,000) and steadily increased with age. In both sexes, the proportion of cervical to trochanteric hip fractures was approximately 3:2. The age-adjusted incidence of cervical hip fractures was 1.3-fold higher in women than in men. No significant differences of geometrical parameters (NSA and FNAL) were noted in either sex in plain pelvic radiographs taken in a routine clinical setting. Before sustaining hip fracture, the majority of hip fracture patients functioned well: most of the patients (91.4%) were home-dwelling or lived in retirement homes; and 90.7% managed activities of daily living independently. More than one in four, however, had sustained a previous fracture. A substantial proportion of hip fractures (41.9%) occurred in institutions while the majority of patients (79.2%) were there for short-term care.

In mortality analyses of the present study, chronic lung disease and male sex emerged as independent predictors of increased mortality after cervical hip fracture, both over the short- (30 days and 6 months) and long-term (3 years). In women, the use of psychoactive drugs was not associated with mortality. In contrast, use of potent anticholinergics was associated with excess male mortality from 30 days up to 3 years after surgery. During the mortality follow-up of 7 to 9 years, the risk of mortality was 3-fold higher in hip fracture patients than in the general population and included every major cause-of-death. After hip fracture, the overall 1-year postoperative mortality was 27.3% and at the end of the follow-up (December 31, 2007) mortality was 79.0%. The mortality risk for men after hip fracture was higher than that for women and the difference persisted over the entire follow-up.

6.1.1 Limitations of the present study

The basic survey design of the present study was retrospective. In descriptive studies in general, it is difficult to establish the direction of an association, i.e., cause and effect: retrospective studies can only point to statistical associations between variables; these studies cannot alone establish causality.[182] Retrospective studies are frequently criticised because they involve collecting data of past phenomena and have the potential for selectivity in recall and hence recall bias.

Retrospective studies rely on the accuracy of written records without a primary research purpose and important data may not always be available; therefore, it is difficult to control confounding variables.[183] In the present study, data relating to patient comorbidities and medications were collected from the original medical records, which are usually based on the information received from previous hospital records, referral documents, and patient and/or proxy interviews. These are not always reliable, however, or fully comprehensive. Similar problems are encountered in analysing geometrical measures of hip anatomy because pelvic radiographs were taken in a routine clinical setting in contrast to a strictly standardised and calibrated setting. Nevertheless, a retrospective study can help to focus the study question, clarify the hypothesis, determine an appropriate sample size, and identify feasibility issues for a prospective study.[183] In the mortality studies of the present paper, retrospective longitudinal surveys were performed which enabled analytic, rather than descriptive, data interpretation.

6.1.2 Strengths of the present study

The sampling frame for population-based cohort studies includes any well-defined population; in the present study, the population encompassed those that were defined by the geographic boundaries of Satakunta. In general, the most important justification for conducting a population-based study is its external validity – that is, the applicability of its results to a defined population.[184]

As for cohort studies in general,[184] data collection of this population-based survey relied both on available databases (the Finnish Hospital Discharge Register and the Official Cause-of-Death Statistics of Finland) and on information collected from the original patient records. In the cause-of-death study, the age-matched control cohort included the whole Finnish population and its mortality was registered comprehensively. The older population in Finland is quite homogeneous and e.g. ethnic differences are rare. Furthermore, the population-based study setup enhances the generalisability of the results of the present study. On the other hand, the study population represents only 4.6% of the total population in Finland which may limit the generalisation of the results.

Despite the inevitable limitations of the retrospective study design, the subjects of the present study collected from one central hospital district represent 'the real life'. All the patients aged 65 years or older that sustained a surgically treated hip fracture during the 2-year period were enrolled in the study. In Finland, even those who sustain a hip fracture while travelling are usually transferred to a hospital in their health care district for the surgical treatment.[40] A few patients may have died before referral to a hospital, and some impacted cervical fractures in sedentary patients may have gone undiagnosed.

The accuracy of registering severe injuries like hip fractures is generally good in Finland. The completeness and accuracy of data from the Finnish Health Care Register and the Cause-of-Death Register are suitable for assessing hip fracture treatment.[185] The coverage of the Official Cause-of-Death Statistics of Finland is 100% and the accuracy of the data is ensured by triple-checking.[180] The National Hospital Discharge Register, the oldest established nationwide discharge register in the world, has been operating since 1967 and its accuracy is well-established.[186]

6.2 Incidence of hip fractures

On December 31, 2000, the population of Satakunta was 237,661 and, in 1999-2000, 461 surgically treated hip fractures occurred in the population aged 65 years or older. The age-specific incidence of hip fractures in 1999-2000 was 557/100,000 in the area and it was 2-fold higher in women (688/100,000) than in men (350/100,000). This difference may be explained by age; women live longer than men and thus, a greater number of women reach "the hip fracture age".[187] Prior to the hip fracture, the majority of older people were home-dwelling (63.4%), were able to ambulate without a mobility device or help (65.1%), and 90.7% of them independently managed activities of daily living. Approximately one in four hip fracture patients (26.9%) had sustained a previous fracture, which may indicate an increased tendency to fall and impaired bone strength.

The majority of hip fractures occurred indoors (91.1% in women, 75.7% in men), consistent with previous findings.[188] Men may be more likely to ambulate outdoors and it has been postulated that those who can go outside have greater muscle strength and better neuromuscular function than those that stay indoors.[189] Men also fall less often than women.[107] When sustaining a hip fracture, 63.5% of the patients were home-dwelling and 28.0% of the patients lived retirement homes. More than a third (41.9%) of hip fractures occurred while patients were in an institution, and the majority of patients (79.2%) were in short-term care. It is plausible that orientating to a new environment (toilet, furniture, lighting) is not easy for older people and may be associated with an increased risk of falling. A German cohort-study of more than 69,000 women and men recently admitted to nursing homes showed that the hip fracture incidence rates were highest in the first months after admission to the nursing homes.[190] In the present study,

there was a slight tendency towards an increased risk of sustaining a hip fracture during the slippery season in November-March. The impact of seasonal variation, however, was not substantial, because the majority of hip fractures (87.3%) occurred indoors.

The Finnish National Hospital Discharge Register has proved to be a useful data source for epidemiological studies of hip fractures.[8 185 191] The annual number of first hip fractures in the Finnish population aged 50 years and older was reported to be 5618 in 2002-2003.[192] In 2002, the age-adjusted incidences were 408/100,000 PY for women and 190/100,000 PY for men. Another Finnish study estimated the number of hip fractures to be 7083 in 2004, and the adjusted incidences were reported to be 412/100,000 for women and 223/100,000 for men.[8] The differences in these results are mainly due to methodological issues of selecting and evaluating the data from the Hospital Discharge Register.[187] In addition, the standard populations at risk of the studies were based on different time periods 1998-2002[192] vs 1970-2004.[8] The higher incidence rates in the present study than in the national surveys may be due to the fact that the results of the present study were not adjusted according to the general Finnish population.

In Finland, the alarming increase in the incidence of hip fracture noted in 1970-1997[149] levelled off in 1998-2004.[8] In 1998-2004, a nationwide decline in the incidence of hip fracture was obvious in women and a tendency toward a decline was also observed in men. The exact reasons for the change in the trend are unknown. Possible explanations are a cohort effect toward a healthier ageing population, increased average body weight, and improved functional ability among older people.[8] Some minor reasons for the decline may be specific actions taken to prevent and treat osteoporosis and changes in lifestyle factors: smoking cessation, increased exercise, taking calcium and vitamin D, hormone replacement therapy, and anti-osteoporotic medication.[8] In addition, the effects of interventions to prevent falling, such as strength and balance training, reduction of psychotropic medications, correction of visual impairment, modification of environmental hazards, and use of hip protectors and gait-stabilising devices may have contributed to the decline in hip fracture incidence.[8] Contrary to the results of a nationwide survey in Finland, the age-adjusted incidence rates increased for both sexes in Central Finland between 1992-1993 and 2002-2003 but no evident reasons for this trend could be presented.[40]

As in many previous studies, the incidence of hip fractures was higher in women than in men in the present study. The increased risk of sustaining hip fractures indoors and in institutions, even during a short stay, was also clear. Fall and fracture prevention programmes in institutions must be intensified because fracture rates in these settings were especially high. There is evidence that people with low care needs are mobile, and by default, expose themselves to riskier situations that result in falls.[190] Hence, prevention should be focused on institutionalised older people requiring lower levels

of care, and measures should be implemented immediately after admission, because the risk of a hip fracture is highest during the first 3 months.[190] Several means to prevent falls have been suggested, such as an adjustable bed height, antislip stockings, walking stick, appropriate lighting, pressure mats, and hip protectors.

6.3 Hip geometry and hip fracture type

In addition to BMD measurement, several variables of hip geometry are proposed to provide prognostic information on the risk of future fractures. The geometrical parameters of proximal femur in hip fracture patients were analysed in the present study. Trochanteric hip fractures may be related to severe osteoporosis mainly in the trabecular compartment, whereas cervical fractures may be associated with pelvic and hip geometry.[95] NSA and FNAL were measured separately for cervical and trochanteric fractures from preoperative plain pelvic radiographs taken in clinical settings. Distributions of parameters and distributions of fracture types were also compared between sexes. No significant differences in NSA or FNAL were noted between the two hip fracture types in either sex. The ratio of cervical to trochanteric hip fracture was approximately 3:2 in both sexes. NSA was higher in men (mean 136°) than in women (mean 133º, $p<0.001$), and FNAL was longer in men (mean 101 mm) than in women (mean 93 mm, $p<0.001$). In theory, these geometrical findings are unfavourable for men when assessing the hip fracture risk; nevertheless, it is probable that other risk factors of hip fracture overcome this sex difference in hip geometry.

The clinical assessment of bone strength and hip fracture risk is currently based on measuring BMD with DXA. In a prospective population-based study, most fractures occurred in people without osteoporosis as defined by DXA (i.e., T score less than -2.5).[12] Hence, it is necessary to develop more accurate tools and parameters for assessing hip fracture risk. In accurately standardised and calibrated circumstances, the combination of BMD and radiological measures of upper femur geometry improved the assessment of the risk of hip fracture and hip fracture type compared to BMD alone.[193] In those settings, NSA was significantly larger in cervical hip fracture patients than in controls. HAL predicts hip fractures independently of age and BMD in older women.[92 194] Unlike HAL, FNAL does not include the acetabular component of the pelvis. Although FNAL is the major component of HAL, its role as a risk factor for hip fracture is controversial.[195] FNAL was longer in cervical fractures of women than in trochanteric fractures in one study,[196] but some other reports showed no difference.[97 197] In clinical settings, there is yet no standardised method of measuring hip geometry and accurate measurements are difficult to obtain because the apparent femur neck length is position-dependent.[197]

Increased HAL and NSA are often considered independent risk factors for osteoporosis, but studies have demonstrated that this is not always the case. The exact mechanism

of how an increased HAL predicts a hip fracture is not clear, although it is thought to relate specifically to the shape and structure of the hip.[87 194] One hypothesis is that HAL is a marker for the ability of the femur and/or pelvis to absorb the impact of a fall.[91] The contribution of NSA to the risk of hip fracture and fracture type may be caused by variations in the biomechanical environment.[97 198] In primates (including humans), one study on the structural design of the femoral neck indicated that primates with a larger NSA have relatively lower cortical thickness in the inferior than in the superior part of the neck when compared to primates with a smaller NSA.[199] This structural weakness combined with disadvantageous hip geometry results in a situation in which the thinned femoral neck cortex with high NSA is unable to resist bending stress, predisposing the neck to a greater fracture risk.[199]

Although the present study did not show an association between patient age and hip geometry, it has been reported that NSA tends to decrease during ageing.[200] Interestingly, changes in hip geometry have been noted over time; medieval and contemporary hip anatomies were compared and, within approximately the last 1000 years, remarkable alterations of proximal femur macroanatomy (e.g., elongated femoral neck axis) were detected.[201] These changes over time increase hip fracture risk especially when combined with osteoporosis.

Bone densitometry does not provide reliable estimates of a person's true BMD. Hence, using BMD (measured by DXA) alone has been criticized to be a poor predictor of fractures in individuals.[11] Overall evidence suggests that assessing hip geometry parameters can significantly improve the ability of identifying people at risk of fracture, but improved measurement software and more research are necessary to make measurements of hip geometry applicable in clinical settings.

6.4 Incidence of cervical hip fractures and mortality of cervical hip fracture patients

The vast majority of hip fractures occur in people aged 65 years or older; however, hip fracture patients are not a homogeneous group. Cervical and trochanteric hip fractures should be evaluated separately to increase both the knowledge and the future likelihood of preventing hip fractures.[95] In the present study, the age-adjusted incidence of cervical hip fractures was 1.3-fold higher in women (364/100,000) than in men (271/100,000). Consistent with the present findings, the ratio of cervical to trochanteric hip fractures is commonly reported to be 3:2.[40 202] In Central Finland, the proportion of cervical hip fractures constantly decreased over two decades: 75.4% in 1982-1983, 65.5% in 1992-1993, and 60.5% in 2002-2003 and a similar trend was reported from Sweden and Norway.[40] This changing epidemiology of hip fracture types may reflect a cohort effect where the exposure to site-specific aetiologic factors differs over time, because

the two fracture types have different risk factors; or it may simply be a consequence of the increasing mean age at hip fracture, because trochanteric fractures on average occur later in life than cervical fractures.[203]

The overall mortality of cervical hip fracture patients in the present study increased from 9.4% at 30 days after surgery to 39.5% at 3 years after surgery. The 1-year mortality of 22.6% is quite similar to recent reports of rates of any type of hip fracture.[159] The 10-year survival rates are 42% in patients with cervical hip fractures and 24% in those with intertrochanteric fractures.[172] The increased mortality immediately after hip fracture may result from a combination of comorbidity and the acute effects of the injury. The long-term increased mortality is proposed to be largely due to comorbidity.[204] The patients of the present study were mostly functioning well before sustaining a hip fracture: the majority of the patients (67.3%) were able to walk without a walking aid; furthermore, majority of the patients (58.1%) had only 0-1 comorbidity. Consistent with previous findings,[152] higher mortality rates in men than in women were obvious in the present study. The reasons for this sex difference are unclear. In Satakunta, the mean life span of men is shorter than that of women and, in addition, men are more likely to suffer chronic lung disease, which was an independent predictor of excess mortality.

Of the two risk factors of excess mortality identified in the present study, chronic lung disease is modifiable, but sex is not. Hence, any intervention should focus on patients with lung diseases. Such measures could include optimisation of lung physiotherapy and intensified broncholytic medication in patients with asthma, chronic obstructive lung disease, and emphysema. In Finland, smoking is more common in older men than in older women.[205] Smoking cessation campaigns should be promoted, because smoking may have a particular role with regard to lung disease and postoperative complications, such as infection and wound healing. Also, smoking is associated with osteoporosis.[206] Smoking is considered a risk factor for hip fracture, because in addition to lowering the BMD and body weight, smoking decreases the levels of parathyroid hormone and 25-hydroxyvitamin.[207]

Most of the hip fracture patients (65.8%) in the present study underwent surgery within 2 days of admission. Delaying surgery did not influence mortality during the follow-up. The effect of a surgical delay on mortality is controversial. The timing of surgery is typically decided on the basis of several factors including the patient's pre-existing medical condition, the orthopaedic surgeon's preference, and operating room availability. The results of a recent systematic review and meta-analysis indicated that delaying hip fracture surgery is especially harmful to patients at relatively low risk and to young patients.[168] Definitive conclusions, however, were limited due to potential confounding factors in the observational studies. Moreover, it has been argued that surgical delay itself is not responsible for the increase in mortality. Patients whose surgery was delayed

could have been sicker on admission than others and they may have required more preoperative examinations to stabilise their medical condition; subsequently, they may have been more likely to die.[168]

Most of the cervical hip fractures (94.7%) in the present study were classified as displaced and 80% of the fractures were treated with arthroplasty. The type of surgical treatment was not associated with mortality during the follow-up. At present, there are a number of controversies concerning the methods used to treat displaced femoral neck fractures and the main problem is whether to reduce the fracture and to use internal fixation or to perform total or partial hip replacement arthroplasty.[208 209] For displaced fractures, the results of hemiarthroplasty in worst cases are better than those of internal fixation in best cases.[210] In Denmark, however, a register-based cohort study of more than 160,000 hip fracture patients showed significantly greater mortality in patients undergoing arthroplasty than in those undergoing osteosynthesis.[144] Reasons for the difference were not clear, but arthroplasty is considered to be a potentially more extensive and complex procedure than osteosynthesis. Hemiarthroplasty is usually not as a complex procedure as total hip arthroplasty. On the other hand, according to a recent review, randomised trials showed that total hip arthroplasty is a cost-effective treatment with lower revision rates than internal fixation in patients with concomitant osteoarthritis, rheumatoid arthritis, or renal failure.[211] In addition, total hip arthroplasty may also be superior to hemiarthroplasty in specific subgroups, but larger trials are needed to confirm this observation.

6.5 Effects of potent anticholinergics, sedatives, and antipsychotics on mortality after hip fracture surgery

Use of several cognition-impairing medications for somatic and mental disorders is common in older people: in the present study, 56% of women and 46% of men with hip fracture were using sedatives, antipsychotics, or potent anticholinergics. Taking potent anticholinergics was associated with excess mortality over both the short-term (30 days, 3 months, and 6 months) and long-term (3 years) in men, but not in women at any time-point. Use of these drugs was an independent predictor of excess mortality in men at 3 months and 3 years. Anticholinergic drugs in the present study included drugs for COPD (ipratropium bromide); urinary incontinence (oxybutynin and tolterodine); antipsychotics (e.g., chlorpromazine, thioridazine, melperone); tricyclic antidepressants (clomipramine, amitriptyline, doxepin); and other anticholinergics (e.g., metoclopramide and hydroxyzine).

Anticholinergic drugs block muscarinic receptors and thus reduce the effects of acetylcholine on the CNS and other target organs. Older people are particularly vulnerable, because of the mild but definite decline in cortical cholinergic neurotransmission associated with advancing age. The therapeutic potency of some

drugs (e.g., atropine for bradycardia, ipratropium bromide for bronchodilatation, and oxybutynin for overactive bladder) is based on their anticholinergic effects, but anticholinergic adverse activity is the most common cause of drug-induced confusion.[212] In clinical settings, medication of older people should be very carefully managed, because many drugs other than classical anticholinergics have anticholinergic effects.[213] Pharmacokinetics and pharmacodynamics change with advancing age; the half-life of many drugs is prolonged and drugs tend to accumulate, making older people particularly sensitive to the adverse effects of drugs.[214] Moreover, the toxicity of anticholinergics and psychotropics in the CNS may be facilitated by the increased blood-brain barrier permeability in older age.[215]

Anticholinergic delirium is characteristically associated with agitated behaviour and visual hallucinations, and signs of peripheral autonomic anticholinergic toxicity (e.g., pupil dilatation, reddish dry skin, muscle twitches). Delirium is associated with a prolonged hospital stay and a high rate of discharge to institutional care; furthermore, hip fracture patients with cognitive disorders have an increased risk of death.[216] The proportion of men with dementia in the present study was relatively low (15%). The diagnosis of dementia is, however, challenging and time-consuming which may result in oversight of the symptoms of dementia.[217]

The exact reasons for men's susceptibility to potent anticholinergics remained unclear in the present study. Chronic lung diseases were more common in men (20%) than in women (8%). In men, chronic lung disease was an independent risk factor for excess mortality over both the short- and long-term. In general, smoking is more common in older men than in older women in Finland.[205] One possible explanation for the excess male mortality is that men are more susceptible to the adverse anticholinergic effects in the peripheral system (decreased secretion in the airways) as well as in the CNS (impaired activities of daily living), leading to subsequent chest infection. After hip fracture surgery, infections, including pneumonia have been proposed to explain the higher mortality in men than in women.[166] In addition to chronic lung disease, cardiovascular diseases predicted excess mortality in men at 6 months and 3 years after hip fracture surgery. Coronary heart disease may be more severe in older men than in older women which may partly explain men's vulnerability to the adverse effects anticholinergics.

Cognitive disorders are common in older people and are often drug-induced. Combinations of both somatic and psychiatric medications can result in a significant anticholinergic burden. Hence, careful use of potent anticholinergics may reduce adverse outcomes, including mortality, and improve functional recovery after hip fracture surgery, especially in men. Drug-induced problems can be prevented by avoiding polypharmacy and adhering to the maxim of 'start low and go slow'.[213]

6.6 Mortality and cause-of-death in hip fracture patients

Hip fracture is considered an 'international barometer of osteoporosis', because hip fracture patients worldwide are almost always referred to hospitals and fracture, which is extremely unlikely to go unnoticed, is therefore routinely and accurately counted.[218] Hence, mortality after hip fracture represents the ultimate burden of osteoporosis for both the individual and society. In the present study, the overall 1-year postoperative mortality was 27.3%. Age-adjusted mortality after hip fracture surgery was higher in men than in women over the entire follow-up, up to 9 years. In the first half of the follow-up, circulatory system disease was more commonly the cause of death in men than in women; in the latter half, dementia and Alzheimer's disease were more commonly the cause of death in men. All-cause age- and sex-standardised mortality after hip fracture was 3-fold higher than that in the general population and the difference was obvious for each cause of death (i.e., malignant neoplasm, dementia, circulatory system disease, respiratory system disease, digestive system disease, and other).

Several studies report a sudden rise in mortality in the first 30 days after hip fracture, followed by a gradual decrease in the mortality rate. The exact moment when and whether the excess mortality (i.e., deaths due to hip fracture that might be prevented) related to hip fracture disappears and becomes similar to the general population's rate is controversial and ranges from 3 months to as long as 10 years after the index fracture.[219] The difficulty in attributing excess death to the hip fracture per se relates to the fact that hip fractures tend to occur among older people who already have an increased risk of death from other causes.[158] Hence, it is difficult to control for characteristics such as frailty and impaired health and functional status.

In the present study, circulatory system diseases were a more common cause of death in men than in women from 30 days to 3 years after hip fracture; dementia and Alzheimer's disease were more likely the cause of death in men than in women at 7 years after hip fracture and at the end of follow-up. Preoperatively, however, circulatory system diseases were as common in men (62.1%) as in women (69.9%); women were more likely (28.6%) to suffer dementia and Alzheimer's disease than men (14.6%).

The role of comorbidities in hip fracture mortality is controversial. Regarding comorbidities, two different patterns of mortality were observed in a prospective study of hip fractures in women aged 70 years and older.[220] Patients with pre-existing comorbidities and functional impairments experienced greater excess mortality soon after the fracture, which decreased significantly after 2 years and disappeared after 4 years. For patients without pre-existing comorbidities, the initial impact on mortality after the fracture was less pronounced; however, the excess mortality increased steadily for up to 5 years. One problem in defining the relation of comorbidities to excess mortality is that ascertaining how much the fracture and previous chronic illnesses contributed to the morbid sequence

of events that ultimately led to death depends on the pathophysiological models adopted by the researchers.[219]

The present study clearly showed the general long-term fragility of hip fracture patients, emphasising the importance of optimal long-term treatment of all major comorbidities postoperatively. In general, reducing mortality after hip fracture should begin with prevention. Efforts should be put into preventing falls instead of treating low BMD. Patients experiencing one fragility-related fracture are at increased risk for subsequent fractures.[221] To reduce the morbidity and mortality after hip fracture, efforts are needed to identify the patients at increased risk (in the present study, men with circulatory system disease and dementia and patients with a cervical hip fracture) and to improve the treatment after discharge from the hospital. Specialist medical assessment and management of older people with hip fracture before and after surgery are also recommended.[174]

Interventions such as nutritional supplementation and dietetic assessment, comprehensive multidisciplinary intervention programs, and in-hospital programs may improve outcomes, including mortality.[222 223] The United States Office of the Surgeon General has stated that unless preventive interventions are undertaken, the number of hip fractures and their associated costs are projected to increase dramatically due to the ageing 'baby-boomer' population.[224] A similar trend is also probable in Finland, as the large post-war generations reach the age of increased risk for hip fracture. Although hip fracture is generally associated with poor outcomes, appropriate management can ensure optimal recovery and survival.

7. CONCLUSIONS

1. The age-specific incidence of surgically treated hip fractures was 2-fold higher in women than in men. Prior to the fracture, 91% of the patients managed activities of daily living independently and two in three patients lived at home. More than one in four hip fracture patients had sustained a previous fracture, which highlights the need for overall fracture prevention. Hip fractures occurred mostly indoors and often in institutions, even during short-term care. Measures for indoor safety, especially in institutions, should be implemented.

2. Using radiographs taken in routine clinical settings, NSA and FNAL were similar in both cervical and trochanteric hip fracture patients. Men had significantly higher NSA and FNAL than women, but age was not related to NSA or FNAL. The ratio of cervical to trochanteric hip fractures was approximately 3:2 in both sexes. To assess the role of hip geometry in fracture patterns, a more accurate and standardised measurement method than routine plain pelvic radiographs is needed.

3. The age-adjusted incidence of cervical hip fractures in women was 1.3-fold higher than that in men. Delayed hip fracture surgery was not related to mortality over the short-term or long-term. Chronic lung disease and male sex were independent predictors of excess mortality after hip fracture surgery. Of these, chronic lung disease is modifiable. Hence, chronic lung disease should be addressed in cervical hip fracture patients, especially in men.

4. Approximately half of the hip fracture patients were taking potent anticholinergics, sedatives, or antipsychotics when the fracture was sustained. In men, but not in women, taking potent anticholinergics was associated with excess age-adjusted mortality during the follow-up of 3 years. Cardiovascular disease and chronic lung disease were independent risk factors for excess mortality after hip fracture surgery in men.

5. Almost one in three hip fracture patients died within 1 year after surgery. Age-adjusted mortality was higher in men than in women during the follow-up of 7 to 9 years. Men were more likely to die from circulatory disease and dementia than women. All-cause age- and sex-adjusted mortality after hip fracture surgery was 3-fold higher than that of the general population and excess mortality was related to every cause-of-death class. Optimal treatment of all major comorbidities postoperatively is essential to reduce mortality.

8. ACKNOWLEDGEMENTS

The present study was carried out at the Departments of Surgery of Satakunta Central Hospital and Pori City Hospital and at the Department of Surgery, University of Turku, Turku University Hospital.

I wish to express my most sincere gratitude to my supervisors, Professor Sirkka-Liisa Kivelä, MD, PhD, and Professor Pertti Aarnio, MD, PhD, for their encouragement and guidance throughout the course of this study. It was a pleasure to consult them; despite their administrative and clinical obligations and other research duties, they were always willing to promote this study. Professor Sirkka-Liisa Kivelä evaluated and revised every manuscript very thoroughly which kept the scientific novice busy, but it certainly was worthwhile. The overall credit of the present study belongs to Professor Pertti Aarnio who designed the basic idea of this study. He kindly offered me the opportunity to join the study group. During the process, he kept the goals clear and visible.

I am very grateful to the reviewers of this thesis. Docent Jari Parkkari, MD, PhD, University of Tampere, reviewed the present study from the epidemiological point of view; and Docent Tuomo Visuri, MD, PhD, University of Helsinki, with the expertise of orthopaedics and traumatology. Their precise and insightful suggestions certainly improved the quality of my thesis.

I am deeply grateful to my co-worker, Docent Pekka T. Jaatinen, MD, PhD, Rauma health office, for his enthusiasm and encouragement, as well as criticism. When starting the present study I learned the essential basics of scientific work from him. Without his guidance e.g., on statistical analysis or skills of scientific reading, transforming from a clinician to a researcher would have been impossible.

I owe my special thanks to my co-worker, Docent Harri Pihlajamäki, MD, PhD, Centre for Military Medicine. In addition to contributing to the articles, I thank you for your true friendship of three decades.

I express my gratitude and warmest thanks also to my other co-authors. Matti Sävelä, MD, orthopaedic surgeon, made a huge effort in analysing preliminary data and clinical radiographs. Tero Vahlberg, MSc, performed statistical analyses and answered patiently even the most peculiar questions from a clinician. Juha Puustinen, MD, contributed to the study with his expertise of the medication of older people; and Docent Ville M. Mattila MD, PhD, offered his knowledge of epidemiology in the mortality analyses.

I also wish to thank Harri Panula, MD, PhD, orthopaedic surgeon, and Kari Panula, DDS, PhD, maxillofacial surgeon, for their brotherly advice in preparing this thesis.

I thank my dear and energetic mother-in-law Tuula and father-in-law Ahti for their affection. They have pricelessly supported me and especially my family during my absence due to work or research.

I thank SciTechEdit International for reviewing the language of this thesis.

Finally, I thank my dear wife Leila and our beloved children Tuukka, Iiris, and Elias. May be, navigation, gardening, and research are the only things that are necessary; but without any doubt, the family is the one which is most important.

This work has been financially supported by Satakunta Central Hospital EVO Financing, the Finnish Cultural Foundation, and the Finnish Medical Foundation.

Pori, June 2010

9. REFERENCES

1. Haleem S, Lutchman L, Mayahi R, Grice JE, Parker MJ. Mortality following hip fracture: trends and geographical variations over the last 40 years. *Injury* 2008;39(10):1157-63.

2. Cooper C. The crippling consequences of fractures and their impact on quality of life. *Am J Med* 1997;103(2A):12S-17S.

3. Suomalaisen Lääkäriseuran Duodecimin ja Suomen Ortopediyhdistyksen asettama työryhmä. Lonkkamurtumapotilaiden hoito. 2006; Available at: *http://www.kaypahoito.fi*. Accessed November 11, 2009.

4. Melton LJ, 3rd. Epidemiology worldwide. *Endocrinol Metab Clin North Am* 2003;32(1):1-13.

5. Leslie WD, O'Donnell S, Jean S, Lagace C, Walsh P, Bancej C, et al. Trends in hip fracture rates in Canada. *JAMA* 2009;302(8):883-9.

6. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. *JAMA* 2009;302(14):1573-9.

7. Abrahamsen B, Vestergaard P. Declining incidence of hip fractures and the extent of use of anti-osteoporotic therapy in Denmark 1997-2006. *Osteoporos Int* 2010;21(3):373-80.

8. Kannus P, Niemi S, Parkkari J, Palvanen M, Vuori I, Järvinen M. Nationwide decline in incidence of hip fracture. *J Bone Miner Res* 2006;21(12):1836-8.

9. Orwig DL, Chan J, Magaziner J. Hip fracture and its consequences: differences between men and women. *Orthop Clin North Am* 2006;37(4):611-22.

10. Parkkari J, Kannus P, Palvanen M, Natri A, Vainio J, Aho H, et al. Majority of hip fractures occur as a result of a fall and impact on the greater trochanter of the femur: a prospective controlled hip fracture study with 206 consecutive patients. *Calcif Tissue Int* 1999;65(3):183-7.

11. Järvinen TL, Sievänen H, Khan KM, Heinonen A, Kannus P. Shifting the focus in fracture prevention from osteoporosis to falls. *BMJ* 2008;336(7636):124-6.

12. Schuit SC, van der Klift M, Weel AE, de Laet CE, Burger H, Seeman E, et al. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. *Bone* 2004;34(1):195-202.

13. Wehren LE, Magaziner J. Hip fracture: risk factors and outcomes. *Curr Osteoporos Rep* 2003;1(2):78-85.

14. Espino DV, Bazaldua OV, Palmer RF, Mouton CP, Parchman ML, Miles TP, et al. Suboptimal medication use and mortality in an older adult community-based cohort: results from the Hispanic EPESE Study. *J Gerontol A Biol Sci Med Sci* 2006;61(2):170-5.

15. Cruz-Jentoft AJ, Franco A, Sommer P, Baeyens JP, Jankowska E, Maggi A, et al. Silver paper: the future of health promotion and preventive actions, basic research, and clinical aspects of age-related disease--a report of the European summit on age-related disease. *Aging Clin Exp Res* 2009;21(6):376-85.

16. Palvanen M, Kannus P, Parkkari J, Pitkäjärvi T, Pasanen M, Vuori I, et al. The injury mechanisms of osteoporotic upper extremity fractures among older adults: a controlled study of 287 consecutive patients and their 108 controls. *Osteoporos Int* 2000;11(10):822-31.

17. Robinson CM, Court-Brown CM, McQueen MM, Christie J. Hip fractures in adults younger than 50 years of age. Epidemiology and results. *Clin Orthop Relat Res* 1995(312):238-46.

18. Kannus P, Parkkari J. Prevention of hip fracture with hip protectors. *Age Ageing* 2006;35(Suppl 2):ii51-ii54.

19. Eaton S.B ESB. An evolutionary perspective on human physical activity: implications for health. *Comp Biochem Physiol A Mol Integr Physiol* 2003 Sep;136(1):153-9.

20. Dequeker J, Ortner DJ, Stix AI, Cheng XG, Brys P, Boonen S. Hip fracture and osteoporosis in a XIIth Dynasty female skeleton from Lisht, upper Egypt. *J Bone Miner Res* 1997;12(6):881-8.

21. Degeling C. Fractured hips: surgical authority, futility and innovation in nineteenth century medicine. *Endeavour* 2009;33(4):129-34.

22. Speed K. The classic. The unsolved fracture. *Clin Orthop Relat Res* 1980;152:3-9.

23. Moore AT. The self-locking metal hip prosthesis. *J Bone Joint Surg Am* 1957;39-A(4):811-27.

24. Siris ES. Patients with hip fracture: what can be improved? *Bone* 2006;38(2 Suppl 2):S8-12.

25. Berglund-Roden M, Swierstra BA, Wingstrand H, Thorngren KG. Prospective comparison of hip fracture treatment. 856 cases followed for 4 months in The Netherlands and Sweden. *Acta Orthop Scand* 1994;65(3):287-94.

26. Salkeld G, Cameron ID, Cumming RG, Easter S, Seymour J, Kurrle SE, et al. Quality of life related to fear of falling and hip fracture in older women: a time trade off study. *BMJ* 2000;320(7231):341-6.

27. Cooper C, Campion G, Melton LJ, 3rd. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992;2(6):285-9.

28. Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. *Osteoporos Int* 1997;7(5):407-13.

29. Keene GS, Parker MJ, Pryor GA. Mortality and morbidity after hip fractures. *BMJ* 1993;307(6914):1248-50.

30. Thorngren KG, Hommel A, Norrman PO, Thorngren J, Wingstrand H. Epidemiology of femoral neck fractures. *Injury* 2002;33(Suppl 3) C:1-7.

31. Kannus P, Niemi S, Parkkari J, Palvanen M, Heinonen A, Sievänen H, et al. Why is the age-standardized incidence of low-trauma fractures rising in many elderly populations? *J Bone Miner Res* 2002;17(8):1363-7.

32. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med* 1988;319(26):1701-7.

33. Allolio B. Risk factors for hip fracture not related to bone mass and their therapeutic implications. *Osteoporos Int* 1999;9(Suppl 2):S9-S16.

34. Cummings SR. Treatable and untreatable risk factors for hip fracture. *Bone* 1996;18(3 Suppl):165S-7S.

35. Kanis JA, Johnell O. On behalf of the Committee of Scientific Advisors of the International Osteoporosis Foundation. Requirements for DXA for the management of osteoporosis in Europe. . *Osteoporos Int* 2005;16:220-238.

36. Shi N, Foley K, Lenhart G, Badamgarav E. Direct healthcare costs of hip, vertebral, and non-hip, non-vertebral fractures. *Bone* 2009;45(6):1084-90.

37. Verheyen CC, Smulders TC, van Walsum AD. High secondary displacement rate in the conservative treatment of impacted femoral neck fractures in 105 patients. *Arch Orthop Trauma Surg* 2005;125(3):166-8.

38. Sambrook P, Cooper C. Osteoporosis. *Lancet* 2006;367(9527):2010-8.

39. Icks A, Haastert B, Wildner M, Becker C, Meyer G. Trend of hip fracture incidence in Germany 1995-2004: a population-based study. *Osteoporos Int* 2008;19(8):1139-45.

40. Lönnroos E, Kautiainen H, Karppi P, Huusko T, Hartikainen S, Kiviranta I, et al. Increased incidence of hip fractures. A population based-study in Finland. *Bone* 2006;39(3):623-7.

41. Bergstrom U, Jonsson H, Gustafson Y, Pettersson U, Stenlund H, Svensson O. The hip fracture incidence curve is shifting to the right. *Acta Orthop* 2009;80(5):520-4.

42. Kanis JA, Johnell O, De Laet C, Jonsson B, Oden A, Ogelsby AK. International variations in hip fracture probabilities: implications for risk assessment. *J Bone Miner Res* 2002;17(7):1237-44.

43. Theobald TM, Cauley JA, Gluer CC, Bunker CH, Ukoli FA, Genant HK. Black-white differences in hip geometry. Study of Osteoporotic Fractures Research Group. *Osteoporos Int* 1998;8(1):61-7.

44. Gronskag AB, Forsmo S, Romundstad P, Langhammer A, Schei B. Incidence and seasonal variation in hip fracture incidence among elderly women in Norway. The HUNT Study. *Bone* 2010;46(5):1294-8.

45. Sanders KM, Nicholson GC, Ugoni AM, Seeman E, Pasco JA, Kotowicz MA. Fracture rates lower in rural than urban communities: the Geelong Osteoporosis Study. *J Epidemiol Community Health* 2002;56(6):466-70.

46. Lofthus CM, Osnes EK, Falch JA, Kaastad TS, Kristiansen IS, Nordsletten L, et al. Epidemiology of hip fractures in Oslo, Norway. *Bone* 2001;29(5):413-8.

47. Lin HC, Xiraxagar S. Seasonality of hip fractures and estimates of season-attributable effects: a multivariate ARIMA analysis of population-based data. *Osteoporos Int* 2006;17(6):795-806.

48. Wei TS, Hu CH, Wang SH, Hwang KL. Fall characteristics, functional mobility and bone mineral density as risk factors of hip fracture in the community-dwelling ambulatory elderly. *Osteoporos Int* 2001;12(12):1050-5.

49. Greenspan SL, Myers ER, Kiel DP, Parker RA, Hayes WC, Resnick NM. Fall direction, bone mineral density, and function: risk factors for hip fracture in frail nursing home elderly. *Am J Med* 1998;104(6):539-45.

50. Tinetti ME, Doucette J, Claus E, Marottoli R. Risk factors for serious injury during falls by older persons in the community. *J Am Geriatr Soc* 1995;43(11):1214-21.

51. Tinetti ME, Williams CS. Falls, injuries due to falls, and the risk of admission to a nursing home. *N Engl J Med* 1997;337(18):1279-84.

52. Tinetti ME, Kumar C. The patient who falls: "It's always a trade-off". *JAMA* 2010;303(3):258-66.

53. Luukinen H, Koski K, Hiltunen L, Kivelä SL. Incidence rate of falls in an aged population in northern Finland. *J Clin Epidemiol* 1994;47(8):843-50.

54. Rubenstein LZ, Josephson KR. The epidemiology of falls and syncope. *Clin Geriatr Med* 2002;18(2):141-58.

55. Winner SJ, Morgan CA, Evans JG. Perimenopausal risk of falling and incidence of distal forearm fracture. *BMJ* 1989;298(6686):1486-8.

56. Cumming RG, Klineberg RJ. Fall frequency and characteristics and the risk of hip fractures. *J Am Geriatr Soc* 1994;42(7):774-8.

57. Nuffield Institute for Health University of Leeds, and NHS Centre for Reviews and Dissemination. Preventing falls and subsequent injury in older people. *Effective Healthcare* 1996;2(4):1-16.

58. Parker MJ, Gillespie WJ, Gillespie LD. Effectiveness of hip protectors for preventing hip fractures in elderly people: systematic review. *BMJ* 2006;332(7541):571-4.

59. Formiga F, Lopez-Soto A, Duaso E, Chivite D, Ruiz D, Perez-Castejon JM, et al. Characteristics of falls producing hip fractures in nonagenarians. *J Nutr Health Aging* 2008;12(9):664-7.

60. Kannus P, Sievanen H, Palvanen M, Järvinen T, Parkkari J. Prevention of falls and consequent injuries in elderly people. *Lancet* 2005;366(9500):1885-93.

61. Oliver D, Connelly JB, Victor CR, Shaw FE, Whitehead A, Genc Y, et al. Strategies to prevent falls and fractures in hospitals and care homes and effect of cognitive impairment: systematic review and meta-analyses. *BMJ* 2007;334(7584):82.

62. Holroyd C, Cooper C, Dennison E. Epidemiology of osteoporosis. *Best Pract Res Clin Endocrinol Metab* 2008;22(5):671-85.

63. Consensus Development Conference. Prophylaxis and treatment of osteoporosis. *Am J Med* 1991;90:107-110.

64. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Technical Report Series. WHO, Geneva. 1994.

65. Nelson HD, Morris CD, Kraemer DF, Mahon S, Carney N, Nygren PM, et al. Osteoporosis in postmenopausal women: diagnosis and monitoring. *Evid Rep Technol Assess (Summ)* 2001(28):1-2.

66. Johnell O, Kanis J. Epidemiology of osteoporotic fractures. *Osteoporos Int* 2005;16(Suppl 2):S3-7.

67. Osteoporosis prevention, diagnosis, and therapy. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. *JAMA* 2001;285(6):785-795.

68. Kamel HK. Male osteoporosis: new trends in diagnosis and therapy. *Drugs Aging* 2005;22(9):741-8.

69. Orwoll ES, Klein RF. Osteoporosis in men. *Endocr Rev* 1995;16(1):87-116.

70. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996;312(7041):1254-9.

71. Black DM, Steinbuch M, Palermo L, Dargent-Molina P, Lindsay R, Hoseyni MS, et al. An assessment tool for predicting fracture risk in postmenopausal women. *Osteoporos Int* 2001;12(7):519-28.

72. Wagner H, Melhus H, Gedeborg R, Pedersen NL, Michaelsson K. Simply ask them about their balance--future fracture risk in a nationwide cohort study of twins. *Am J Epidemiol* 2009;169(2):143-9.

73. Huopio J, Kroger H, Honkanen R, Jurvelin J, Saarikoski S, Alhava E. Calcaneal ultrasound predicts early postmenopausal fractures as well as axial BMD. A prospective study of 422 women. *Osteoporos Int* 2004;15(3):190-5.

74. Lips P. Vitamin D physiology. *Prog Biophys Mol Biol* 2006;92(1):4-8.

75. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlson EW, et al. Higher

25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. *Am J Clin Nutr* 2004;80(3):752-8.

76. DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) Group. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. *BMJ* 2010;340:b5463.

77. Boonen S, Laan RF, Barton IP, Watts NB. Effect of osteoporosis treatments on risk of non-vertebral fractures: review and meta-analysis of intention-to-treat studies. *Osteoporos Int* 2005;16(10):1291-8.

78. Rizzoli R, Bruyere O, Cannata-Andia JB, Devogelaer JP, Lyritis G, Ringe JD, et al. Management of osteoporosis in the elderly. *Curr Med Res Opin* 2009;25(10):2373-87.

79. Kroger H, Santavirta S, Aro H, Hamalainen M. Osteoporosis and the orthopaedic surgeon. *Scand J Surg* 2003;92(3):232-4.

80. Currey JD. How well are bones designed to resist fracture? *J Bone Miner Res* 2003;18(4):591-8.

81. Kannus P, Parkkari J, Niemi S, Pasanen M, Palvanen M, Järvinen M, et al. Prevention of hip fracture in elderly people with use of a hip protector. *N Engl J Med* 2000;343(21):1506-13.

82. Parker MJ, Gillespie WJ, Gillespie LD. Hip protectors for preventing hip fractures in older people. *Cochrane Database Syst Rev* 2005(3):CD001255.

83. Karlsson KM, Sernbo I, Obrant KJ, Redlund-Johnell I, Johnell O. Femoral neck geometry and radiographic signs of osteoporosis as predictors of hip fracture. *Bone* 1996;18(4):327-30.

84. Currey JD. Role of collagen and other organics in the mechanical properties of bone. *Osteoporos Int* 2003;14(Suppl 5):S29-36.

85. Pihlajamäki HK, Ruohola JP, Kiuru MJ, Visuri TI. Displaced femoral neck fatigue fractures in military recruits. *J Bone Joint Surg Am* 2006;88(9):1989-97.

86. Javaid MK, Cooper C. Prenatal and childhood influences on osteoporosis. *Best Pract Res Clin Endocrinol Metab* 2002;16(2):349-67.

87. Brownbill RA, Ilich JZ. Hip geometry and its role in fracture: what do we know so far? *Curr Osteoporos Rep* 2003;1(1):25-31.

88. Szulc P. Bone density, geometry, and fracture in elderly men. *Curr Osteoporos Rep* 2006;4(2):57-63.

89. Peacock M, Liu G, Carey M, Ambrosius W, Turner CH, Hui S, et al. Bone mass and structure at the hip in men and women over the age of 60 years. *Osteoporos Int* 1998;8(3):231-9.

90. Crabtree NJ, Kroger H, Martin A, Pols HA, Lorenc R, Nijs J, et al. Improving risk assessment: hip geometry, bone mineral distribution and bone strength in hip fracture cases and controls. The EPOS study. European Prospective Osteoporosis Study. *Osteoporos Int* 2002;13(1):48-54.

91. Faulkner KG, Cummings SR, Black D, Palermo L, Gluer CC, Genant HK. Simple measurement of femoral geometry predicts hip fracture: the study of osteoporotic fractures. *J Bone Miner Res* 1993;8(10):1211-7.

92. Faulkner KG, McClung M, Cummings SR. Automated evaluation of hip axis length for predicting hip fracture. *J Bone Miner Res* 1994;9(7):1065-70.

93. Nakamura T, Turner CH, Yoshikawa T, Slemenda CW, Peacock M, Burr DB, et al. Do variations in hip geometry explain differences in hip fracture risk between Japanese and white Americans? *J Bone Miner Res* 1994;9(7):1071-6.

94. Pulkkinen P. Radiographical assessment of hip fragility. Thesis. *Acta Universitatis Ouluensis D Medica 1004* 2009.

95. Mautalen CA, Vega EM, Einhorn TA. Are the etiologies of cervical and trochanteric hip fractures different? *Bone* 1996;18(3 Suppl):133S-7S.

96. Gluer CC, Cummings SR, Pressman A, Li J, Gluer K, Faulkner KG, et al. Prediction of hip fractures from pelvic radiographs: the study of osteoporotic fractures. The Study of Osteoporotic Fractures Research Group. *J Bone Miner Res* 1994;9(5):671-7.

97. Partanen J, Jamsa T, Jalovaara P. Influence of the upper femur and pelvic geometry on the risk and type of hip fractures. *J Bone Miner Res* 2001;16(8):1540-6.

98. Swiontkowski MF. Intracapsular fractures of the hip. *J Bone Joint Surg Am* 1994;76(1):129-38.

99. Bachiller FG, Caballer AP, Portal LF. Avascular necrosis of the femoral head after femoral neck fracture. *Clin Orthop Relat Res* 2002(399):87-109.

100. Thorngren KG. Optimal treatment of hip fractures. *Acta Orthop Scand Suppl* 1991;241:31-4.

101. Bjorgul K, Reikeras O. Outcome of undisplaced and moderately displaced femoral neck fractures. *Acta Orthop* 2007;78(4):498-504.

102. Bhandari M, Devereaux PJ, Swiontkowski MF, Tornetta P, 3rd, Obremskey W, Koval KJ, et al. Internal fixation compared with arthroplasty for displaced fractures of the femoral neck. A meta-analysis. *J Bone Joint Surg Am* 2003;85-A(9):1673-81.

103. Cserhati P, Kazar G, Manninger J, Fekete K, Frenyo S. Non-operative or operative treatment for undisplaced femoral neck fractures: a comparative study of 122 non-operative and 125 operatively treated cases. *Injury* 1996;27(8):583-8.

104. Szulc P, Duboeuf F, Schott AM, Dargent-Molina P, Meunier PJ, Delmas PD. Structural determinants of hip fracture in elderly women: re-analysis of the data from the EPIDOS study. *Osteoporos Int* 2006;17(2):231-6.

105. Greenspan SL, Myers ER, Maitland LA, Kido TH, Krasnow MB, Hayes WC. Trochanteric bone mineral density is associated with type of hip fracture in the elderly. *J Bone Miner Res* 1994;9(12):1889-94.

106. Meriläinen S, Nevalainen T, Luukinen H, Jalovaara P. Risk factors for cervical and trochanteric hip fracture during a fall on the hip. *Scand J Prim Health Care* 2002;20(3):188-92.

107. Kannus P, Parkkari J, Sievanen H, Heinonen A, Vuori I, Järvinen M. Epidemiology of hip fractures. *Bone* 1996;18(1 Suppl):57S-63S.

108. Riggs BL, Wahner HW, Seeman E, Offord KP, Dunn WL, Mazess RB, et al. Changes in bone mineral density of the proximal femur and spine with aging. Differences between the postmenopausal and senile osteoporosis syndromes. *J Clin Invest* 1982;70(4):716-23.

109. Fox KM, Cummings SR, Williams E, Stone K. Femoral neck and intertrochanteric fractures have different risk factors: a prospective study. *Osteoporos Int* 2000;11(12):1018-23.

110. Luukinen H, Herala M, Koski K, Honkanen R, Laippala P, Kivelä SL. Fracture risk associated with a fall according to type of fall among the elderly. *Osteoporos Int* 2000;11(7):631-4.

111. Baudoin C, Fardellone P, Sebert JL. Effect of sex and age on the ratio of cervical to trochanteric hip fracture. A meta-analysis of 16 reports on 36,451 cases. *Acta Orthop Scand* 1993;64(6):647-53.

112. Petersen MB, Jorgensen HL, Hansen K, Duus BR. Factors affecting postoperative mortality of patients with displaced femoral neck fracture. *Injury* 2006;37(8):705-11.

113. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. *Osteoporos Int* 2009;20(10):1633-50.

114. Haentjens P, Autier P, Barette M, Venken K, Vanderschueren D, Boonen S. Survival and functional outcome according to hip fracture type: a one-year prospective cohort study in elderly women with an intertrochanteric or femoral neck fracture. *Bone* 2007;41(6):958-64.

115. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004;57(1):6-14.

116. Barry PJ, Gallagher P, Ryan C. Inappropriate prescribing in geriatric patients. *Curr Psychiatry Rep* 2008;10(1):37-43.

117. Salazar JA, Poon I, Nair M. Clinical consequences of polypharmacy in elderly: expect the unexpected, think the unthinkable. *Expert Opin Drug Saf* 2007;6(6):695-704.

118. Greenblatt DJ. Reduced serum albumin concentration in the elderly: a report from the Boston Collaborative Drug Surveillance Program. *J Am Geriatr Soc* 1979;27(1):20-2.

119. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother* 2007;5(4):345-51.

120. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. *JAMA* 2002;287(3):337-44.

121. Tune LE, Bylsma FW. Benzodiazepine-induced and anticholinergic-induced delirium in the elderly. *Int Psychogeriatr* 1991;3(2):397-408.

122. Tune L, Carr S, Hoag E, Cooper T. Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delirium. *Am J Psychiatry* 1992;149(10):1393-4.

123. Nishtala PS, Fois RA, McLachlan AJ, Bell JS, Kelly PJ, Chen TF. Anticholinergic activity of commonly prescribed medications and

neuropsychiatric adverse events in older people. *J Clin Pharmacol* 2009;49(10):1176-84.

124. Spigset O, Martensson B. Fortnightly review: drug treatment of depression. *BMJ* 1999;318(7192):1188-91.

125. Ensrud KE, Blackwell T, Mangione CM, Bowman PJ, Bauer DC, Schwartz A, et al. Central nervous system active medications and risk for fractures in older women. *Arch Intern Med* 2003;163(8):949-57.

126. Haney EM, Chan BK, Diem SJ, Ensrud KE, Cauley JA, Barrett-Connor E, et al. Association of low bone mineral density with selective serotonin reuptake inhibitor use by older men. *Arch Intern Med* 2007;167(12):1246-51.

127. Miller PS, Richardson JS, Jyu CA, Lemay JS, Hiscock M, Keegan DL. Association of low serum anticholinergic levels and cognitive impairment in elderly presurgical patients. *Am J Psychiatry* 1988;145(3):342-5.

128. Starr JM, Farrall AJ, Armitage P, McGurn B, Wardlaw J. Blood-brain barrier permeability in Alzheimer's disease: a case-control MRI study. *Psychiatry Res* 2009;171(3):232-41.

129. Farrall AJ, Wardlaw JM. Blood-brain barrier: ageing and microvascular disease--systematic review and meta-analysis. *Neurobiol Aging* 2009;30(3):337-52.

130. Swift CG, Ewen JM, Clarke P, Stevenson IH. Responsiveness to oral diazepam in the elderly: relationship to total and free plasma concentrations. *Br J Clin Pharmacol* 1985;20(2):111-8.

131. Ray WA. Psychotropic drugs and injuries among the elderly: a review. *J Clin Psychopharmacol* 1992;12(6):386-96.

132. Wagner AK, Zhang F, Soumerai SB, Walker AM, Gurwitz JH, Glynn RJ, et al. Benzodiazepine use and hip fractures in the elderly: who is at greatest risk? *Arch Intern Med* 2004;164(14):1567-72.

133. Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Zolpidem use and hip fractures in older people. *J Am Geriatr Soc* 2001;49(12):1685-90.

134. Herrmann N, Lanctot KL. Atypical antipsychotics for neuropsychiatric symptoms of dementia: malignant or maligned? *Drug Saf* 2006;29(10):833-43.

135. Alexopoulos GS, Streim J, Carpenter D, Docherty JP. Using antipsychotic agents in older patients. *J Clin Psychiatry* 2004;65(Suppl 2):5-99; discussion 100-102; quiz 103-4.

136. Halbreich U. Osteoporosis, schizophrenia and antipsychotics: the need for a comprehensive multifactorial evaluation. *CNS Drugs* 2007;21(8):641-57.

137. Hummer M, Malik P, Gasser RW, Hofer A, Kemmler G, Moncayo Naveda RC, et al. Osteoporosis in patients with schizophrenia. *Am J Psychiatry* 2005;162(1):162-7.

138. Levine J, Belmaker RH. Osteoporosis and schizophrenia. *Am J Psychiatry* 2006;163(3):549-50.

139. Howard L, Kirkwood G, Leese M. Risk of hip fracture in patients with a history of schizophrenia. *Br J Psychiatry* 2007;190:129-34.

140. Bilici M, Cakirbay H, Guler M, Tosun M, Ulgen M, Tan U. Classical and atypical neuroleptics, and bone mineral density, in patients with schizophrenia. *Int J Neurosci* 2002;112(7):817-28.

141. Robbins JA, Biggs ML, Cauley J. Adjusted mortality after hip fracture: From the cardiovascular health study. *J Am Geriatr Soc* 2006;54(12):1885-91.

142. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK. The components of excess mortality after hip fracture. *Bone* 2003;32(5):468-73.

143. Beer C, Xiao J, Flicker L, Almeida OP. Long-term mortality following stroke, myocardial infarction and fractured neck of femur in Western Australia. *Intern Med J* 2007;37(12):815-9.

144. Vestergaard P, Rejnmark L, Mosekilde L. Has mortality after a hip fracture increased? *J Am Geriatr Soc* 2007;55(11):1720-6.

145. Poor G, Atkinson EJ, O'Fallon WM, Melton LJ, 3rd. Determinants of reduced survival following hip fractures in men. *Clin Orthop Relat Res* 1995(319):260-5.

146. Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ, 3rd. Population-based study of survival after osteoporotic fractures. *Am J Epidemiol* 1993;137(9):1001-5.

147. Farahmand BY, Michaelsson K, Ahlbom A, Ljunghall S, Baron JA. Survival after hip fracture. *Osteoporos Int* 2005;16(12):1583-90.

148. Browner WS, Pressman AR, Nevitt MC, Cummings SR. Mortality following fractures in older women. The study of osteoporotic fractures. *Arch Intern Med* 1996;156(14):1521-5.

149. Kannus P, Niemi S, Parkkari J, Palvanen M, Vuori I, Järvinen M. Hip fractures in Finland between 1970 and 1997 and predictions for the future. *Lancet* 1999;353(9155):802-5.

150. Penrod JD, Litke A, Hawkes WG, Magaziner J, Doucette JT, Koval KJ, et al. The association of race, gender, and comorbidity with mortality and function after hip fracture. *J Gerontol A Biol Sci Med Sci* 2008;63(8):867-72.

151. Pioli G, Barone A, Giusti A, Oliveri M, Pizzonia M, Razzano M, et al. Predictors of mortality after hip fracture: results from 1-year follow-up. *Aging Clin Exp Res* 2006;18(5):381-7.

152. Bass E, French DD, Bradham DD, Rubenstein LZ. Risk-adjusted mortality rates of elderly veterans with hip fractures. *Ann Epidemiol* 2007;17(7):514-9.

153. de Luise C, Brimacombe M, Pedersen L, Sorensen HT. Comorbidity and mortality following hip fracture: a population-based cohort study. *Aging Clin Exp Res* 2008;20(5):412-8.

154. Hindmarsh DM, Hayen A, Finch CF, Close JC. Relative survival after hospitalisation for hip fracture in older people in New South Wales, Australia. *Osteoporos Int* 2009;20(2):221-9.

155. Bentler SE, Liu L, Obrizan M, Cook EA, Wright KB, Geweke JF, et al. The aftermath of hip fracture: discharge placement, functional status change, and mortality. *Am J Epidemiol* 2009;170(10):1290-9.

156. Söderqvist A, Ekström W, Ponzer S, Pettersson H, Cederholm T, Dalen N, et al. Prediction of mortality in elderly patients with hip fractures: a two-year prospective study of 1,944 patients. *Gerontology* 2009;55(5):496-504.

157. Vestergaard P, Rejnmark L, Mosekilde L. Loss of life years after a hip fracture. *Acta Orthop* 2009;80(5):525-30.

158. Tosteson AN, Gottlieb DJ, Radley DC, Fisher ES, Melton LJ, 3rd. Excess mortality following hip fracture: the role of underlying health status. *Osteoporos Int* 2007;18(11):1463-72.

159. Tsuboi M, Hasegawa Y, Suzuki S, Wingstrand H, Thorngren KG. Mortality and mobility after hip fracture in Japan: a ten-year follow-up. *J Bone Joint Surg Br* 2007;89(4):461-6.

160. Paksima N, Koval KJ, Aharanoff G, Walsh M, Kubiak EN, Zuckerman JD, et al. Predictors of mortality after hip fracture: a 10-year prospective study. *Bull NYU Hosp Jt Dis* 2008;66(2):111-7.

161. von Friesendorff M, Besjakov J, Akesson K. Long-term survival and fracture risk after hip fracture: a 22-year follow-up in women. *J Bone Miner Res* 2008;23(11):1832-41.

162. Thwaites JH, Mann F, Gilchrist N, Frampton C, Rothwell A, Sainsbury R. Shared care between geriatricians and orthopaedic surgeons as a model of care for older patients with hip fractures. *N Z Med J* 2005;118(1214):U1438.

163. Fisher AA, Davis MW, Rubenach SE, Sivakumaran S, Smith PN, Budge MM. Outcomes for older patients with hip fractures: the impact of orthopedic and geriatric medicine cocare. *J Orthop Trauma* 2006;20(3):172-8; discussion 179-80.

164. McGinn T, Conte JG, Jarrett MP, ElSayegh D. Decreasing mortality for patients undergoing hip fracture repair surgery. *Jt Comm J Qual Patient Saf* 2005;31(6):304-7.

165. Kannegaard PN, van der Mark S, Eiken P, Abrahamsen B. Excess mortality in men compared with women following a hip fracture. National analysis of comedications, comorbidity and survival. *Age Ageing* 2010;39(2):203-9.

166. Wehren LE, Hawkes WG, Orwig DL, Hebel JR, Zimmerman SI, Magaziner J. Gender differences in mortality after hip fracture: the role of infection. *J Bone Miner Res* 2003;18(12):2231-7.

167. Endo Y, Aharonoff GB, Zuckerman JD, Egol KA, Koval KJ. Gender differences in patients with hip fracture: a greater risk of morbidity and mortality in men. *J Orthop Trauma* 2005;19(1):29-35.

168. Shiga T, Wajima Z, Ohe Y. Is operative delay associated with increased mortality of hip fracture patients? Systematic review, meta-analysis, and meta-regression. *Can J Anaesth* 2008;55(3):146-54.

169. Orosz GM, Hannan EL, Magaziner J, Koval K, Gilbert M, Aufses A, et al. Hip fracture in the older patient: reasons for delay in hospitalization and timing of surgical repair. *J Am Geriatr Soc* 2002;50(8):1336-40.

170. Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007;357(18):1799-809.

171. Nurmi-Luthje I, Luthje P, Kaukonen JP, Kataja M, Kuurne S, Naboulsi H, et al. Post-fracture prescribed calcium and vitamin D supplements alone or, in females, with

concomitant anti-osteoporotic drugs is associated with lower mortality in elderly hip fracture patients: a prospective analysis. *Drugs Aging* 2009;26(5):409-21.

172. Karagiannis A, Papakitsou E, Dretakis K, Galanos A, Megas P, Lambiris E, et al. Mortality rates of patients with a hip fracture in a southwestern district of Greece: ten-year follow-up with reference to the type of fracture. *Calcif Tissue Int* 2006;78(2):72-7.

173. Giversen IM. Time trends of mortality after first hip fractures. *Osteoporos Int* 2007;18(6):721-32.

174. Roche JJ, Wenn RT, Sahota O, Moran CG. Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study. *BMJ* 2005;331(7529):1374.

175. Partanen J, Syrjälä H, Vähänikkilä H, Jalovaara P. Impact of deep infection after hip fracture surgery on function and mortality. *J Hosp Infect* 2006;62(1):44-9.

176. Deakin DE, Boulton C, Moran CG. Mortality and causes of death among patients with isolated limb and pelvic fractures. *Injury* 2007;38(3):312-7.

177. Statistics Finland. Available at: *http:// www.tilastokeskus.fi.* Accessed November 20, 2009.

178. ICD-10. International Statistical Classification of Diseases and Related Health Problems 10. Revision, WHO, 2006; Available at: *http://www.who.int/classifications/apps/icd/icd10online/*.

179. Garden RS. Low-angle fixation in fractures of the femoral neck. *J Bone Joint Surg* 1961;43B:17.

180. Kivistö JE, Mattila VM, Parkkari J, Kannus P. Incidence of poisoning deaths in Finland in 1971-2005. *Hum Exp Toxicol* 2008;27(7):567-73.

181. National Agency of Medicines. Classification of medicines (ATC) and defined daily doses (DDD). Helsinki: National Agency of Medicines. 2004.

182. Bowling A. Survey methods. In: Bowling A. Research methods in health. United Kingdom: Open University Press. 2006:197.

183. Hess DR. Retrospective studies and chart reviews. *Respir Care* 2004;49(10):1171-4.

184. Szklo M. Population-based cohort studies. *Epidemiol Rev* 1998;20(1):81-90.

185. Sund R, Nurmi-Luthje I, Luthje P, Tanninen S, Narinen A, Keskimaki I. Comparing properties of audit data and routinely collected register data in case of performance assessment of hip fracture treatment in Finland. *Methods Inf Med* 2007;46(5):558-66.

186. Mattila VM, Sillanpää P, Iivonen T, Parkkari J, Kannus P, Pihlajamäki H. Coverage and accuracy of diagnosis of cruciate ligament injury in the Finnish National Hospital Discharge Register. *Injury* 2008;39(12):1373-6.

187. Lönnroos E. Hip fractures and medication-related falls in older people. Doctoral dissertation. *Kuopio University Publications D. Medical Sciences 467* 2009.

188. Campbell AJ, Borrie MJ, Spears GF, Jackson SL, Brown JS, Fitzgerald JL. Circumstances and consequences of falls experienced by a community population 70 years and over during a prospective study. *Age Ageing* 1990;19(2):136-41.

189. Boonyaratavej N, Suriyawongpaisal P, Takkinsatien A, Wanvarie S, Rajatanavin R, Apiyasawat P. Physical activity and risk factors for hip fractures in Thai women. *Osteoporos Int* 2001;12(3):244-8.

190. Rapp K, Becker C, Lamb SE, Icks A, Klenk J. Hip fractures in institutionalized elderly people: incidence rates and excess mortality. *J Bone Miner Res* 2008;23(11):1825-31.

191. Parkkari J, Kannus P, Niemi S, Pasanen M, Järvinen M, Luthje P, et al. Increasing age-adjusted incidence of hip fractures in Finland: the number and incidence of fractures in 1970-1991 and prediction for the future. *Calcif Tissue Int* 1994;55(5):342-5.

192. Sund R. Lonkkamurtumien ilmaantuvuus Suomessa 1998-2002. *Duodecim* 2006;122(9): 1085-1091.

193. Pulkkinen P, Partanen J, Jalovaara P, Jamsa T. Combination of bone mineral density and upper femur geometry improves the prediction of hip fracture. *Osteoporos Int* 2004;15(4):274-80.

194. Faulkner KG, Cummings SR, Nevitt MC, Pressman A, Jergas M, Genant HK. Hip axis length and osteoporotic fractures. Study of Osteoporotic Fractures Research Group. *J Bone Miner Res* 1995;10(3):506-8.

195. Center JR, Nguyen TV, Pocock NA, Noakes KA, Kelly PJ, Eisman JA, et al. Femoral neck axis length, height loss and risk of hip fracture in males and females. *Osteoporos Int* 1998;8(1):75-81.

196. Pulkkinen P, Eckstein F, Lochmuller EM, Kuhn V, Jamsa T. Association of geometric factors and

failure load level with the distribution of cervical vs. trochanteric hip fractures. *J Bone Miner Res* 2006;21(6):895-901.

197. Michelotti J, Clark J. Femoral neck length and hip fracture risk. *J Bone Miner Res* 1999;14(10):1714-20.

198. Duboeuf F, Hans D, Schott AM, Kotzki PO, Favier F, Marcelli C, et al. Different morphometric and densitometric parameters predict cervical and trochanteric hip fracture: the EPIDOS Study. *J Bone Miner Res* 1997;12(11):1895-902.

199. Rafferty KL. Structural design of the femoral neck in primates. *J Hum Evol* 1997;34:361-383.

200. Isaac B, Vettivel S, Prasad R, Jeyaseelan L, Chandi G. Prediction of the femoral neck-shaft angle from the length of the femoral neck. *Clin Anat* 1997;10(5):318-23.

201. Sievänen H, Jozsa L, Pap I, Järvinen M, Järvinen TA, Kannus P, et al. Fragile external phenotype of modern human proximal femur in comparison with medieval bone. *J Bone Miner Res* 2007;22(4):537-43.

202. Bjorgul K, Reikeras O. Incidence of hip fracture in southeastern Norway : A study of 1,730 cervical and trochanteric fractures. *Int Orthop* 2006.

203. Lofman O, Berglund K, Larsson L, Toss G. Changes in hip fracture epidemiology: redistribution between ages, genders and fracture types. *Osteoporos Int* 2002;13(1):18-25.

204. Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Petterson C, et al. Mortality after osteoporotic fractures. *Osteoporos Int* 2004;15(1):38-42.

205. Laaksonen M, Uutela A, Vartiainen E, Jousilahti P, Helakorpi S, Puska P. Development of smoking by birth cohort in the adult population in eastern Finland 1972-97. *Tob Control* 1999;8(2):161-8.

206. Torgerson DJ, Reid DM, Campbell MK. Meta-analysis of cigarette smoking, bone mineral density, and risk of hip fracture. Three studies were omitted from meta-analysis. *BMJ* 1998;316(7136):1017.

207. Mellstrom D, Johansson C, Johnell O, Lindstedt G, Lundberg PA, Obrant K, et al. Osteoporosis, metabolic aberrations, and increased risk for vertebral fractures after partial gastrectomy. *Calcif Tissue Int* 1993;53(6):370-7.

208. Lu-Yao GL, Keller RB, Littenberg B, Wennberg JE. Outcomes after displaced fractures of the femoral neck. A meta-analysis of one hundred and six published reports. *J Bone Joint Surg Am* 1994;76(1):15-25.

209. Partanen J. Etiopathology and treatment-related aspects of hip fracture. *Acta Universitatis Ouluensis D Medica 742* 2003.

210. Bjorgul K, Reikeras O. Hemiarthroplasty in worst cases is better than internal fixation in best cases of displaced femoral neck fractures: a prospective study of 683 patients treated with hemiarthroplasty or internal fixation. *Acta Orthop* 2006;77(3):368-74.

211. Heetveld MJ, Rogmark C, Frihagen F, Keating J. Internal fixation versus arthroplasty for displaced femoral neck fractures: what is the evidence? *J Orthop Trauma* 2009;23(6):395-402.

212. Leinonen E, Alanen H-M. Antikolinergiset lääkehaitat ovat varsin tavallisia vanhuksilla. *Suomen Lääkärilehti* 2009;64(48):4164-4166.

213. Moore AR, O'Keeffe ST. Drug-induced cognitive impairment in the elderly. *Drugs Aging* 1999;15(1):15-28.

214. Pollock BG. Psychotropic drugs and the aging patient. *Geriatrics* 1998;53 Suppl 1:S20-4.

215. Kay GG, Abou-Donia MB, Messer WS, Jr., Murphy DG, Tsao JW, Ouslander JG. Antimuscarinic drugs for overactive bladder and their potential effects on cognitive function in older patients. *J Am Geriatr Soc* 2005;53(12):2195-201.

216. Magaziner J, Simonsick EM, Kashner TM, Hebel JR, Kenzora JE. Survival experience of aged hip fracture patients. *Am J Public Health* 1989;79(3):274-8.

217. Raivio M. Pitfalls in the treatment of persons with dementia. Academic dissertation. *University of Helsinki* 2007.

218. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002;359(9319):1761-7.

219. Vidal EI, Coeli CM, Pinheiro RS, Camargo KR, Jr. Mortality within 1 year after hip fracture surgical repair in the elderly according to postoperative period: a probabilistic record linkage study in Brazil. *Osteoporos Int* 2006;17(10):1569-76.

220. Magaziner J, Lydick E, Hawkes W, Fox KM, Zimmerman SI, Epstein RS, et al. Excess mortality attributable to hip fracture in white women aged 70 years and older. *Am J Public Health* 1997;87(10):1630-6.

221. Elliot-Gibson V, Bogoch ER, Jamal SA, Beaton DE. Practice patterns in the diagnosis and treatment of osteoporosis after a fragility fracture: a systematic review. *Osteoporos Int* 2004;15(10):767-78.

222. Eneroth M, Olsson UB, Thorngren KG. Nutritional supplementation decreases hip fracture-related complications. *Clin Orthop Relat Res* 2006;451:212-7.

223. Kannus P, Uusi-Rasi K, Palvanen M, Parkkari J. Non-pharmacological means to prevent fractures among older adults. *Ann Med* 2005;37(4):303-10.

224. Office of the Surgeon General: Bone health and osteoporosis: A report of the surgeon general. U.S. Department of Health and Human Services, Rockville, MD. 2004.