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EIJA LÖNNROOS

Hip Fractures and Medication-related Falls in Older People

Doctoral dissertation

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ABSTRACT

Falls are the leading cause of unintentional injuries in older people, and hip fractures are among the most serious consequences of falls. Most falls have a multifactorial etiology with drug-related adverse effects being one of the contributors that may increase the risk of falling.

The goals of this thesis work were to review recent original publications concerning medications as a risk factor for falls, to determine the overall incidence and recurrence rate of hip fractures, and to assess the effects of hip fractures on the utilization of inpatient care and mortality.

Twenty nine original articles met the inclusion criteria for the systematic review. Benzodiazepines, antidepressants, and antipsychotics were associated with an increased risk of falls in older people. However, randomized controlled trials were rare, and many of the observational studies had methodological limitations.

The incidence of hip fractures in Central Finland in 2002-2003 was determined using hospital registers and medical records. The results were compared with those of an earlier hip fracture study conducted in the same area. The hip fracture patients and the general population living in the study area were followed up for hospitalizations and cases of death.

In 2002-2003, 597 hip fractures occurred in Central Finland. The number was 70% higher than in 1992-1993, and the age adjusted incidence of hip fractures increased in both genders. The median length of perioperative stay in the Central Finland Hospital was 7 days, and after that the majority of hip fracture patients were transferred to primary care wards of their home municipalities. The cumulative incidence of second hip fractures was 5% at one year after the initial fracture and 8% at two years.

Of the ≥ 70 -year-old hip fracture patients, 8% died during their primary stay in the Central Finland Hospital, 15% died within the first postfracture month and 33% in the first postfracture year. The first-year mortality ratio between the hip fracture patients and the same-aged general population was 2.9.

The rate ratio of age-adjusted hospital days per person-year between the hip fracture group and the general population was 1.3 in the prefracture year, 6.9 in the first postfracture year and 3.6 in the second postfracture year. Throughout the 3-year period, the number of hospital days due to injuries was higher in the hip fracture group than in the general population. An excess of hospital days was also seen in six other diagnostic classes in the first and in four diagnostic classes in the second postfracture year.

Based on the incidence rates, and mortality and morbidity following hip fracture, more attention should be paid to prevention of falls and fall-related fractures. There is also room for improvement in the perioperative management of hip fracture patients. After surgical treatment, centralized multidisciplinary care and rehabilitation could lead to better outcomes. As a part of fall and hip fracture prevention, regular medication reviews are important

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To my parents

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This work was carried out in Central Finland Hospital and Department of Geriatrics, School of Public Health, University of Kuopio. First study plans were made in 2003, and the hip fracture data was collected in 2004 and 2006. To be honest, plans of the hip fracture study were quite flexible, or would I say research induced. The ideas for a new article developed during preparations of the previous one. The ProFaNE project plays an important role why picking up drugs and falls as one of my research interests. In May 2007, I realized that this work might lead to academic dissertation and finally, was ready for registration of this thesis study. The present study was supported by EVO-grants from the Central Finland Health Care District and scholarship awarded by the Finnish Medical Foundation.

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Kuopio, November 2009

Eija Lönnroos

ABBREVIATIONS

ACE	Angiotensin converting enzyme
ADL	Activities of daily living
ATC	Anatomic Therapeutic Chemical
BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
CNS	Central nervous system
HRT	Hormone replacement therapy
ICD-10	International Classification of Diseases, tenth revision
IQR	Interquartile range
OR	Odds ratio
PROFANE	Prevention of Falls Network Europe
PY	Person-year
RCT	Randomized controlled trial
SD	Standard deviation
SMR	Standardized mortality ratio
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications referred to in the text by their corresponding Roman numerals (I-IV). In addition, some unpublished results will be presented.

- I. Hartikainen S, Lönnroos E, Louhivuori K. Medication as a risk factor for falls: critical systematic review. *J Gerontol A Biol Sci Med Sci* 2007;62A:1172-81.
- II. Lönnroos E, Kautiainen H, Karppi P, Huusko T, Hartikainen S, Kiviranta I, Sulkava R. Increased incidence of hip fractures. A population-based study in Finland. *Bone* 2006;39:623-7.
- III. Lönnroos E, Kautiainen H, Karppi P, Hartikainen S, Kiviranta I, Sulkava R. Incidence of second hip fractures. A population-based study. *Osteoporos Int* 2007;18:1279-85.
- IV. Lönnroos E, Kautiainen H, Sund R, Karppi P, Hartikainen S, Kiviranta I, Sulkava R. Utilization of inpatient care before and after hip fracture. *Osteoporos Int* 2009;20:879-86.

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1. INTRODUCTION

As life expectancy increases older people will make up a large and rapidly growing percentage of the Finnish population. Aging is related to several physiological changes and decline in health, including for example reduced muscle and bone strength, gait and balance problems and visual deficits which can increase risk for falling and fall-related injuries.

More than one third of people aged 65 or over fall each year, and approximately one in ten falls results in a serious injury (1). Hip fractures are one of the most devastating and costly consequences of falls (2). The lifetime risk of hip fracture varies from 11 to 23% for women and 3 to 11% for men (3). In Finland, over 7000 hip fractures occur annually (4,5).

Many of the risk factors for falls and hip fractures are modifiable and reversible. However, screening and prevention of falls and fall-related injuries is often sub-optimal (6-8). Health care professionals are more experienced at managing discrete diseases than managing multifactorial conditions, such as falling. Maybe assessing the risk of falls has not considered being physician's work. Even in the case of fall-related injuries, attention is often paid to the treatment of the present trauma only, while forgetting its etiology and strategies to prevent future events. Therefore well-established care pathways are needed to improve medical management of older people at risk of falls or with hip fracture.

Providing current information, and from local settings, may be a worthwhile strategy for raising awareness among clinicians and decision-makers to promote falls prevention and better care of older people with hip fracture. Against this background, a population-based study on epidemiology of hip fractures was performed in Central Finland.

The aims of this thesis work were to determine incidence and recurrence rate of hip fractures, mortality after hip fracture, and the impact of hip fractures on the inpatient care utilization. Furthermore, a systematic review on recent publications regarding medication use and risk of falls and hip fractures was conducted.

2. REVIEW OF THE LITERATURE

2.1 Epidemiology of falls

Though fall accidents occur at all ages, the incidence and severity of falls increase with age. The majority of falls have a multifactorial etiology, and with advancing age, the significance of intrinsic risk factors, such as morbidity, increases. Medications may also increase risk of falls. Morbidity, use of medicines and adverse drug reactions all become more common in older age. Yet, few of the risk factors for falls are as potentially preventable or reversible as medication use. The section “Epidemiology of falls” deals with literature on research methodology, and incidence, risk factors and consequences of falls.

2.1.1 Definition and ascertainment of falls

A crucial methodological issue in epidemiological research is to provide a clear and preferably a standardized definition of the outcome. Thus studies on falls should determine events that are considered as falls. One of the most commonly used definitions of a fall was provided by the Kellogg group (9). A fall was defined as “unintentional coming to the ground or some lower level and other than sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in stroke or an epileptic seizure”. If falls due to cardiovascular and neurological causes (e.g. dizziness, syncope, and orthostatic hypotension) are also addressed, the definition of the Prevention of Falls Network Europe (ProFaNE) collaborators is more suitable. They define a fall as an unexpected event in which the participant comes to rest on the ground, floor, or lower level (10). The definition is comparable to that published by the World Health Organization (WHO): a fall is an event which results in a person coming to rest inadvertently on the ground or floor or other lower level (11). Above all, the outcome definition should be clear and understandable for the outcome observers, i.e. for participants in community-based studies and for nursing staff in institution-based studies.

Studies focusing on fall-related injuries should also provide a definition for the term injury. The WHO's International Classification of Diseases (ICD) defines injuries and their occurrence mechanisms (12). These codes and definitions are often used in studies focusing on fall-related injuries. Peripheral fractures account for the majority of costs, morbidity and mortality generated by fall-related injuries, and therefore registration of these accidents has been recommended (10,13).

Another methodological issue is how the data on falls is gained. In the retrospective studies, information on falls is based on recall. The participants are asked whether and/or how many times they had fallen over a defined period, most often within past 12 months. It is questionable whether falls are remembered accurately over a prolonged period (14). Utilizing a prospective study design provides a better basis for the follow-up of falls. In community studies, participants should be asked to record their falls. Then the data is collected by postal questionnaires (15,16), fall calendars (17,18,19) or telephone interviews (20). Prospective daily recording of falls with a minimum of monthly reporting is recommended by the ProFaNE collaborators (10). Additional information about the circumstances of falls can be gained by attaching a case-specific fall questionnaire to the fall calendar. In residential care settings, prospective follow-up and systematic recording of falls by nursing staff is a recommended and feasible method (15).

Unfortunately, there is a considerable methodological heterogeneity in the studies reporting falls. A systematic review of randomized controlled fall prevention trials showed that the term fall was defined in one half (46/90) of the studies, and falls were registered prospectively only in 39 of 90 trials (21).

2.1.2 Incidence of falls in community-dwelling older people

Approximately 30% of community-dwelling people aged 65 years or more fall at least once a year (20,22,23), and 10 - 20% fall recurrently (19,22,24). Older people with health problems and impairment in basic ADLs tend to fall more often. Approximately 37% of those receiving home care reported they had fallen in the past three months (25). The proportion of fallers increases also with age, being 40 - 50%

in people aged 80 years or more (19,20). Furthermore, falls are more common in older women than men (26-28). In Northern Finland, the overall incidence rate of falls was 611 per 1000 person-years (py) in women and 368/1000 in men aged 70 years or over (23,29).

The incidence of falls may also vary between different ethnic and race groups, though rigorous data from non-Caucasian populations is limited. Nine percent of 65 years old or older community-dwelling Japanese men and 19% of women reported that they had fallen one or more times during the previous year (30). Among older people residing in Hong Kong, the proportion of fallers was 20% (31), whereas among Finns, it was 30% (23).

The location of falls seems to be related to functional capacity, gender, and age. In community-dwelling older people, about 50% of falls occurred in their homes or immediate home surroundings, and the remaining falls were sustained in public places or other people's homes (32,33). Women were more likely than men to fall inside the home (65% vs. 44%) (22). In women, the proportion of falls occurring at home on a level surface increased with age (34). In general, indoor falls were associated with frailty and limited mobility, and most of the falls occurred during mornings or afternoons in situations where older people were undertaking their usual daily activities (22,23). Additionally, the ambient temperature may have an impact on the frequency of falls, and in some studies, seasonal variation in the incidence of falls has been observed. Luukinen et al. found that the frequency of outdoor falls was higher in periods of extreme cold (29).

2.1.3 Incidence of falls in institutional care facilities

The incidence of falls in institutional settings has been widely studied. The frequency of falls is high among older people living in institutions. The rate of falling in residential care populations has been reported to be two- to threefold that in community-dwellers (23,28).

Approximately 50% of nursing home residents fall at least once a year. In an early prospective study performed in institutional care settings, the proportion of fallers

was 42%; 30% in men and 46% in women (35). Thereafter, higher percentages have been reported, ranging from 54% to 57% (36-38). Recurrent falls are also common. Forty four percent of nursing home residents fell recurrently during a 7-month observation period (39), and in two other studies, 40% to 56% of ambulatory residents fell two or more times within six months (40,41). Furthermore, 54 recurrent falls per 100 py were observed in an American nursing home population (42). Rubenstein et al. summarized the findings from 16 studies and reported that the mean annual incidence of falls in nursing homes was 1.5 falls per bed (range: 0.2 to 3.6 falls) (43).

Inhospital falls are also common. During their hospital stays, 17% of patients fell in an acute geriatric ward (44), and 14% of patients experienced one or more falls in a geriatric rehabilitation hospital (45). In older patients undergoing stroke rehabilitation, the rate of fallers was up to 39% (46-48).

2.1.4 Risk factors for falls

Causes of falls can be categorized to predisposing and precipitating factors, the former representing long-term and the latter short-term risks (1). Another approach is to define the risk factors as either intrinsic (e.g., lower extremity weakness, balance disorders, functional and cognitive impairments, visual deficits) or extrinsic (e.g., polypharmacy, use of certain medications) and environmental factors such as poor lightning, loose carpets, and lack of bathroom safety equipments (49). Furthermore, the role of environmental risks can be supplemented with exposure to risk (50). Most falls have more than one cause, and it is important to be aware of interactions and synergism between the risk factors.

2.1.4.1 Age and gender

Age has been assessed as a potential risk factor for falls in many studies, and several studies have shown that the incidence of falls increases with age (17,19,20,51-53). In a systematic review of falls risk, age was addressed in 11 studies but it proved to be an independent predictor of falls in four studies only (54). This is understandable

because falls are generally considered to be a marker of frailty and decreased mobility, both of which become more common with increasing age.

In addition to the probability of falling, age is associated with severity of falls. Injurious falls become more common with advanced age (43,55,56). Furthermore, an increasing long-term trend has been observed in the incidence of injurious falls (57). Between 1970 and 1995 in Finland, the number of fall-induced injuries increased more than could be explained merely by population aging. The increasing trend was greatest in persons aged 80 years or older. The explanation behind this phenomenon might be deterioration of bone strength and an increase in the incidence of falls. Increased survival of ill and frail older individuals may also increase the frequency of falls and fall-related injuries.

Gender may have an impact on the risk of falling. It has been shown that women fall more often than men (20,23,26,27,51,53,58). This has been explained by women's weaker muscle strength and greater visual field dependence, i.e. greater reliance on visual input in maintaining balance (59). However, some studies have not found any gender difference in the incidence of falls (17,19,22,60), or the difference has been age dependent leveling off with advanced age (20,23,53).

2.1.4.2 Gait and balance

The physiological systems that are involved in maintenance of stability decline with age. Impairments in vision, vestibular system, peripheral sensation, muscle strength, and integration of sensorimotor functions (e.g. reaction time) may predispose to falls. In addition to age-related changes, many diseases (e.g. diabetes, musculoskeletal and neurological diseases) may interfere and impair gait and balance control. The association between visual impairment and increased falls risk has been shown in several studies (61-66). Ganz et al. summarized findings of 15 studies that considered gait or balance abnormalities and the risk of falling (54). In 10 of 15 studies, older people with impaired gait or balance had an increased risk of falls. The systematic review by Rubenstein and Josephson assessed impacts of several factors on the risk of falling (28). Table 1 summarizes the findings of their review. Gait deficits were

related to falls in 10 of 12 studies and balance deficits in eight of 11 studies. Muscle weakness was also strongly associated with falls.

Table 1. The most common risk factors for falls identified in 16 studies, findings are based on univariate analyses. Adapted from Rubenstein and Josephson (28).

Risk factor	Significant / Total ^a	Mean
		RR / OR ^b (range)
Muscle weakness	10 / 11	4.4 (1.5 to 10.3)
History of falls	12 / 13	3.0 (1.7 to 7.0)
Gait deficit	10 / 12	2.9 (1.3 to 5.6)
Balance deficit	8 / 11	2.9 (1.6 to 5.4)
Use of assistive device	8 / 8	2.6 (1.2 to 4.6)
Visual deficit	6 / 12	2.5 (1.6 to 3.5)
Arthritis	3 / 7	2.4 (1.9 to 2.9)
Impaired ADL	8 / 9	2.3 (1.5 to 3.1)
Depression	3 / 6	2.2 (1.7 to 2.5)
Cognitive impairment	4 / 11	1.8 (1.0 to 2.3)
Age > 80 years	5 / 8	1.7 (1.1 to 2.5)

^a Number of studies with significant relative risk ratio or odds ratio / total number of studies addressing each risk factor

^b Relative risk ratios or odds ratios calculated for studies

2.1.4.3 Medical conditions

Several medical conditions can contribute to the risk of falling. Cognitive impairment and acute confusional states may increase the risk by influencing an older person's ability to appropriately deal with environmental hazards, and by causing behavioral symptoms such as wandering and altering gait patterns (67,68). Several investigators have reported that dementia is a strong and consistent risk factor for falls, especially for injurious falls in older people (69). Falls related to cognitive impairment are of particular concern in long-term care facilities, because the prevalence of dementia is

high in these populations. For example in Finland, over 90% of older people living in long-term care institutions are demented (70).

In addition to dementia, some other neurological conditions are also associated with falls in older people. There is strong evidence of increased risk of falls among persons with a diagnosis of stroke, and a probable risk in those with Parkinson's disease or peripheral neuropathy (69). These conditions are capable to decrease muscle strength and impair gait and balance control.

Furthermore, depression, which is common in older people (71,72) is associated with falls (28,73). Mechanisms through which it increases the risk of falls have not been fully evaluated. Decline in physical activity and muscle strength is a possible explanation, but the use of antidepressant medications may also have a role.

Musculoskeletal diseases have been related to falls. Inflammatory or degenerative joint disease was found to be a risk factor for falls in three of seven studies in the systematic review of Rubenstein and Josephson (Table1) (28). Osteoarthritis is the commonest cause of musculoskeletal disability in older people (74). It leads to structural deformity, decreased range of motion and pain of the affected joint. People with hip and knee osteoarthritis tend to walk and exercise less and therefore often suffer wasting of lower extremity muscle groups. Joint deformity also impairs proprioception. Therefore quite logically, reduced knee extension strength and increased postural sway were identified as significant predictors of falls in older people with lower limb osteoarthritis (75).

A strong link between orthostatic hypotension and falls has not been documented (54). This can be of an intermittent nature of orthostatic hypotension, i.e. it is not necessarily present all the time and the diagnosis is easily missed if orthostatic blood pressure is measured only once. The association may also be stronger to underlying cause of orthostatic hypotension than to the reaction itself. For example Parkinson's disease and diabetes can cause orthostatic hypotension through autonomic neuropathy, but both of these diseases can also have other manifestations that are fall-risk-increasing. Similarly, antipsychotics may cause orthostatic hypotension but also extrapyramidal side effects that increase the risk of falling. Some falls have a cardiovascular etiology. Especially in case of syncopal or unexplained falls, the

underlying cause can be cardiovascular, such as carotid sinus hypersensitivity, atrioventricular block, or sick sinus syndrome (49, 76, 77).

Lower urinary tract symptoms and incontinence may contribute to the risk of falling in older people (24,78-81). Falls related to incontinence are generally thought to result from loss of balance when rushing to the toilet. However, there is debate about whether incontinence is a primary cause of falls or is it simply a marker of generalized physical frailty (82).

2.1.4.4 Medications

The aging process is associated with changes in pharmacokinetics and pharmacodynamics (83) which may contribute to the risk of falling. Age-related changes in the body composition have effects on the drug distribution. The volume of distribution of lipid-soluble drugs (e.g. many the psychotropic agents) increases, and the elimination half-life and duration of action of these drugs tend to be prolonged. Decrease in the total body water content leads to higher concentrations from given amounts of water-soluble drugs, such as digoxin and certain beta-blockers. Bioavailability of drugs tends to increase with age due to decreasing first pass metabolism, whereas hepatic biotransformation tends to decline. Renal function and the excretion of drugs decline with age, especially those eliminated predominantly by the kidneys, e.g. many angiotensin converting (ACE) inhibitors, metformin, digoxin. Furthermore, changes in tissue sensitivity and receptor affinity may affect drug responses, for example adverse reactions related to centrally acting medications (e.g. sedation, dizziness, extrapyramidal symptoms) become more prevalent with age.

With regard to falls, psychotropic drugs (i.e. benzodiazepines, antidepressants and antipsychotics) are the most often researched medication group. Leipzig et al. conducted a systematic review and meta-analysis on psychotropic drugs and falls (84). Their literature search covered studies published through 1966 to 3/1996, and 43 original articles were included in the review. The meta-analysis on the use of any psychotropic drug covered 20 studies and the pooled odds ratio (OR) for one or more falls was 1.73 [95% confidence intervals (CI): 1.52 to 1.97]. A total of 13 studies

provided data on benzodiazepines. The use of any benzodiazepine was associated with an increased risk of falls, the pooled OR was 1.48 (95% CI: 1.23 to 1.77). Short-acting benzodiazepines were no safer than the long-acting benzodiazepines. Antidepressants were addressed in 27 studies. The use of any antidepressant increased the risk of falls, the pooled OR was 1.66 (95% CI: 1.41 to 1.95). The OR for tricyclic antidepressants (TCAs) was 1.51 (95% CI: 1.14 to 2.00). Only one study paid attention to selective serotonin reuptake inhibitors (SSRI), and the percentage of fallers was larger among the SSRI than TCA users (85). For antipsychotics the pooled OR was 1.5 (95% CI: 1.25 to 1.79), this analysis based on 22 studies.

Table 2. Pooled odds ratios for one or more falls associated with the use of cardiac and analgesic drugs. Adapted from Leipzig et al (86).

Treatment	Number of studies	OR (95% CI)
Cardiac drugs:		
Any diuretic	26	1.08 (1.02 to 1.16)
Thiazides	12	1.06 (0.97 to 1.16)
Loop diuretics	11	0.90 (0.73 to 1.12)
Digoxin	17	1.22 (1.05 to 1.42)
Nitrates	14	1.13 (0.95 to 1.36)
Beta-blockers	18	0.93 (0.77 to 1.11)
Calcium channel blockers	13	0.94 (0.77 to 1.14)
ACE inhibitors	10	1.20 (0.92 to 1.58)
Centrally acting antihypertensives	11	1.16 (0.87 to 1.55)
Type IA antiarrhythmics	10	1.59 (1.02 to 2.48)
Analgesic drugs:		
Narcotic analgesics	13	0.97 (0.78 to 1.20)
Nonnarcotic analgesics	9	1.09 (0.88 to 1.34)
Nonsteroidal anti-inflammatories	13	1.16 (0.97 to 1.38)
Aspirin	9	1.21 (0.80 to 1.57)

Associations between the use of cardiac or analgesic drugs and falls were examined in another systematic review and meta-analysis by Leipzig et al. (86). The results on cardiac drugs are presented in Table 2. Digoxin, type IA antiarrhythmics, and diuretics were associated weakly with falls in older people, whereas no association was found between the use of analgesics and falls. Fourteen studies provided data on multiple medication use and falling. Use of more than three or four drugs was associated with an increased risk of single falls in 6/14 studies and with recurrent falls in 4/5 studies.

Studies on medication use and falls published in 1996 – 2004 are evaluated in our systematic review (Study 1). Table 3 shows summary of studies on psychotropic drug use and falls published in 2005 - 2008. In addition to the studies referred above, falls have been associated with the use anxiolytic, anti-Parkinson, sedative/hypnotic and diabetes medications in hospital settings (87,88), but younger patients were also included in these studies. Few studies on medication classes other than psychotropics were found. Nitrates and anti-diabetic drugs were associated with falls in community-dwelling older people (31,89) and ACE inhibitors in nursing home residents without dementia (90). Polypharmacy was related to an increased risk of falls in a Dutch population (91), in women with a recent fracture (92), and in nursing home residents with dementia (90).

Table 3. Summary of studies published in 2005-2008 and reporting on the use of psychotropic drugs and risk of falls in older people

Reference	Setting	Number and age of subjects	Association between psychotropic drugs and falls	
			Risk increase	No association
Hien et al. 2005 (93)	RC, NH	N= 2005 Age \geq 65	antidepressants, olanzapine	risperidone, typical antipsychotics, sedatives/anxiolytics
Landi et al. 2005 (25)	CD	N= 2854 Mean age = 77	antipsychotics, benzodiazepines	antidepressants, benzodiazepine like hypnotics
Avidan et al. 2005 (94)	NH	N= 34,163 Age \geq 65		hypnotics
Souchet et al. 2005 (89)	CD	N = 67464 Mean age = 76	benzodiazepines, TCA and SSRI antidepressants	
Lee et al. 2005 (31)	CD	N= 4000 Age \geq 65		psychotropics
Ziere et al. 2006 (91)	PB	N= 6928 Mean age = 71	benzodiazepines	
Cooper et al. 2007 (95)	NH	N= 177 Mean age = 84	number of psychotropic drugs	
Pariente et al. 2008 (96)	CD	N= 3777 Age \geq 65	benzodiazepines	
Kerse et al. 2008 (97)	CD	N = 20636 Age \geq 60	any antidepressants, SSRIs	antipsychotics, anxiolytics, hypnotics

CD = community-dwelling, NH = nursing home, PB = population-based, RC = residential care

2.1.4.5 Environmental factors

Most home environments contain factors that may contribute to falling (98), e.g. slippery floor surfaces, loose carpets, upended carpet edges, obstructed walkways, too high or low set shelves or cupboards, stairs, and unsafe bathroom surroundings. Environmental factors associated with outdoor falls are for example sloping, slippery, obstructed, or uneven pathways, ramps and stairways, certain weather conditions, crowds of people, and lack of places to rest. However, it is less clear to what extent these hazards are causally related to falls. For example two case-control studies reported that there were differences in the prevalence of home environment risk factors between fallers and non-fallers (99,100), but in three studies the prevalence of hazards was similar in both groups (101-103). The literature suggests that in addition to the existence of hazards, an interaction to an older person's physical or cognitive abilities, i.e. coexisting impairment, is needed.

Level of activity seems to play a role, too. In two prospective cohort studies on environmental hazards and falls, the subjects were classified as either vigorous or frail (104,105). Though falls were more frequent among frail persons, environmental hazards, outdoor hazards in particular, were more likely to contribute falls in vigorous older people than in the frail ones. It probably is more likely that vigorous people go outside, even in worse weather conditions, have outdoor activities, and do more hazardous housekeeping tasks than frail persons.

Furthermore, external causes such as poor footwear (106) and inappropriate spectacles (107) are risk factors for falls. The role of assistive devices is ambiguous. Use of a walking aid has been associated with falls (28), but this does not mean that the device causes falls. Instead, it may simply be a marker of gait and balance problems.

2.1.4.6 History of falls and fear of falling

History of falls is a strong predictor of future falls. In the systematic review of Ganz et al., each of the 11 studies reporting on history of falls found a statistically significant relationship to future falls (54). This is in concordance with the results of systematic review and meta-analysis by Rubenstein and Josephson, in which a previous fall predicts future falls in 12 of 13 studies (Table 1) (28).

Fear of falling was also associated with future falls (24,108), mostly because those who are fearful of falling tend to restrict or eliminate their social and physical activities (24,109). This risk factor seems to be interrelated with the history of falls: falls cause fear of falling and visa versa.

2.1.5 Consequences of falls

Depending on the population studied and definition of outcome, from 20% up to 60% of falls in older people result in some sort of injury, and approximately 10% of falls cause major injuries (28,43,56,110-112). Falls are the leading cause of injury-related admissions to hospital, and they account for 10-20% of visits to emergency department and 4-6% of hospitalizations in older people (113-117).

Approximately 5% of falls in older people lead to fracture (56,65,118). Though fracture of the hip occurs only in around 1% of all fall incidents (114), almost all hip fractures (97%) in older people are fall-induced (119). In terms of morbidity, disability, mortality, and costs, a fracture of the hip is one of the most serious consequences of falls (2).

Falling is associated with subsequent admission to a nursing home (120-122). Tinetti et al. assessed all nursing home placements in a large prospective cohort of older people (123). They found an independent relation between falls and long-term care placements: one noninjurious fall represented threefold, recurrent noninjurious falls fivefold, and injurious falls a tenfold risk increase. They concluded that along with other risk factors, falls, particularly frequent and injurious ones contribute strongly to the decision by older persons and their families to pursue placement in a nursing facility.

Injuries are the fifth leading cause of death in older adults, and most of these fatal injuries are related to falls (1,57,124). Kannus et al. examined trends in fall-induced deaths among ≥ 50 -year-old Finns (125). In 2002, the total number of fall-induced deaths was 1039, and the age-adjusted rates of fall-induced deaths were 55.4/100 000 and 43.1/100 000 for men and women, respectively. The incidence rate in men was increasing, whereas in women, it stayed relatively stable between 1975 and 2002.

In conclusion, falls in older people occur in every day life situations, and in most cases, they are associated with more than one predisposing and precipitating factors. Falls are the leading cause of unintentional injuries and constitute a significant health

care cost through inflicting disabling conditions, hospital stays, and death. In terms of morbidity and mortality, hip fracture is among the most serious consequences of falls.

2.2 Epidemiology of hip fractures

Hip fracture is a common, devastating, and often fatal, trauma in older people (2). Lifetime risk of hip fracture is estimated to vary between 9% and 23% in women and 4% and 11% in men, depending on the population studied (3,126-128). Hip fractures are rare before age of 50, but thereafter, the incidence increases exponentially with advancing age (129,130). Therefore in many countries, the absolute number of hip fractures is expected to rise as a consequent of population aging (131). Besides age, female gender is also associated with higher rates of hip fracture (132). Epidemiology of hip fractures has been widely studied during the past 20 to 30 years. The following literature review deals with incidence, risk factors, and consequences of hip fractures.

2.2.1 Incidence of hip fractures

The worldwide number of hip fractures was estimated to be 1.26 million in 1990; 338 000 in men and 917 000 in women (133). In 2000, the estimated number was 1.62 million (134), and assuming no change in the age- and sex-specific incidences, the projections for the years 2025 and 2050 were 2.6 and 4.5 million respectively (133). The highest hip fracture incidences have been reported in Northern Europe, Scandinavia in particular, North America and Australia (2,129,131).

2.2.1.1 Incidence of hip fractures in Finland

The Finnish national hospital discharge register has proved to be a useful data source for studies on epidemiology of hip fractures (4,5,135,136-138). Based on the data of this register, the total number and age-adjusted incidence of hip fractures increased steadily in both genders between 1970 and 1997 (136,137). During the next five years, the age-adjusted hospital admissions for fractures of hip showed leveling off and stabilizing (4,138). Furthermore, a declining trend was observed by the end of the year 2004, among women in particular (5).

Among ≥ 50 -year-old Finns, the yearly mean number of first hip fractures was reported to be 5618 in 2000-02 (138). In 2002, the age-adjusted incidence rates were 4.08 and 1.90 per 1000 py for women and men, respectively. In another Finnish study, the estimated number of hip fractures was 7083 in 2004, and the adjusted incidences were 4.12 per 1000 women and 2.23 per 1000 men (5). Discrepancies between these results are mainly due to methodological issues; how to select and evaluate the data of hospital discharge register. In addition, the populations at risk differed. The standard populations of the studies based on different periods of time, 1998-2002 (138) vs. 1970-2004 (5).

Some regional differences have been observed in the incidence of hip fractures in Finland. Between 1998 and 2002, the incidence was highest in Helsinki and Central Finland, and lowest in South Karelia, Southern Ostrobothnia and Kainuu regions (138). Furthermore, the incidence trends differed between the regions. The age- and sex-adjusted annual incidence of hip fractures increased in North and South Savo and decreased in Helsinki and Kanta Häme during the five-year period. In other health care districts, the incidences were stable or fluctuating. In an earlier cross sectional study, no statistically significant change was observed in the age-adjusted incidence of hip fractures in Central Finland between the years 1982-83 and 1992-93 (139).

Furthermore, hip fracture incidence rates between urban and rural populations have been compared. The study of Lüthje et al. covered populations of Central Finland and Kymenlaakso health care districts in 1989 (140). The incidences between the urban and rural populations did not differ statistically significantly in either of the districts.

A slight seasonal variation in the incidence of hip fractures has been observed (138,141-143), though the winter peak for hip fractures was relatively small compared to that of the other peripheral fractures (143). This may be explained by the fact that regardless of the season, the vast majority of hip fractures occur indoors (22,142,144).

Hip fracture incidence was different between institution- and home-dwelling older Finns. The age- and -gender adjusted incidence was markedly higher in institution-dwellers than home-dwellers (138,142). Furthermore, the gender-specific rates differed, too. In institutional populations, the age-adjusted incidence rates were equal for both genders, whereas in community-dwellers, the rate was higher for women than men (138).

2.2.1.2 Variation in hip fracture incidence in different countries

Up until the 1980's to 1990's, both the absolute number and adjusted incidence of hip fractures were on the increase in several countries (2,131,145). Thereafter, changes and different trends in incidence rates have been described. In Norway, hip fracture incidence has stabilized (130,146,147). A similar phenomenon was observed in Ontario, Canada, during the 1990's (148). The age-specific rates of hospital admissions for femoral fractures in UK and for hip fractures in Australia remained practically unchanged during the 1990's (149,150). In northern Spain, the age-adjusted incidence rates were similar in 1988 and 2002 (151).

A decline in hip fracture incidence was observed in the early 1990's in Malmö, Sweden (152). A similar trend break was found for women but not for men in Östergötland (153). The age-adjusted incidence of hip fractures also decreased in Swiss women but not in men during the 1990's (154). The latter reduction was mainly due to incidence changes in institution-dwelling women (155). In the USA, the age-adjusted rates of hip fractures showed a declining trend, at least for white women (156-158). In Denmark, a secular increase in the age-adjusted rates of first hip fractures was observed until the late 1990's (159), and a decreasing trend was described thereafter (160).

The causes of the observed leveling off and decline in the incidence of hip fracture are unknown. A combination of period and cohort effects is a possible explanation. In earlier birth cohorts, the early-life risk factors for fracture, such as nutrition, may have had stronger impact on the late-life fracture risk than in others (5). The trend break might also be related to healthier aging and improved functionality among the elderly. These changes could represent the compression of morbidity, i.e. delayed onset of disability and reduced proportion of one's life spent in ill health. Canadian investigators attributed the decline in hip fracture incidence to implementation of an osteoporosis screening and treatment program (148). In the Province of Ontario, the increase in BMD testing was over 10-fold between 1992 and 2001 and the use of antiresorptive therapy increased nearly 20-fold between 1996 and 2003.

Upward trends have also been reported in the literature. In Germany between 1995 and 2004, hip fracture incidence increased in older people (161). The increasing trend was less pronounced for females than males and for western than eastern parts of the

country. Though the incidence difference diminished between east and west during the 10-year period, the incidence still remained higher in Western Germany. In Japan, the age-adjusted incidence of hip fractures increased in both genders between 1986 and 2001 (162). In South Korea, the incidence increased in women aged ≥ 50 years, but interestingly, decreased in men during a recent 4-year period (163). In the context of increasing hip fracture incidence, the authors have pointed to increased life expectancy and longer survival of the frailest older people due to better medical treatment, racial factors, level of physical activity and Westernized lifestyle (161,162,163).

The occurrence of hip fractures is strongly associated with age, and therefore a comparison of incidence rates between different populations necessitates the availability of demographic data and age-specific fracture rates. Bacon et al. studied hip fracture rates in nine countries (Canada, Chile, Finland, Hong Kong, Scotland, Sweden, Switzerland, the United States and Venezuela) using national hospital discharge register data of the years 1988-89 (132). In all nine countries, the hip fracture rates increased by age and were higher for women than men. The highest rates were observed in Finland, Scotland and Sweden and the lowest in Venezuela and Chile. The rates for Venezuela and Chile were three to 11 times lower than those for the seven other countries. When further adjustments for differences in case definition were made, the risk of hip fracture was largely similar in the four European and two North American countries.

Furthermore, differences in mortality should be taken into account when hip fracture probabilities are compared. Kanis et al. examined variations in hip fracture probabilities in 27 countries using incidence data of studies published in the 1990's (129). The hip fracture probabilities were computed from the hazard functions of hip fracture and death, and they were standardized to the probabilities of Sweden (set 1.00). The results are presented in Table 4. The risk of hip fracture varied considerably. Standardized to the Swedish figures, the 10-year probability of hip fracture for Norway was 15-times higher than that for Chile.

Table 4. The ten-year probability of hip fracture averaged for age and gender and adjusted to the probabilities of Sweden. Adapted from Kanis et al. (129).

Very high risk		Medium risk	
Norway	1.24	China, Hong Kong	0.49
Iceland	1.02	France	0.41
Sweden	1.0	Japan	0.39
Denmark	0.85	Spain	0.39
USA	0.78	Argentina	0.36
High risk		China	0.29
China, Taiwan	0.72	Low risk	
Germany	0.72	Turkey	0.18
Switzerland	0.71	South Korea	0.18
Finland	0.68	Venezuela	0.17
Greece	0.66	Chile	0.08
Canada	0.65		
Netherlands	0.64		
Hungary	0.63		
Singapore	0.62		
Italy	0.61		
United Kingdom	0.60		
Kuwait	0.59		
Australia	0.57		
Portugal	0.57		

2.2.1.3 Incidence of second hip fractures

The vast majority of older people admitted to a trauma ward, and nearly all of those admitted with hip fracture, will have sustained a fragility fracture (164), i.e. a fracture resulting from only low to moderate trauma, usually a fall from standing height or less. A low trauma fracture is associated with increased risk for subsequent fractures (165,166), including sequential hip fractures. Several retrospective studies have reported on the recurrence rate of hip fractures. Among patients with an acute hip fracture, the prevalence of prior hip fractures ranged between 5.5% and 17% (167-

174). The majority of these studies focused on non-contemporary bilateral hip fractures, i.e. subsequent fractures affecting the opposite hip (167-173). Actually, these data reflect the prevalence rather than the incidence of second hip fractures.

Prospective population-based studies on epidemiology of second hip fractures are still relatively few (175-179). In terms of assessing incidence, the methodology of prospective studies is favorable: follow-up times for second hip fractures are defined and losses due to death are taken into account. Melton et al. reviewed hip fractures in Rochester, Minnesota, between 1943 and 1977 (175). In their study, the cumulative incidence of second hip fractures was 1% at one year after the initial fracture. It rose to 8% at 5 years, to 16% at 10 years, and finally to 29% at 20 years. A recent study of Melton et al. covered the years 1980-2006 (179). They reported that the risk of second hip fracture was 1.7 times greater than that of the first event. Approximately 23% of the second hip fractures occurred during the first year and 70% within five years following the initial fracture. Furthermore, a downward trend was observed in the recurrence rate after 1997. A Danish study covering the years 1970-1985 reported that the mean time between the sequential hip fractures was 3.4 years, and 20% of the second fractures occurred during the first year and 55% within three years (176). Compared with the gender-specific risk of first hip fracture, the risk of second hip fracture was nine times greater for men and 6-fold for women. A later Danish study reviewed hip fractures in 1994-2004 and found a short time-frame between the first and second hip fractures (178). The recurrence risk was highest within the first three months. One half of men's second hip fractures occurred during the first year, and for women the median time was 19 months. After the first year, the risk of second hip fractures declined to the level of first hip fractures. A recent Japanese study reported that the incidence increased during the first eight months, it was 3.8% at one year and decreased linearly during the next two years (177).

Furthermore, three cohort studies reporting on the incidence of second hip fractures were found (180-182). In the Longitudinal Study of Aging, the rate of second hip fractures was one per 33.8 person-years (180). In the Study of Osteoporotic Fractures, an average annual risk of second hip fracture was 2.3%, and the incidence rate was four times greater than that of the first hip fractures (181). In the Framingham Study, the one-year cumulative incidence was 2.5%, and the three- and five-year figures were 5.7% and 8.2%, respectively (182). Risk factors of second hip fractures are presented in the chapter 2.2.2.2.

2.2.2 Risk factors for hip fracture

As with falls, fracture risk in old age is multifactorial. It reflects general frailty, risks of falling and bone fragility. In a prospective study, 16 factors independently associated with an increased risk of hip fracture were identified in a cohort of 9 516 community-dwelling older women (183). These factors were: advanced age, history of maternal hip fracture, weight less than at age of 25 years, tall body height at age 25, fair or poor self-rated health, previous hyperthyroidism, current use of long-acting benzodiazepines or anticonvulsants, high caffeine intake, being on one's feet \leq 4 hours per day, inability to raise from a chair, impaired depth perception, decreased contrast sensitivity, tachycardia at rest, any fracture after age of 50 years, and low bone mineral density (BMD). The effect of most individual risk factors was moderate, but women with multiple risk factors and low bone density were at especially high risk. Later on, more independent risk factors have been identified, including female gender, immobility, sedentary lifestyle, current smoking, low body mass index (BMI), history of falls, cognitive impairment, low socioeconomic status, and diabetes (184-191). According to the Scottish guidelines for the prevention and management of hip fractures (192), the four most prevalent and important risk factors for hip fracture in older women were:

1. Previous low trauma fracture after the age of 50
2. Maternal history of hip fracture
3. Current smoking
4. BMI < 18.5

In general, risk factors for falls (Table 1) and osteoporosis (193,194) are closely related to hip fracture risk. The four easily identifiable shared risk factors for osteoporosis and hip fractures are listed above. Risk factors are of most importance if they also are potentially reversible. Shared risk factors for falls and hip fractures fulfilling these two conditions are e.g. poor visual acuity, use of certain medications, neurological diseases, abnormality of gait or balance, muscle weakness, arthritis, foot problems, and environmental hazards (192,195-197). Table 5 shows the strong risk factors for hip fracture presented in the Finnish current care guidelines for the treatment of patients with hip fracture.

Table 5. Hip fracture risk factors with strong (Level A) research based evidence (198).

Risk Factor
<ul style="list-style-type: none"> • Previous fall or fracture • Advanced age • Impaired mobility and muscle weakness • Sedentary lifestyle • Use of assistive device • Low BMI • Stroke, Parkinson's disease, Dementia • Impaired vision • Use of <ul style="list-style-type: none"> ○ psychotropic drugs ○ long-acting benzodiazepines ○ antidepressants (SSRI, TCA) ○ antipsychotics

The type and severity of falling are crucial in determining whether or not a fracture occurs (199-201). These factors include for example height, energy, direction, and mechanism of a fall, anatomical site of the impact, and impact force attenuation by the body and landing surface. Sideway falls onto the hip were associated to 20 times higher hip fracture risk than falls in general (200), and these kind of falls were capable to cause a hip fracture even in young healthy men (202).

2.2.2.1 Medications and hip fracture risk

Psychotropic drugs are associated with an increased risk of hip fracture. Benzodiazepines in particular have received a great deal of research attention probably because they are recognized as risk factors for falls and are widely used by older people. For example in Kuopio, 30% of home-dwelling persons aged ≥ 75 years

used one or more benzodiazepine preparations or benzodiazepine like hypnotics in 1998 (203). Based on a review of epidemiological studies, Cumming and Couteur concluded that use of benzodiazepines increased older people's hip fracture risk by 50%, and about 10% of hip fractures among community-dwellers were related to benzodiazepine use (204). The latter percentage (attributable risk) was estimated by assuming that the prevalence of benzodiazepine use was 20%. The hip fracture risk was greatest for those who had recently started taking benzodiazepines and for those receiving higher doses. In addition, the benzodiazepine-like hypnotic zolpidem increased the fracture risk (205). The effect of elimination half-life on hip fracture risk is controversial. Ray et al. found short-acting benzodiazepines less harmful (206), whereas Wagner et al. reported opposite findings (207). In a recent study, daily dose appeared to be more important factor than the half-life (208).

The evidence related to antidepressant use and hip fracture risk is less clear than that on the risk of falls. In an earlier study, TCAs were associated with an increased risk for hip fracture (209,210). SSRIs were originally thought to be safer. However, rates of hip fractures were equally high among older women taking SSRIs and those using TCAs (211). A recent finding is that SSRI use may cause bone loss. Functional serotonin transporters have been described in osteoblasts, osteoclasts, and osteocytes (212,213), and serotonin may play a role in bone metabolism. The use of SSRIs has been associated with a decline in BMD both in men and women (214,215).

There are a few reports on antipsychotic use and hip fractures, though antipsychotics may cause extrapyramidal symptoms and impair gait and balance and thereby contribute to falls. Ray et al. reported that conventional antipsychotics were associated with a 2-fold increased risk for hip fracture (209), and Liperoti et al. found that both typical and atypical antipsychotics were weakly associated with femur fractures in nursing home residents (216). Antipsychotic use can also disturb bone metabolism by inducing hyperprolactinemia and secondary hypogonadism. In patients with a history of schizophrenia, use of prolactin-raising antipsychotics was independently associated with an increased hip fracture risk (217).

Alpha-blockers, used for treating functional symptoms of prostatic hyperplasia and lowering the risk of urinary retention, may cause hypotension and contribute to falling and consequent fractures. One study reported that current use of alpha-blockers was associated with an increased risk of femur fractures (218), whereas another study found no association (219).

Long-term use of corticosteroids reduces bone mass, weakens the skeletal architecture and reduces the biomechanical competence of the skeleton (220). An increased hip fracture risk related to corticosteroid use has been found in several studies (220,221). Long-term use of antiepileptic drugs was also associated with increased rates of bone loss and risk for fractures, especially in women (222,223). Furthermore, long-term proton pump inhibitor therapy, particular at high doses, can interfere calcium absorption and may increase hip fracture risk (224,225).

2.2.2.2 Risk factors for second hip fractures

Compared to data on risk factors for first hip fractures, less is known about factors affecting risk for second hip fractures. Egan et al. conducted a systematic review on factors associated with second hip fractures (226). Older age and cognitive impairment (227) and lower bone density (181,227) tended to increase the risk of second hip fracture. Additionally, dizziness and poor or fair self-perceived health (180), impaired depth perception (181), impaired mobility and previous falls (227) appeared to increase the risk. Unfortunately, only one (181) of the three studies quoted above was rated as good in quality in the review article of Egan et al. (226).

Furthermore, three more recent studies have investigated risks of second hip fractures. Patients with dementia or Parkinson's disease showed significantly increased risk for second hip fracture (177). Greater age independently predicted the recurrence of hip fracture (179,182), and finally, better functional status was also associated with an increased recurrence rate (182).

2.2.3 Consequences of hip fractures

2.2.3.1 Morbidity and hospitalizations

Almost all patients with hip fracture are admitted to hospital and the vast majority are treated surgically (228,229). In Finland, an average total length of hospital stay after hip fracture was 50 days in 1994-95 according to the national discharge register data (230). In Central Finland in the late 1990's, the median length of hospitalization after hip fracture was 34 days for home-dwelling older people receiving multidisciplinary geriatric rehabilitation and 42 days for those receiving conventional care (231). In

Canada and the Netherlands the average period of hospitalization for hip fractures were 22 and 34 days respectively (232,233). International comparisons regarding the lengths of hospital stays, however, may be of limited value because health care systems and care pathways vary from country to country. For example shorter hospitalization periods may be explained by abundant nursing home use.

The lengths of stays at the orthopedic wards have shortened substantially during the past couple of decades in Finland. In Central Finland, the median length of stay after hip fracture was 18 days in 1982-83 and five days in 1992-93 (231). However, the proportion of patients discharged directly to their homes decreased and transfers to primary care wards increased concurrently. In South-East Finland the average perioperative stay was 21 days in 1989 and nine days in 1999 (234,235).

Rehospitalizations are common among hip fracture patients. Within 30 days following the initial discharge, 18% of hip fracture patients were readmitted to hospital (236). Of these 30-day readmissions, 21% were due to diseases of the respiratory system, 16% related to musculoskeletal and connective tissue diseases and 15% to diseases of the circulatory system. Several of the comorbidities that were present at the time of initial hospitalization predicted readmissions within 30 days. Cardiac arrhythmias, chronic pulmonary diseases, and congestive heart failure were both prevalent and significantly increased the risk for rehospitalizations. The 6-month readmission rate was 32%, with 8% of the patients readmitted more than once (237). The majority of these postfracture rehospitalizations (89%) were for nonsurgical problems, of which infectious (21%) and cardiac (12%) diseases were the most common.

Cognitive impairment, depressive symptoms and delirium were also common in hip fracture patients, and they frequently occurred in combination (238). All three were independently associated with prolonged hospital stays (239), and they increased risk for poor outcome, such as institutionalization, death, or permanent decline in ambulation or ADL functions (238).

The overall impact of hip fracture on the hospital care utilization was measured in the Longitudinal Study of Aging (240). The follow-up of the 70+ cohort lasted approximately for 2.3 years. Hip fracture tripled the likelihood of subsequent hospitalizations, and the number of hospital episodes increased by 9% and that of hospital days by 21%.

2.2.3.2 Mortality

First-year mortality after hip fracture has been reported to range from 14% to 36% depending on the population studied (241). In Finnish population-based studies, the overall one-year mortality was 25% in Oulu region between 1989-97 (242), 30% in Central Finland in 1982-83 and 1992-93 (243), and 32% in the catchment area of the Kuusankoski Regional Hospital in 1999 (244). The age-specific and age-adjusted mortality rates remained practically unchanged during the 1980's and 1990's (149,243,245).

Deaths after hip fracture were related to advanced age, male sex, poor prefracture health status and postfracture events, such as infections and cardiac complications (246-253). Causally related deaths, i.e. deaths due to hip fracture, were estimated to comprise 24 to 70% of deaths in hip fracture patients (254-256), and this fraction increased with advanced age (254). The vast majority of deaths causally related to the fracture event occurred in the first postfracture month (257). In death certificates, however, the hip fracture was relatively seldom assigned as a contributing cause of death and hardly ever as the first underlying cause of death (258).

Excess mortality related to hip fractures has been described in several studies (247,251,252,254,258-264). The majority of excess deaths occurred within the first three to six months following the fracture. In the first postfracture year, hip fracture patients' risk of death was at least twice or three times higher than that of the same-aged control population (260,261). In women, an increased risk of death persisted for several years, independently of prefracture health status (259,261,262). In a 12-year population-based follow-up study, Piirtola et al. found that a hip fracture was a powerful independent predictor of long-term excess mortality in both genders, and the risk in men was more than 2-fold that in women (264).

2.2.3.3 Disability, institutionalization, and quality of life

Hip fractures are associated with disability, increased institutionalization rate, and decreased quality of life. Of those who survived the first postfracture year, half did not regain prefracture functional status (265). In a US study, 13% of previously independent persons needed total assistance to ambulate at six months after hip fracture (266). Nurmi et al. reported that one year after fracturing a hip, the

proportion of previously independent ambulators had decreased from 59% to 19% , and 11% of all hip fracture patients had become bedridden (244). In addition, long-term difficulties in coping with essential ADLs were observed. One year after hip fracture, 60% of patients had still difficulty with at least one basic ADL, and 80% were restricted in instrumental activities, such as driving and grocery shopping (267). According to Finnish administrative registers, 29% of previously home-dwelling persons needed long-term institutional care year after hip fracture (268). Similar institutionalization rates have been reported in other studies (269-272). Furthermore, a substantial decrease in quality of life has been observed (228,273). Poor postfracture quality of life was associated with decline in functional status and persistent hip pain (274).

2.2.3.4 Costs

The average care costs in the first postfracture year were €14,410 per hip fracture patient according to the 2003 price level in Finland (235). Less than one-fourth of these costs were caused by acute orthopedic care. If a previously home-dwelling patient was admitted to long-term institutional care, the average first-year costs rose to €35,700. In a Belgian study, the first-year costs of hip fracture patients were three times greater than those resulting from treatment of matched controls without hip fracture (275). Two-thirds of these excess costs were attributable to nursing home and rehabilitation center stays, and one-third comprised of acute hospitalizations and home physiotherapy services. In Italy, the direct costs of hospitalizations for hip fractures were greater than those for acute myocardial infarcts (276).

Of the lifetime attributable costs of hip fracture, 33% occurred in the first-half of postfracture year, and 56% after the first year (277). Even the patients returning to home after hip fracture have substantial disability resulting from hip fracture. Patients with new permanent ADL deficits had shorter life expectancy (33% reduction), spent longer time in nursing home (75% increase) and had multifold care costs compared with those fully recovered after hip fracture.

2.3 Prevention strategies of falls and hip fractures

2.3.1 Prevention of falls

The main challenges of fall prevention are to identify persons at risk of falling, find interventions effective in reducing falls, make these interventions feasible and attractive for older people, and to do this all cost-effectively. With respect to identification, the clinical practice guideline for the prevention of falls suggests that all older persons who are under the care of a health care professional should be asked about falls at least once a year (49). The guideline also recommends that all who report a single fall should be tested with “Get Up and Go Test” (278,279), which involves looking for unsteadiness as the patient gets up from a chair without using his or her arms, walks a few meters, and returns. Those demonstrating difficulty or unsteadiness performing this test require further assessment. Above all, high-risk groups such as older people who present for medical attention because of a fall, report recurrent falls, or have gait and/or balance problems should have a fall evaluation performed.

In addition to “Get Up and Go Test”, other screening tools for identifying people at risk of falling have also been developed (280-282). However, their predictive value has been questioned because they may not be optimal for identifying high-risk individuals for fall prevention, at least in inpatient settings (282,283). Energies may be more productively directed towards identifying common modifiable risk factors in all patients and ensuring that people who fall during a hospital stay or are hospitalized due to a fall-related injury receive a proper post-fall assessment.

In general, studies on the prevention of falls have two different approaches: a single intervention strategy (such as exercise or vitamin D) or multiple intervention strategy, including individually tailored programs (49,113). In a recent Cochrane review, multidisciplinary and multifactorial risk factor screening and intervention programs were found to be beneficial both in unselected community-dwellers (4 trials, 1651 participants, pooled risk 0.73, 95% CI 0.63 to 0.85) and in selected high-risk populations (5 trials, 1176 participants, pooled risk 0.86, 95% CI 0.76 to 0.98) (197). The meta-analysis of Chang et al. showed that a multifactorial strategy was the most effective method to prevent falls in older people (284). Similar effectiveness was found in residential care settings (197) and in psychogeriatric nursing home patients

(285). On the other hand, less promising conclusions have been drawn as well. Based on their systematic review and meta-analysis, Gates et al. stated that the evidence of multifactorial fall prevention programs was limited (286).

Exercise programs combined with balance training have shown to be effective in preventing falls. Based on the Cochrane review, muscle strengthening and balance training reduced falls by 20% (3 trials, 566 participants, pooled risk 0.80, 95% CI 0.66 to 0.98) (197). Similar figures were reported in a more recent meta-analysis, and programs that included a combination of a higher total dose of exercise and challenging balance training were found to be most beneficial (287). However, a recent review showed only a vague effect of Tai Chi exercise on the risk of falls (288).

Medication review has been included in the protocol of many multifactorial fall prevention studies (197). However, studies that specifically assess the effects of medication optimization are few. In one study, the risk of falling decreased significantly after withdrawal of psychotropic drugs, the hazard ratio was 0.34 (95% CI: 0.16 to 0.74) (289). Despite the fact that the intervention was successful, permanent withdrawal was difficult to achieve; psychotropics “tended to come back”. In a more recent study, withdrawal of drugs that predispose to falls appeared to be effective and profitable both in terms of falling and healthcare costs (290,291). In addition to psychotropic drugs, review and optimization of cardiovascular drugs was also beneficial (290,292).

Vitamin D was not effective in improving strength or physical function or reducing the risk of falls in older people according to the systematic review performed by Latham et al. (293). By contrast, a meta-analysis of five randomized controlled trials (RCT) showed that vitamin D supplementation reduced the risk of falls by more than 20% among ambulatory or institutionalized older individuals with stable health (294). Furthermore, there is some evidence that long-term daily supplementation with 800 I.U. of vitamin D combined with 1000 mg of elemental calcium improves muscle strength and balance control and reduces the number of falls in older community-dwellers (295).

Cardiac pacing reduced falls effectively (by 58%) in fallers with cardioinhibitory carotid sinus hypersensitivity (296). On its part, home hazard assessment and modification was profitable only for those with a history of falling (197).

Interventions using cognitive or behavioral approaches alone were not effective, and thus far, the data on correction of visual deficiency was insufficient (197).

With regard to older adults' attitudes and views about fall prevention, relatively little literature exists. Collectively, these studies suggest that if older adults do not believe that they are at risk of falling, they are unlikely to take up measures to prevent falls (297). Especially, those entering old age were not motivated to initiate or maintain exercise purely to help prevent falls. Nevertheless, strength and balance training was found necessary and acceptable in the light of wider health benefits and well-being (298,299).

2.3.2 Prevention of hip fractures

2.3.2.1 Case finding

With respect to case finding, at present there is no universally accepted policy for population screening in Europe to identify patients with osteoporosis or those at high risk of fracture (300). Although the diagnosis of osteoporosis relies on the quantitative measure of BMD, which is a major determinant of bone strength, the clinical significance of osteoporosis lies in the fractures that arise. Screening for osteoporosis may be justified because the hip fracture risk more than doubles for every standard deviation (SD) that bone density decreases (301), and moreover, almost all types of fractures have an increased incidence in persons with low BMD (302). However, BMD alone may not be a superior predictor of fracture risk. In the Study of Osteoporotic Fractures, the proportion of fractures attributable to osteoporosis (based on a standard definition of osteoporosis: BMD T-score < -2.5 SD) was modest, ranging from 10% to 44% (302). Furthermore, the study group estimated that less than one third (28%) of female hip fracture cases were attributable to osteoporosis as defined using total hip BMD. On the other hand, in a large cohort of community-dwellers aged ≥ 65 years, screening for osteoporosis (hip BMD) was associated with 36% fewer incident hip fractures over a six-year period (303). The mechanism of this association, however, was unclear, the study did not include other interventions than BMD scans.

Case finding could be more effective if several risk factors are considered. A novel, computer-driven fracture risk assessment tool FRAX[®] has been developed under the

WHO (304-306). An individual's risk factors such as age, sex, weight, height, and femoral neck BMD if available, are entered into the website tool, followed by clinical risk factors which include a prior fragility fracture, parental history of hip fracture, current tobacco smoking, long-term use of glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis and daily alcohol consumption. The FRAX[®] algorithm then provides a figure indicating a ten-year probability of any major osteoporotic fracture and hip fracture. Suggestions for the intervention threshold and clinical management are also available. As limitations, the FRAX[®] assessment tool does not cover risk factors for falls, and it has not been validated by therapeutic trials in patients selected based on FRAX[®] scores (306,307).

Falling is stated to be the strongest single risk factor for hip fractures in older people (196,201,308). Therefore case finding and prevention strategies should not be focused on the skeletal risk factors alone. History of falls, gait and balance problems, and poor vision were found to be significant and independent predictors of hip fracture (196,198). A simple question about balance can be of value. Self-reported impaired balance was associated with an almost 4-fold increased risk of incurring a hip fracture in a cohort of older Swedish twins (309). Approximately 40% of all hip fractures were attributable to impaired balance in this twin cohort.

2.3.2.2 Fall prevention

There are effective methods for fall prevention, and preventing falls is a logical strategy to prevent fall-related fractures. But regrettably, no study has had sufficient power to test this hypothesis (197,310). A fall prevention study large enough for using fractures as a primary outcome has not been conducted. However, several RCTs have reported that preventing falls also reduces the number of fractures. A multifactorial intervention program reduced the number of femoral fractures in residential care (311), rate of any fractures in older community-dwelling fallers (116), and subsequent fractures in patients with cervical hip fracture (312). The number of fractures also decreased in older women who participated in impact exercise (313) or underwent cataract surgery (314). In these studies, the reduction of fall-induced fractures was at least 50%. Exercise can reduce bone loss in older age (315), and multi-component programs including balance, impact and strength training might be most beneficial regarding prevention of falls and fall-induced fractures (316).

2.3.2.3 Hip protectors

Since the great majority of hip fractures are caused by a sideways fall with direct impact on the greater femoral trochanter, injury site protection might be a feasible fracture prevention strategy. However, the evidence relating to hip protectors is controversial. Kannus et al. reported very promising results in 2000 (317). In their RCT, the fracture risk was 60% lower in the hip protector 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. Unfortunately, less encouraging conclusions have been drawn thereafter. The Cochrane review of hip protectors found some evidence of risk reduction in institutional settings, but no benefit was found for the majority of older people living in their own homes (318). No important adverse effects of the hip protectors were reported but compliance, particularly long term compliance, was poor. Furthermore, in a multicenter RCT conducted in US nursing homes, no protective effect was observed despite good adherence to the protocol (319). However, a recent Japanese study reported that hip protectors reduced the rate of hip fractures in female nursing home residents with a history of falls and low BMI (320).

2.3.2.4 Calcium and vitamin D

The risk of hip fracture may be reduced by a number of dietary and pharmacological agents. Calcium plus vitamin D has been shown to significantly reduce the incidence of all fractures (including hip fractures) in institutionalized elderly women at high risk for fractures (321,322) and in independently living men and women aged 65 or over (323). This was also confirmed in the systematic Cochrane review (324). The evidence on vitamin D alone is less clear, although higher doses (700 to 800 IU/day at minimum) have been reported to be beneficial (325,326). Calcium alone may not be effective in preventing hip fractures (327).

2.3.2.5 Bisphosphonates and strontium ranelate

Bisphosphonates act by inhibiting the dynamic resorption of bone by osteoclasts, reducing the rate of bone turnover, and thereby preserving bone mass. Most of the studies on bisphosphonates have been designed to test their efficacy on vertebral

fracture risk, whereas hip fracture risk, if assessed, has been largely considered as a secondary outcome. Thus far the evidence about effectiveness of bisphosphonates in preventing hip fractures is scant. Meta-analysis has been used to increase the statistical power by pooling data from RCTs. A meta-analysis of studies on alendronate reported that in women with a T-score ≤ -2.0 SD, or with a vertebral fracture alendronate therapy reduced hip fracture risk by 45% (95% CI: 16% to 64%) (328). The risk reduction was greater (55%) for those with a T-score ≤ -2.5 SD. Another meta-analysis was based on pooled data of 12 trials (329); bisphosphonates as a group reduced risk for hip fracture by 42% in postmenopausal women with osteoporosis or low BMD. The probability that bisphosphonates reduce hip fracture risk by at least 30% was estimated to be 90%. But still, the evidence is scant in the groups at greatest risk for hip fracture, i.e. those aged over 75 or 80 years and those who have already suffered a peripheral fracture including a previous hip fracture (330).

The therapeutic mechanism of strontium ranelate is partly different to that of bisphosphonates. It reduces bone resorption but in addition to that it also stimulates formation of new bone tissue (331). Hence, it affects both sides of the bone remodeling imbalance seen in osteoporosis. Strontium ranelate was the only agent that demonstrated reduction in nonvertebral and hip fracture events in a high risk elderly female population (332). Over three years, hip fractures occurred in 7.4% of the women receiving placebo and in 5.2% of women receiving strontium ranelate. The risk reduction was 32%, however, it did not reach statistical significance ($p=0.112$). In a 5-year follow-up, strontium ranelate decreased the risk of hip fracture by 43% ($p=0.036$), hip fracture incidence was 7.2% in the treatment group and 10.2% in the placebo group (333). The finding was based on post hoc analysis of 1128 patients; their mean age was 79.2 SD 4.4 years and mean femoral neck BMD T-score was -3.6 SD.

Adherence to osteoporosis medications is often suboptimal, and as could be expected, this results in a substantial reduction in clinical benefit (334). For example, 43% of 2124 women with postmenopausal osteoporosis remained on bisphosphonate therapy for one year (335), and in a large database study, only 20% of patients used bisphosphonates for 2 years (336). Dosing regimen seems to have impact on adherence: once-weekly dosing was better than daily dosing (337) and once-monthly regimen may be better than once-weekly (338). Furthermore, a medication

administered once a year, such as intravenous zoledronate, could improve adherence to treatment. With regard to secondary prevention of fractures, zoledronic acid significantly reduced new fractures in patients with hip fracture and improved survival after hip fracture (339).

In conclusion, evidence about the efficacy of antiresorptive drug therapy on reducing hip fracture risk is limited. Most studies of these drugs have been designed to demonstrate their efficacy on vertebral fracture risk. Adequately sized RCTs testing their efficacy in preventing hip fractures among older people are rare. Treatment decisions should be based on sound evidence, i.e. significant reductions in absolute fracture risk, acceptable NNT (number needed to treat) figures and costs, rather than reductions in relative fracture risks drawn from re- and post hoc analyses (310,330, 340).

2.3.2.6 Other medications

Hormone replacement therapy (HRT) has been reported to reduce hip fracture risk by 34-38% (341,342). Due to its negative effects on the risk of breast cancer and cardiovascular outcomes, HRT is no longer considered an optimal choice for osteoporosis. Selective estrogen receptor modulator raloxifene has been shown to reduce vertebral fracture risk, but there is no evidence of its efficacy on hip fractures or other nonvertebral fractures (343,344).

The use of thiazide diuretics may protect against age-related bone loss and hip fracture risk by reducing urinary calcium excretion. Findings of several observational studies support this hypothesis (345-348). Statin use has also been associated with lower fracture rates. The mechanism is unclear, but increased bone formation and BMD as well as better bone health through anti-inflammatory effects have been hypothesized (349). Bayesian type meta-analysis concluded that there was a 95% probability that statins reduce hip fracture risk by 27 to 58% (350). In a meta-analysis of 18 studies, protective effect was found in observational studies, but not in post hoc analyses of RCTs (351). Heterogeneity and potential residual confounding of observational studies have been the main sources of criticism (351,352).

2.3.2.7 Withdrawal of fall-risk-increasing medications

Unfortunately, there is little or no evidence on withdrawal of fall-risk-increasing medications and fracture risk. One regulatory intervention showed that a statewide mandatory policy was not profitable in reducing the rate of hip fractures. Benzodiazepine prescribing policy was tightened up in the New York State, and consequently the use of benzodiazepines suddenly decreased by more than 50% among elderly persons (353). Despite of this, the rate of hip fractures did not decrease. Abrupt discontinuation of long-standing benzodiazepine use may cause adverse effects, or the benzodiazepines might have been changed to drugs with more harmful adverse effects (354). In some cases, the use might have continued without insurance reimbursements. However, the lack of evidence in this field does not mean that medication optimization is ineffective at preventing hip fractures. Rather it is a matter of research methodology and resources. Due to the relatively low incidence of the fracture event, a large sample size and long observation period are required, equally as in studies on antiresorptive drugs. Furthermore, conducting medication withdrawal or regimen optimization is a challenging process. The intervention may need to be individually tailored, and expertise in pharmacology and geriatric medicine are needed.

3. AIMS OF THIS THESIS

1. To review and systematically analyze original publications concerning medications as a risk factor for falls or fall-related fractures.
2. To define characteristics of hip fracture patients and the incidence of hip fractures, including changes in the incidence within a 10-year period in Central Finland.
3. To determine the incidence of second hip fractures and describe the characteristics of patients with two incident hip fractures.
4. To assess the effects of hip fractures on the utilization of inpatient care and mortality.

4. MATERIALS AND METHODS

4.1 Methods of the systematic review (Study I)

4.1.1. Literature search

The main data source for this systematic review was the bibliographic database Medline. The search was limited to English articles published through 1996 to 2004. Data retrieval with the combination of Medical Subject Headings (MeSH) search terms “accidental falls” and “pharmaceutical preparations” was performed to find articles reporting medication use and the risk of falls or fall-related fractures. It yielded only 20 hits. Combinations of terms "falls" and "medication" or "medicines" or specific medication groups (benzodiazepines, antidepressants, antipsychotics, antiepileptics, analgesics, antihypertensive agents, statins, and cholinesterase inhibitors) gave altogether 673 hits. We also searched the Cochrane library and examined the reference lists of the retrieved papers.

4.1.2 Study selection

The abstracts of the articles found in the literature search were reviewed, and full text copies of potentially includable articles were retrieved. *Numbers within the square brackets refers to the reference list of the Study I.* A total of 48 original articles [11-29, 31-59] reporting on an association between medication use and falls or fall-related fractures were found. Nineteen studies [30-58] were excluded for the following reasons:

1. Not controlled with non-fallers or -users of the target medication [11-14]
2. Persons aged ≤ 60 years were included, and results for older persons were not reported separately [15-18]
3. Target medications were not defined properly [19-22]
4. The period between medication ascertainment and occurrence of a fall or fall-related fracture was longer than one year [23-28]
5. The dropout rate was more than 30% [29]

4.1.3 Definition and classification of medicines

The Anatomical Therapeutic Chemical (ATC) classification system (355) was applied to define main groups and subgroups of drugs. In the ATC classification system, the drugs are divided into 14 main groups according to the organ or system on which they act, and further divided, into five different levels on the basis of their chemical, therapeutic and pharmacological properties. According to the ATC classification system, the main group of central nervous system (CNS) medicines is defined as including hypnotics, sedatives, anxiolytics, antipsychotics and antidepressants (i.e. psychotropic drugs), antiepileptics, drugs for Parkinson's and Alzheimer's disease, and opioids.

4.1.4 Statistical methods

The strength of the association between medication use and falls was evaluated using ORs and 95% CIs reported in the original papers. The results were categorized by medication groups or by specific medicines reflecting the grade they were reported in the original papers.

Furthermore, we performed a meta-analysis of studies evaluating the effects of psychotropic drug use on the risk of hip fracture. The pooled OR and 95% CIs were calculated from the raw study data by using the Mantel-Haenszel method (fixed effect model).

4.2 Methods of the hip fracture studies (II-IV)

4.2.1 Study population

The Central Finland Health Care District consists of 30 municipalities, and 5% of the Finnish population lives in the area. Patients with hip fracture are referred to the Central Finland Hospital for surgical assessment, and in this study, hospital registers and medical records were used to identify hip fracture cases. The residents of the three southernmost municipalities (Jämsä, Jämsänkoski and Kuhmoinen) can also be treated in the Jokilaakso Hospital and, therefore, they were excluded from the study. Thus the study area consisted of 27 municipalities in Central Finland. The total

population of the area was 239 000, and 21% (50 000) were aged ≥ 60 years, and 11% (26 000) 70 or over (356).

4.2.2 Identification of patients with hip fracture

The identification of hip fracture patients was based on registers and medical records of the Central Finland Hospital. The lists of emergency operations and two electronic registers were reviewed to detect all the patients who sustained a hip fracture in 2002-2003. The discharge register was screened using the International Classification of Diseases tenth revision (ICD-10) diagnostic codes for femur fractures (S72.0 – S72.9) as search terms (12), and the register of the Department of Anesthesiology was screened with the surgical codes indicative of treatment of hip or femur fractures. Medical records of the identified patients were reviewed, and the residents of the study area with a cervical, trochanteric, or subtrochanteric hip fracture (S72.0-S72.2) were included in the study (Figure 1). A total of 597 hip fractures in 573 patients were identified within the two-year period (Table 6).

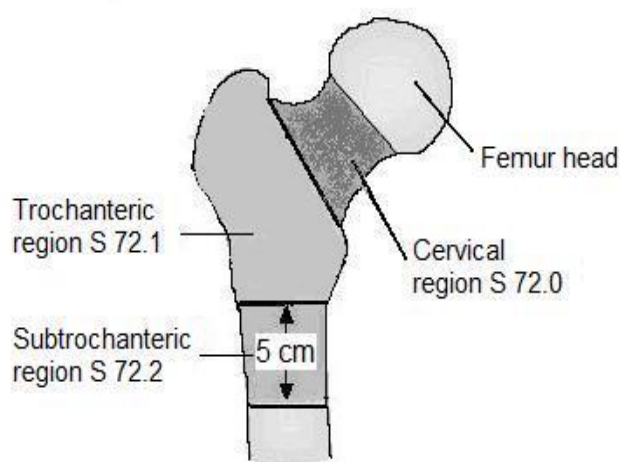


Figure 1. Anterior view of the proximal femur with regions and codes of hip fractures by the International Classification of Diseases, 10th Revision (12).

Table 6. Characteristics of hip fracture patients in 2002-2003 in Central Finland.

Variable	Age						All
	0-49	50-59	60-69	70-79	80-89	90+	
Number of patients	20	12	45	182	262	76	597
Number of women, (%)	3 (15)	6 (50)	17 (38)	112 (62)	217 (83)	60 (79)	415 (69.5)
Body mass index (kg/m ²), mean (SD)	20.9 (5.6)	25.1 (3.5)	24.3 (3.6)	24.8 (4.4)	23.9 (3.5)	22.9 (3.1)	24.0 (3.1)
Living in institution, number (%)	0	3 (25)	2 (4)	27 (15)	66 (25)	34 (45)	132 (22.1)
Number of comorbidities, median (IQR)	1 (0 , 3)	3 (2 , 3)	2 (2 , 3)	3 (2 , 3)	3 (2 , 3)	2 (2 , 3)	3 (2 , 3)
Hip fracture occurred, number (%)							
Indoors	8 (40)	8 (67)	8 (62)	131 (72)	233 (89)	66 (87)	474 (79.4)
With a low-energy mechanism	12 (60)	11 (92)	43 (96)	174 (96)	260 (99)	75 (99)	575 (96.3)
During the night (10pm to 6am)	1 (5)	3 (25)	11 (24)	38 (21)	59 (23)	20 (26)	132 (22)
Fracture type							
Cervical, number (%)	10 (50.0)	9 (75.0)	25 (55.5)	122 (67.0)	161 (61.4)	34 (44.7)	361 (60.5)
Trochanteric, number (%)	6 (30.0)	2 (16.7)	16 (35.6)	51 (28.0)	77 (29.4)	36 (47.4)	188 (31.5)
Subtrochanteric, number (%)	4 (20.0)	1 (8.3)	4 (8.9)	9 (5.0)	24 (9.2)	6 (7.9)	48 (8.0)

4.2.3 Acquisition of baseline data

The following data were retrieved from the hip fracture patients' medical records: age, sex, height, weight, place of residence, prefracture morbidity, place of accident, mechanism of injury, date and time of hip fracture, type of fracture and surgical treatment, length of stay in the Central Finland Hospital and the discharge destination. Patients' prefracture residential status was categorized as follows: home, sheltered home, nursing home, and long-term hospital care. Care homes and sheltered housing with 24-hour staff on site were classified as nursing home care. The "round-the-clock staff on site" criterion was applied to define institutional care, i.e. living in nursing home or long-term hospital care represented institutional care in this study.

Prefracture chronic conditions were categorized as follows: dementia, stroke, other neurological diseases, musculoskeletal diseases, cardiovascular diseases, cancer, mental disorders, diabetes, pulmonary diseases, and other potentially disabling chronic conditions. The category of neurological diseases contained conditions affecting gait and balance such as Parkinson's and other neurodegenerative diseases, cerebrovascular and neuroimmunological diseases, epilepsy, polyneuropathy, and sequelae of brain injuries. The musculoskeletal diseases included conditions likely to impair mobility, such as arthritis, osteoarthritis, osteoporosis and sequelae of injuries. Hypertension, coronary artery disease, valvular and myocardial diseases, persistent arrhythmias and arteriosclerosis of lower extremities were recorded as cardiovascular diseases.

4.2.4 Acquisition of follow-up data

The patients were followed up for second hip fractures (Study III). The final day of follow-up was determined to be one of the following dates (whichever came first): the date of death, the date of a second hip fracture, or December 31st 2005. Subsequent hip fractures were identified thorough the hospital registers and medical records, similarly as the first ones. Only definite new hip fractures were counted as second hip fractures, readmissions due to complications of the prior hip fracture were excluded.

Prefracture ambulatory status and the use of medications were recorded for the patients with two incident hip fractures. The medicines were listed in the emergency room or ward of trauma surgery, most often by a registered nurse. The information on

medication use was obtained by patient and/or proxy interview, reviewing prescriptions and referrals, or contacting referring physicians. Medications were categorized according to the ATC classification system (355). The number of regularly taken drugs, use of psychotropic drugs (i.e. benzodiazepines N03AE01 and N05BA, benzodiazepine-like hypnotics N05CF, antidepressants N06A, antipsychotics N05A), calcium and vitamin D supplements, and antiresorptive drugs for osteoporosis (bisphosphonates M05BA and calcitonin H05BA01) were recorded.

Table 7. ICD-10 main classes in Study IV.

Code	Disease class
A00-B99	Certain infectious and parasitic diseases
C00-D48	Neoplasms
D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
E00-E90	Endocrine, nutritional and metabolic diseases
F00-F99	Mental and behavioral disorders
G00-G99	Diseases of the nervous system
H00-H59	Diseases of the eye and adnexa
H60-H95	Diseases of the ear and mastoid process
I00-I99	Diseases of the circulatory system
J00-J99	Diseases of the respiratory system
K00-K93	Diseases of the digestive system
L00-L99	Diseases of the skin and subcutaneous tissue
M00-M99	Diseases of the musculoskeletal system and connective tissue
N00-N99	Diseases of the genitourinary system
R00-R99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
S00-T98 -S00-T14	Injury, poisoning and certain other consequences of external causes - <i>Injuries</i>
Z00-Z99	Factors influencing health status and contact with health services

Data on hospital days in the 70+ hip fracture patients and general population were obtained from the nationwide hospital discharge register maintained by the National Research Centre for Welfare and Health (STAKES). The register covers all inpatient

care in hospitals and primary care wards. The hospitalization data were categorized by patients' age and gender and the ICD-10 diagnostic main classes. The ICD-10 classes are listed in Table 7. Within the diagnostic class of injury, poisoning and certain other consequences of external causes (ICD-10 codes S00-T98), hospital days due to injuries (S00-T14) were identified, and more specifically, hospital days attributable to fall-related injuries. The data acquisition on fall-related hospitalizations was performed using the following ICD-10 codes: W00-W01 falls on same level, W10 falls on and from stairs or steps, and W19 unspecified falls.

To be able to assess the overall incidence of hip fractures, survival and follow-up time in person-years, data on the population living in the study area and deaths among hip fracture patients and in the general population were obtained from Statistics Finland. The study plan was approved by the Ethics Commission of Central Finland Health Care District.

4.2.4 Statistical analysis

Study II. The patients with hip fracture and the population at risk were stratified by gender and age (55-64, 65-74, 75-84, 85+), and hip fracture incidence rates with 95% CIs were calculated. The results were compared with those from 1992-93 (139). To obtain more detailed information of the oldest old and to improve comparability with other studies, the present data were also stratified into 10-year age groups, starting from 50 years and ending at 90+. Standardized estimates of hip fracture incidence rate ratios (IRR) were calculated by using Poisson regression models or Mantel-Haenszel combined estimate of the incidence ratio. Statistical significance was evaluated by using a t-test, analysis of variance (ANOVA), and Cochran-Armitage trend test with Monte Carlo p-value.

Study III. Results were expressed as means with SDs or medians with range. Statistical comparison between groups was made by using a t-test, Mann-Whitney test, or Chi-Square test, when appropriate. Product limit estimation (Kaplan-Meier method) was used to construct estimated cumulative incidence of second hip fractures, and 95% CIs were obtained by bias corrected bootstrapping (5000 replications). The factors predicting the second hip fractures were analyzed using proportional hazard regression models, called Cox's regression models.

Study IV. The results were expressed as means or medians with SD or inter-quartile range (IQR) and 95% CIs. Standardized estimates for count of hospital days and rate ratios (RR) were calculated using Poisson regression models. The Kaplan-Meier method was used to calculate and illustrate the cumulative probability of survival. The gender and age adjusted ratio between the observed and expected numbers of deaths, the standardized mortality ratio (SMR), was calculated with 95% CIs, assuming a Poisson distribution.

5. RESULTS

5.1 Medication as a risk factor for falls: systematic review (Study I)

5.1.1 Design and methods of the reviewed studies

A total of 29 studies [30-58] met the inclusion criteria of the systematic review (Study I, Table 1). The main objective was to study the association between medication use and risk of falls or fall-related fractures in 20 studies [31,32,34,35-37,39,41-43,45-51,54,55,57], whereas the others focused on multiple risk factors for falls [30,33,38,40,44,52,53,56,58].

The outcome measure was a fall (single or recurrent) in 17 studies [31-33,35,36,38-40,44-46,49,50,52,53,55,56], though eight studies did not include a definition of the term “fall” [31,33,45,48-50,52,55]. Five studies focused on injurious falls [30,34,54,57,58], six on hip fractures [37,41-43,48,51] and one on femur fractures [47]. Medicines were defined and categorized according to a systematic classification system in 11 studies [30,33-36,39,44,53,54-56], whereas more comprehensive and precise definitions would have been needed in 15 studies addressing several drugs or drug groups as either targets or potential confounders of the studies [37,38,40-43,46-52,57,58]. Confounding factors were often incompletely defined.

Only one study was a RCT [31]. It concerned risperidone use in nursing home residents with dementia. Measuring the association between the risperidone use and incidence of falls was not the primary objective of this study but based on the secondary analysis of the data.

Of the 28 observational studies, four were cross-sectional [33,36,50,55], nine had case-control type design [34,37,41-43,47,48,51,54], and 15 were cohort studies [30,32,35,38-40,44-46,49,52,53,56-58]. The cross-sectional studies were conducted in community or population-based settings [33,36,50,55]. The information on the current drug use was obtained from the participants, whereas the data on falls was retrospective: the participants were asked to recall whether they had fallen in the previous 12 months.

In seven of the nine case-control type studies, both the exposure and outcome data were collected retrospectively [34,37,41,42,47,51,54]. The outcome was defined as an injurious fall that led to hospital admission, and hospital registers served as data

sources for case identification. Data on medication use were extracted from prescription databases, and it was also estimated whether the exposure was current at the time of the accident. The prospective case-control studies concerned medication use in patients with hip fracture [43,48]. The data on medication use was collected at the time of hospital admission for an acute hip fracture, and use of benzodiazepines was also ascertained by serum analyses.

Twelve of the 15 cohort studies were prospective [30,32,35,38-40,44,52,53,56-58]. In the five prospective community-based cohort studies, the participants were contacted at one- to four-month intervals, and the data on falls were collected by fall calendars [30,44,56] or questionnaires and/or phone calls [35,38]. The data on medication use was assessed at the baseline only, though the follow-ups lasted from six to 12 months. In the six prospective cohort studies performed in institutional settings, falls were registered by the staff of the care facility, and the potential time period between the exposure ascertainment and outcome (drug intake and fall) varied from one day to one year [32,39,40,52,53,58]. One of these studies utilized a case-crossover design to test whether adding a new drug to a patient's medication regimen may lead to a higher incidence of falls [39]. Furthermore, a large population-based register study was conducted to examine the incidence of fall-related hospitalizations within four weeks after a new benzodiazepine prescription [57].

Three of the cohort studies were retrospective, and they were performed in nursing home settings [45,46,49]. The data on falls were abstracted from the nursing home records and the contemporaneous medication use from the medication administration records or pharmacy reports.

In all the 29 studies, age and gender (if both genders were represented) were included as potential confounding variables. All 20 studies that primarily focused on the association between medication use and risk of falls were controlled at least for one chronic condition [31,32,34,35-37,39,41-43,45-50,51,54,55,57], cognitive impairment being the one addressed most often [31,32,34,35,39,45-49,51,54,55]. Confounding effects related to concomitantly used medicines were taken into account in 14 of these 20 studies [31,34,35,37,39,41-43,46,47,49,50,51,57]. Furthermore, the effects of duration of drug use were evaluated in eight studies [37,39,41,46,49,51,54,57], and the impact of daily doses in six studies [31,41,46,47,49,51].

5.1.2 Psychotropic drugs and falls

5.1.2.1 Benzodiazepines

Benzodiazepines as a group or by certain preparations were evaluated in 22 studies included in the systematic review [30,32-36,39-44,46-48,50-53]. They were found to be related to an increased risk of falls in 12 studies [33,35,36,39,44,46,50,52,53,54,55,57] and to an increased risk of hip fractures in five studies [41,42,43,47,48]. On the contrary, three studies found no association between benzodiazepine use and risk of falls [30,40,56], and in two studies the risk increase was seen only in the initial analyses but not in the final models [32,34]. The results regarding benzodiazepines are presented more specifically in Study I: Table 1 and Figure 1.

5.1.2.2 Antidepressants

Antidepressants were evaluated as a risk factor for falls or fall-related fractures in 20 studies [30,32-35,37-40,42,44,45,49-56]. A statistically significant risk increase was observed in 10 studies concerning falls [32-35,40,45,49,50,53,55] and three hip fracture studies [37,42,51]. Furthermore, SSRIs seemed no safer than TCAs in terms of fall or hip fracture risk (Study 1, Figure 2). On the other hand, the use of antidepressants was not found to contribute falls in seven studies [30,39,44,52,54,56], and in one study, they were associated with orthostatic hypotension but not with falls [38]. Serotonin and noradrenalin reuptake inhibitors (SNRI) were evaluated in one study only, and no association with falls was reported, OR= 0.97 (95% CI: 0.60 to 1.57).

5.1.2.3 Antipsychotics

Antipsychotics were evaluated in 11 studies. They were associated with increased risk of falls or injurious falls in five studies [31,32,39,52,54] and with hip fractures in one study [42]. Additionally, a subgroup analysis showed that antipsychotics contributed to falls in demented patients living in long-term care facilities [53]. However, in one community-based study, the relation between antipsychotics and injurious falls was

no longer significant after controlling for several confounding factors [34], and in three studies no association between the drug group and falls was found [30,40,55]. Studies on atypical antipsychotics were rare, and only two studies gave results for them [31,32]. Neither risperidone nor olanzapine was associated with falls among persons in geriatric care facilities, though an increasing trend of falls was related to higher doses of risperidone in the RCT [31], and antipsychotics as a group were found to be associated with an increased risk in the Swedish study [32].

5.1.3 Other CNS active drugs and falls

Antiepileptics were related to an increased risk of falls in three studies [34,35,44], whereas one study showed no elevated risk [32]. Cholinesterase inhibitors for Alzheimer's disease were evaluated in one study only, and no relation to the risk of falling was found [32]. Opioids were associated with falls in one study [34], but not in another [35].

Use of any psychotropic drug increased the risk of falling in ambulatory nursing home residents, the incidence density ratio for serious fall-related injuries was 2.49 (95% CI: 1.43 to 4.33) [58]. The use of any CNS active drug was related to the fall risk elevation in Brazilian community-dwelling older people [50], and in a population-based sample of older British women [33].

5.1.4 Cardiovascular drugs and falls

Data on the use of other than CNS drugs were collected in 12 studies [30,32-34,36,38-40,44,53,54,56]. Figure 2 shows the results on the use of cardiovascular drugs and risk of falling. Three studies reported that cardiovascular drugs were associated with an increased risk of falling [30,36,56]. Use of antihypertensives increased risk for injurious falls [30], use of beta-blockers and peripheral vasodilators for recurrent falls [36,56], and use of nitrates for any falls [56]. But in nine studies cardiovascular drugs, as a whole or by examined group, were not associated with falls [32-34,38-40,44,53,54], and one study reported that the use of inotropic agents decreased risk of falling [54]. A limitation that should be considered when interpreting the above studies was that the definitions and groupings of the

cardiovascular drugs varied considerably from one study to another, and the results of risk calculations were not reported in three studies [40,44,53].

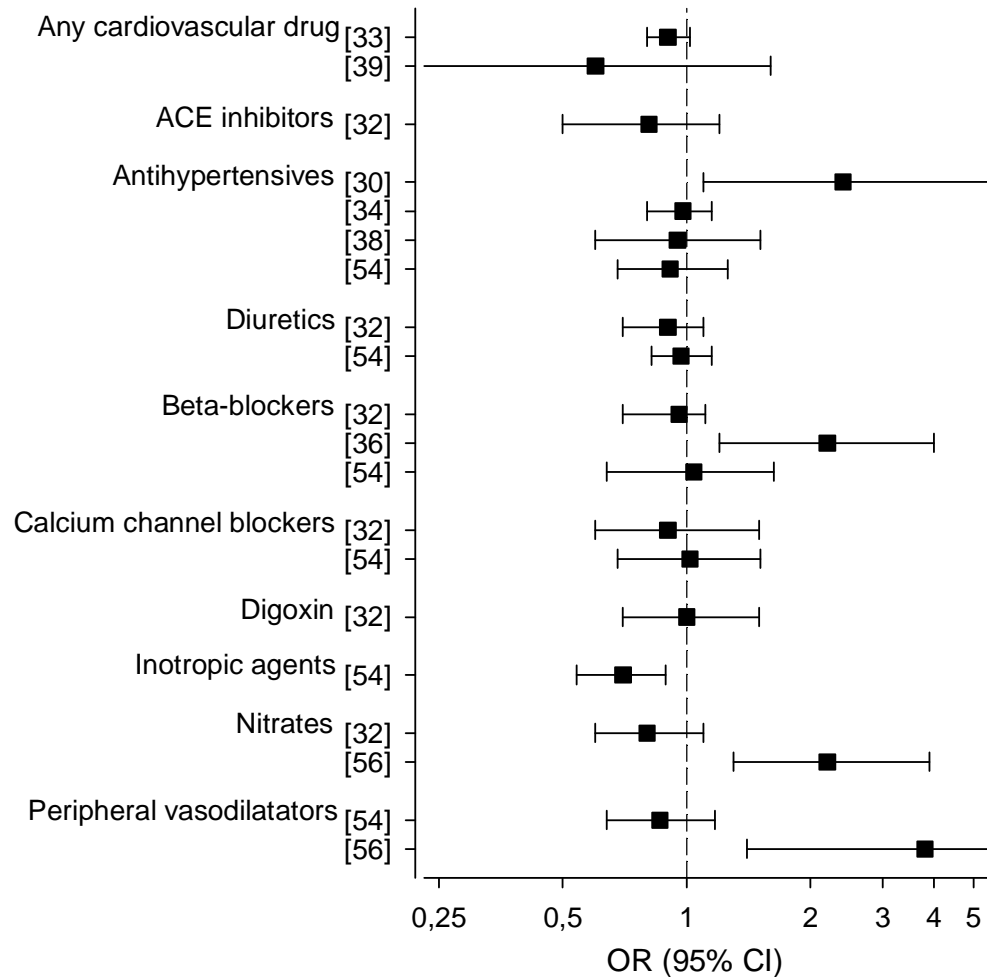


Figure 2. Cardiovascular drugs and risk of falls

5.1.5 Polypharmacy and falls

Polypharmacy was associated with an increased risk of falling in three studies [33,39,44]. In a nursing home population, the use of five to nine drugs increased the risk fourfold, and the use of 10 or more drugs up to 5.5-fold compared with the use of 4 or less drugs [39]. Among community-dwelling older people, the use four or more drugs increased the risk of falling by 30% [44]. However, in older women, the association with falls was stronger for multiple pathologies than for polypharmacy [33].

5.2 Meta-analysis on psychotropic drugs and hip fracture risk

In terms of outcome (hip or femur fracture), seven studies on psychotropic drugs were potentially includable in the meta-analysis [37,41-43,47,48,51]. All of them were case control type studies and data for meta-analysis were available. Hubbard et al. reported on exposure to TCA and SSRI antidepressants in 16 341 hip fracture cases and 29 889 controls [37]. The two studies by Wang et al. concerned the same population: 1 222 hip fracture cases and 4 888 control patients [41,42]. Thus the proportions of benzodiazepine, antipsychotic and antidepressant users were similar in both of the studies. Pierfitte et al. reported on the use of benzodiazepines in 245 cases and 817 controls [43], Sgadari et al. in 9 752 cases 38 564 controls, and in the study of Schwab et al. there were 82 patients in both of the groups [47,48]. The use of antidepressants was investigated in the large register based study of Liu et al. [51]. The number of hip fracture patients was 8 239 and number of controls was 41 195. In addition to exposure to antidepressants (SSRIs and TCAs), several other drug groups were addressed, including anxiolytics. In all of these studies, the controls were age and gender matched to the hip fracture patients.

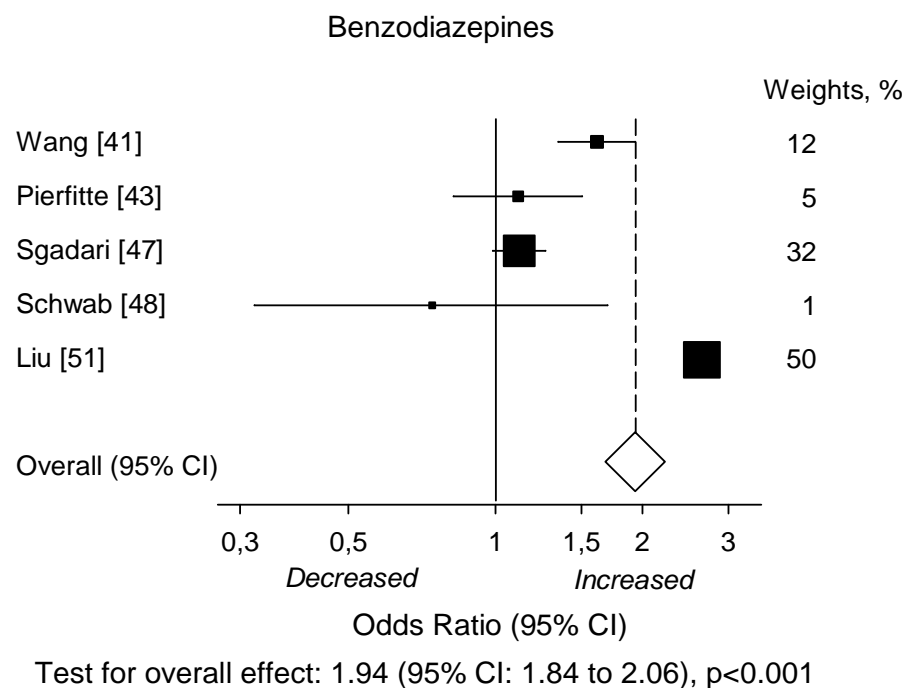


Figure 3. Results of a meta-analysis on benzodiazepines and risk of hip fractures.

5.2.1 Benzodiazepines and hip fracture risk

For the present meta-analysis, data on the exposure to benzodiazepines were extracted from five studies [41,43,47,48,51]. The total number of participants was 105 086. The exposure data based on the history of drug use [43,48] or prescription databases [41,47,51]. Based on these five studies, use of benzodiazepines was associated with an increase in the risk of hip fracture, the pooled OR was 1.94 (95% CI: 1.84 to 2.06), $p < 0.001$ (Figure 3).

5.2.2 Antidepressants and hip fracture risk

Three studies on antidepressants were eligible for meta-analysis [37,41,51]. The total number of participants was 101 774. Two studies covered both TCAs and SSRIs [37,51], whereas Wang et al. did not specify types of antidepressants they addressed [41]. In all studies, both the exposure and outcome data were based on registers. Meta-analysis of these three studies showed that the use of antidepressants was related to an increased risk of hip fracture, the pooled OR was 1.82 (95% CI: 1.75 to 1.86), $p < 0.001$ (Figure 4).

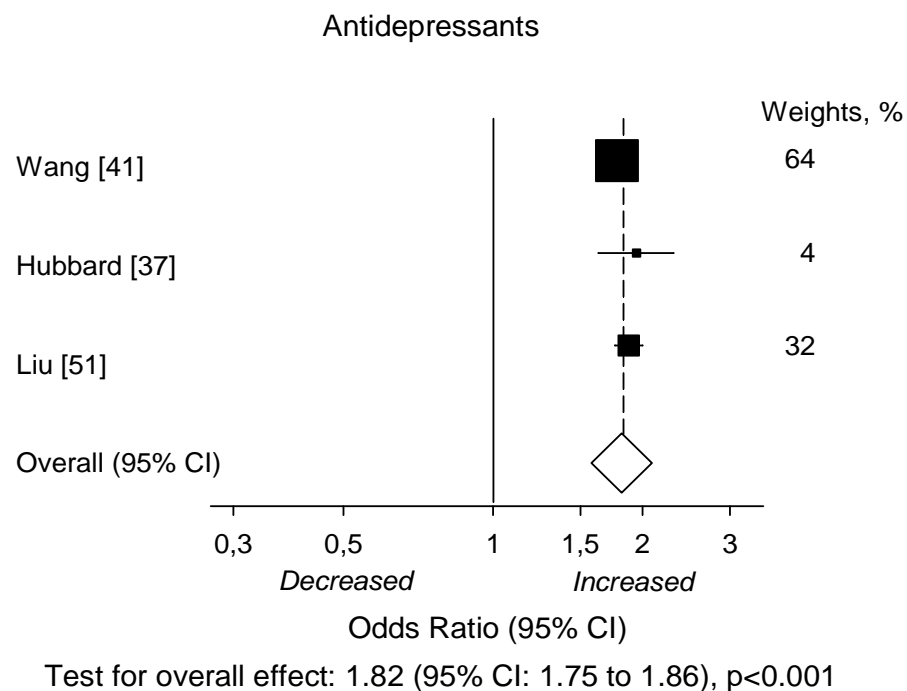


Figure 4. Results of a meta-analysis on antidepressants and risk of hip fractures.

5.3 Incidence of hip fractures (Study II)

5.3.1 Hip fractures in Central Finland in 2002 - 2003

A total of 597 patients were admitted to the Central Finland Hospital for treatment of an acute hip fracture in 2002-2003. The characteristics of the patients are shown in Table 6. Patients' prefracture residential statuses were as follows: 384 (64.3%) were home-dwelling, 80 (13.4%) were in sheltered housing, 114 (19.1%) lived in nursing homes and 19 (3.2%) were in long-term hospital care. Thirty-two (5.4%) persons fractured their hip during acute hospitalization and 10 (1.7%) during short-term nursing home stay.

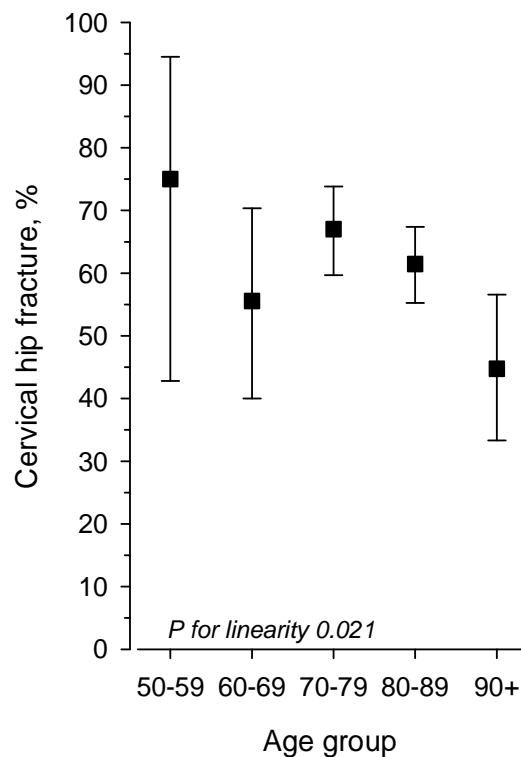


Figure 5. The percentage of cervical fracture type by age groups in 577 hip fracture patients. Error bars show the 95% confidence intervals.

A total of 577 (96.7%) patients were aged ≥ 50 years. The analysis by age groups (50-59, 60-69, 70-79, 80-89 and 90 years or older) showed that mean BMI decreased towards the oldest age group ($p=0.001$), whereas the proportion of institutionalized patients ($p<0.001$), low-trauma fractures ($p=0.014$), and fractures occurring indoors

($p < 0.001$) showed monotonic increase with advancing age. The hip fracture type distribution was the following: 361 (60.5%) cervical, 188 (31.5%) trochanteric and 48 (8.0%) subtrochanteric. The percentage of cervical fractures decreased linearly with age, $p = 0.021$ (Figure 5). In the oldest age group, the proportion of the trochanteric and subtrochanteric fractures exceeded that of the cervical ones (55.3% vs. 44.7%).

The crude incidence of hip fractures was 3.4 per 1000 py in the 50+ population; 4.5 per 1000 py in women and 2.1 per 1000 py in men. The crude incidence rate ratio (IRR) between the genders was 2.09 (95% CI: 1.74 to 2.52), and the age-adjusted IRR was 1.28 (95% CI: 1.07 to 1.55). The incidence of hip fractures increased steeply with age, being 37.1 (95% CI: 28.3 to 47.8) per 1000 py in women and 35.1 (95% CI: 20.1 to 57.1) per 1000 py in men in the 90+ age group. The gender-specific incidence rates diverged the most at the age of 80-89 years.

Through 1992-1993 to 2002-2003, the total number of hip fractures rose by 70%, from 351 to 597. Four-fifths of the total growth took place in the two oldest age groups: the increase was 1.7-fold in the age group of 75-84 years and two-fold among those aged 85 or over (Figure 6).

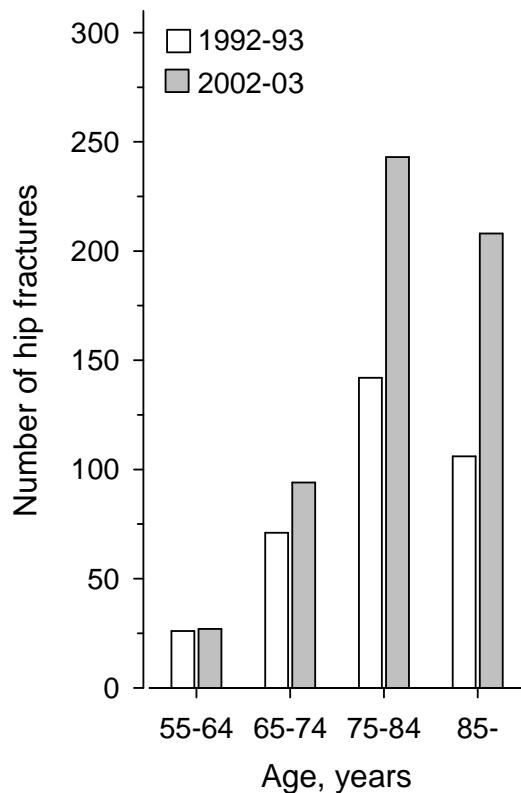


Figure 6. Age distribution of patients with hip fracture in 1992-93 (139) and 2002-03.

5.3.2 Change in the incidence within 10 years

In the female population aged 55 years and over, the hip fracture rate per 1000 py was 3.9 in 1992-1993 and 5.6 in 2002-2003. For the 55+ male population, the incidence rates were 2.0 and 2.8, respectively. The age-adjusted incidence rate ratios (IRR) were 1.25 (95% CI: 1.07 to 1.47), $p=0.006$, and 1.36 (95% CI: 1.06 to 1.76), $p=0.017$, for women and men, respectively, indicating that over the decade, the hip fracture incidence increased statistically significantly in both genders. Further analysis by age groups (55-64, 65-74, 75-84, and 85+ years) showed that the change was most marked in men aged 75-84 years, IRR = 1.67 (95% CI: 1.08 to 2.65), whereas in women the highest IRR, 1.33 (95% CI: 1.02 to 1.75), was seen in the oldest age group.

5.4 Second hip fractures (Study III)

5.4.1 Incidence of second hip fractures in Central Finland

A total of 501 (70.9% women) persons aged ≥ 60 years sustained their first hip fracture in 2002-2003. They were followed up for subsequent hip fractures by the end of year 2005. The follow-up covered 936 py, and the median follow-up time was 25.5 months. Thirty four (6.8%) persons suffered a second hip fracture and 230 (45.9%) died during the follow-up. The overall incidence of second hip fractures was 0.036 (95% CI: 0.025 to 0.051) per py. The one-year cumulative incidence of second hip fractures was 5.1% (95% CI: 3.3 to 7.8), and the two-year rate was 8.1% (95% CI: 5.7 to 11.4). The age-adjusted incidence rate ratio of second hip fractures between men and women was 1.0 (95% CI: 0.4 to 2.4), $p = 0.93$, indicating that there was no statistically significant gender difference in the incidence rate of second hip fractures.

5.4.2 Risk factors for second hip fractures

The patients' characteristics collected at the time of first hip fracture are shown in Table 8. There was no statistically significant difference between the patients with only one hip fracture and patients who suffered a second hip fracture.

Table 8. Baseline characteristics of 501 hip fracture patients (age \geq 60 years) at the time of first hip fracture in 2002-2003. The follow-up for subsequent hip fractures was carried out till the end of the year 2005.

Characteristics	Patients with only one hip fracture (n=467)	Patients who suffered a second hip fracture (n=34)	P-value
Male / Female	138/329	8/26	0.47
Mean age, year (SD)	81 (8)	80 (7)	0.91
Body mass index (kg/m ²), mean (SD)	24.2 (3.9)	23.7 (4.3)	0.47
Living in institution, number (%)	101 (21.6)	6 (17.6)	0.58
Comorbidity, number (%)			
Dementia	125 (26.8)	9 (26.5)	0.97
Neurological disease	96 (20.6)	8 (23.5)	0.68
Musculoskeletal disease	207 (44.3)	12 (35.3)	0.31
Cardiovascular disease	349 (74.7)	25 (73.5)	0.88
Cancer	55 (11.8)	2 (5.9)	0.41
Mental disorder	52 (11.1)	1 (2.9)	0.24
Diabetes mellitus	73 (15.6)	6 (17.6)	0.76
Pulmonary disease	65 (13.9)	4 (10.8)	0.72
Type of first hip fracture			0.074
Cervical, number (%)	277 (59.3)	27 (79.4)	
Trochanteric, number (%)	154 (33.0)	6 (17.6)	
Subtrochanteric, number (%)	36 (7.7)	1 (2.9)	

Bivariate and multivariate analyses were performed to identify potential predictors of a second hip fracture. Gender, age, BMI, long-term institutional care, any of the chronic comorbidities or type of first hip fracture did not predict the occurrence of a second hip fracture (Table 9). The results of the Cox regression models remained non-significant when the specific comorbid conditions were replaced with the number of comorbidities (Study III, Table 2).

Table 9. Cox regression models for potential predictors of a second hip fracture

Predictors	Model	
	Bivariate [†] HR (95% CI)	Multivariate HR (95% CI)
Male gender	0.95 (0.41 to 2.19)	0.88 (0.37 to 2.09)
Mean age	1.01 (0.97 to 1.06)	1.00 (0.96 to 1.05)
Body mass index	0.96 (0.85 to 1.08)	0.95 (0.83 to 1.09)
Living in institution	1.07 (0.44 to 2.60)	1.04 (0.31 to 3.49)
Dementia	1.18 (0.54 to 2.58)	1.16 (0.41 to 3.36)
Neurological disease	1.39 (0.60 to 3.26)	1.19 (0.48 to 2.96)
Musculoskeletal disease	0.57 (0.28 to 1.17)	0.59 (0.27 to 1.28)
Cardiovascular disease	1.08 (0.49 to 2.26)	0.95 (0.40 to 2.23)
Cancer	0.72 (0.17 to 3.02)	0.71 (0.16 to 3.22)
Mental disorder	0.26 (0.03 to 1.98)	0.27 (0.04 to 2.09)
Diabetes mellitus	1.24 (0.51 to 2.99)	1.01 (0.38 to 2.69)
Pulmonary disease	0.91 (0.30 to 2.74)	0.83 (0.28 to 2.49)
Type of first hip fracture		
Cervical	Reference	Reference
Trochanteric	0.40 (0.16 to 1.00)	0.40 (0.16 to 1.01)
Subtrochanteric	0.25 (0.03 to 1.83)	0.27 (0.04 to 1.95)

[†] Adjusted for age and gender.

5.4.3 Medication use in patients with recurrent hip fractures

To assess changes in institutionalization rate, degree of mobility and medication use between the first and second hip fractures, all patients with recurrent hip fractures were identified. In 2002-2003, 573 persons experienced 597 hip fractures, thus 24 residents of the study area sustained two incident hip fractures. In addition, 41 of these 573 persons had experienced one hip fracture prior to 2002 and ten suffered a second hip fracture by the end of 2005. Thus 75 persons (59 women, 16 men) with two non-contemporaneous hip fractures were detected. The time between the first and second hip fracture ranged from 11 days to 14 years. The mean age of the patients was

78 years (range: 46 to 92) at the time of the first hip fracture and 81 (range: 49 to 99) at the time of the second one.

Of these 150 hip fractures, 148 (98.7%) were caused by low-energy trauma such as a fall from a sitting or standing level. Fifty four (72%) of the first and 45 (60%) of the second hip fractures were cervical. The majority of the second fractures were on the contralateral side to the first fracture (n=66, 88%).

Table 10. Medication use in 75 patients with two non-contemporaneous hip fractures.

Characteristics	At the time of the first hip fracture	At the time of the second hip fracture
Regularly used drugs, mean (range)	4.4 (0 - 11)	6.5 (0 - 17)
Using daily, n (%)		
0 to 5 drugs	51 (68)	23 (31)
6 to 9 drugs	21 (28)	43 (57)
≥ 10 drugs	3 (4)	9 (12)
Using daily any psychotropic drug, n (%)	27 (36)	44 (59)
Using daily 2 or more psychotropic drugs, n (%)	12 (16)	23(31)
Using daily, n (%)		
Benzodiazepine	14 (19)	25 (33)
Antidepressant	14 (19)	23 (31)
Antipsychotic	7 (9)	14 (19)
Benzodiazepine like sleeping pill	8 (11)	16 (21)
Using regularly, n (%)		
Calcium and vitamin D	3 (4)	9 (12)
Bisphosphonates or calcitonin	2 (3)	12 (16)

Between the first and second hip fractures, the proportion of patients in long-term institutional care increased by 22% from 8/75 to 25/75, and the number of patients who were able to walk without any aid decreased by 37% from 39 to 11. At the same time, the mean number of regularly used medicines increased from 4.4 (range 0-11) to 6.5 (range 0-17), (Table 10). The corresponding figures were 4.2 and 6.0 when the use of calcium, vitamin D, calcitonin, and bisphosphonates was excluded. Though psychotropic drugs are associated with increased risk of falling, their use became

more prevalent between the fractures. The number of patients using one or more psychotropic drugs daily increased by 23%, from 27 to 44. The relative ratio for starting the use of a psychotropic drug was 1.63 (95% CI: 1.24 to 2.14) between the first and second hip fractures. A total of 8/75 (11%) patients had been diagnosed as having osteoporosis prior to first hip fracture, and at the time of the second hip fracture, the proportion was 17/75 (23%). None of the patients used the combination of calcium, vitamin D, and antiresorptive drug at the time of first hip fracture. At the time of second hip fracture, the combination therapy for osteoporosis was used by 7/75 (9%) patients.

5.5 Utilization of inpatient care before and after hip fracture (Study IV)

5.5.1 Characteristics and treatment of hip fracture patients

A total of 498 (74.9% women) persons aged 70 years or older sustained a hip fracture in 2002-2003 in the study area. Their mean age was 82 (SD 7) years, and 118 (23.7%) of them were in long-term institutional care prior to hip fracture. The median number of prefracture comorbidities was 2 (IQR: 2, 3) in both sexes. Only one man and 10 women did not have diagnosis of chronic disease. Three-fourths (76%) of the patients had a cardiovascular disease. Osteoporosis had been diagnosed in 71 (19%) women, but in only 6 (5%) men. Fifty-three (11%) patients had cancer, and it was active in 13 cases. The prevalence of comorbidities in the 70+ hip fracture patients is presented in Study 4, Table 1.

High-energy trauma, such as a traffic accident or falling from a height, caused only 2.2% (n=11) of the hip fractures. The median duration between the occurrence of the hip fracture and entering the Central Finland Hospital for surgical assessment was three hours (IQR: 2, 6), whereas the median in-hospital delay to surgical repair of hip fracture was 27 hours (IQR: 20, 48). Seventeen (3.4%) patients were not operated on, and the patient's poor condition was the reason for choosing conservative treatment in 13/17 cases. Twenty-two (4.4%) patients were discharged directly to their homes from the traumatology ward, 402 (80.7%) patients were transferred to primary care hospitals and 35 (7.0%) to other institutions. The median length of stay in Central Finland Hospital was seven days (IQR: 5, 12).

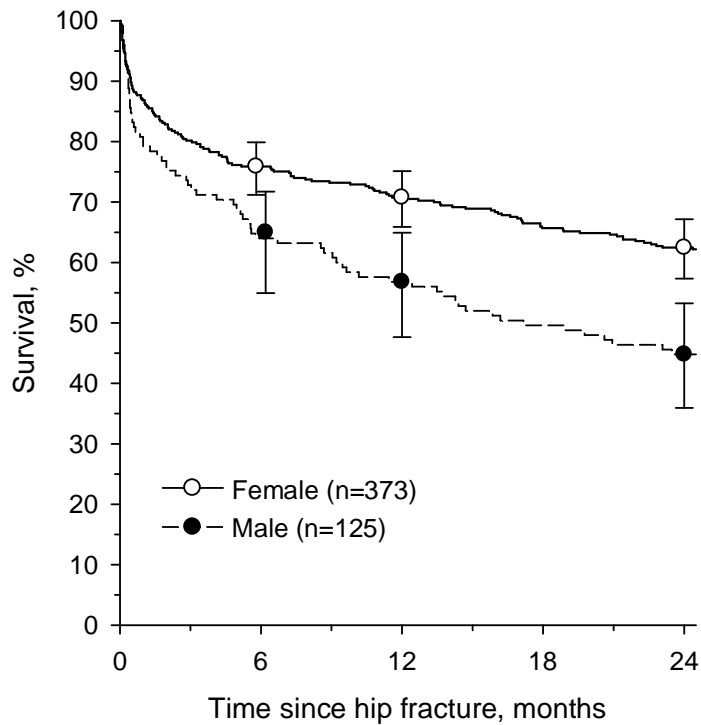


Figure 7. Mortality after hip fracture in 498 patients aged ≥ 70 years. Whiskers show the 95% confidence intervals.

5.5.2 Mortality after hip fracture

A total of 39 (7.8%) patients died during the primary stay in Central Finland Hospital. The steepest decrease in survival was seen during the first month (Figure 7). The overall one-month mortality rate was 15.1% (95% CI: 12.2 to 18.5); 13.1% (95% CI: 10.1 to 17.0) in women and 20.8% (95% CI: 14.7 to 29.0) in men.

At one year after hip fracture, the overall mortality rate was 32.7% (95% CI: 28.6 to 37.0); 29.2% (95% CI: 24.9 to 34.1) in women and 43.2% (95% CI: 35.1 to 52.3) in men. One-year mortality was significantly higher in the hip fracture group than in the general population living in the study area, the age- and sex-standardized mortality ratio (SMR) was 2.9 (95% CI: 2.5 to 3.4). For the female patients the SMR was 2.6 (95% CI: 2.1 to 3.1), and for the males it was 3.9 (95% CI: 2.9 to 5.1) (Figure 8). Excess mortality was seen in all age groups, it increased towards the youngest age group, and the trend was statistically significant, $p < 0.001$. The overall two-year mortality was 42.0% (95% CI: 37.8 to 46.4); 37.5% (95% CI: 32.8 to 42.7) in women, and 55.2% (95% CI: 46.7 to 60.0) in men. The two-year SMR was 3.6 (95% CI: 3.1 to 4.0).

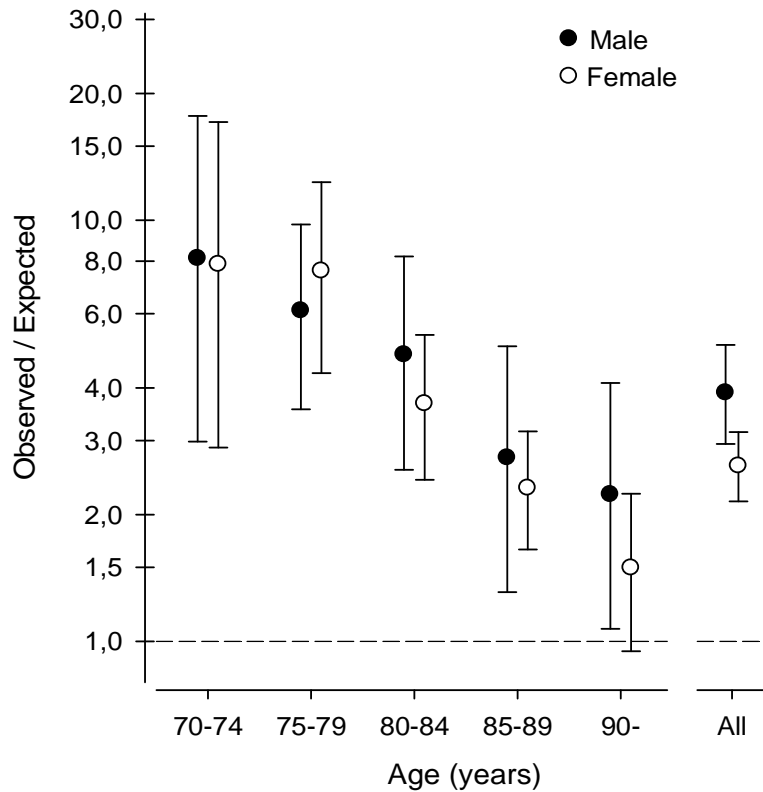


Figure 8. Age- and gender-specific one-year mortality rates in patients with hip fracture (observed death) in relation to death rate in the general population (expected death) living in Central Finland. The term All indicates the standardized mortality ratio (SMR) for male and female hip fracture patients aged ≥ 70 years.

5.5.3 Use of hospital days

In the year preceding hip fracture, hospitalizations among the 498 future hip fracture patients resulted in 11 458 hospital days, 23 days per py. The number of hospital days was 40 244 (107 per py) in the first year following hip fracture and 16 242 (52 per py) during the second postfracture year. In the general population, the number was constantly 11 per year.

The age- and gender-adjusted rate ratio (RR) of hospital days per py between the fracture group and general population was 1.30 (95% CI: 1.27 to 1.32) in the prefracture year. Men had twice as many hospital days as the 70+ male population, the age-adjusted RR was 2.07 (95% CI: 1.28 to 3.36), $p=0.003$, whereas the number of hospital days in women did not differ from that of the female population, RR = 1.08 (95% CI: 0.58 to 2.02), $p=0.80$ (Figure 9).

In the first postfracture year, the age adjusted number of hospital days per py in the hip fracture group was seven times greater than that of the general population, RR = 6.91 (95% CI: 6.85 to 7.00). The rate ratio of hospital days was higher for men than women: RR = 9.62 (95% CI: 7.68 to 12.04) vs. RR = 6.22 (95% CI: 4.95 to 7.80). In the second postfracture year, the RR of hospital days between the fracture group and population was 3.61 (95% CI: 3.55 to 3.67). The gap between the genders narrowed: the RR was 4.53 (95% CI: 3.04 to 6.75) for men and 3.04 (95% CI: 2.73 to 4.23) for women.

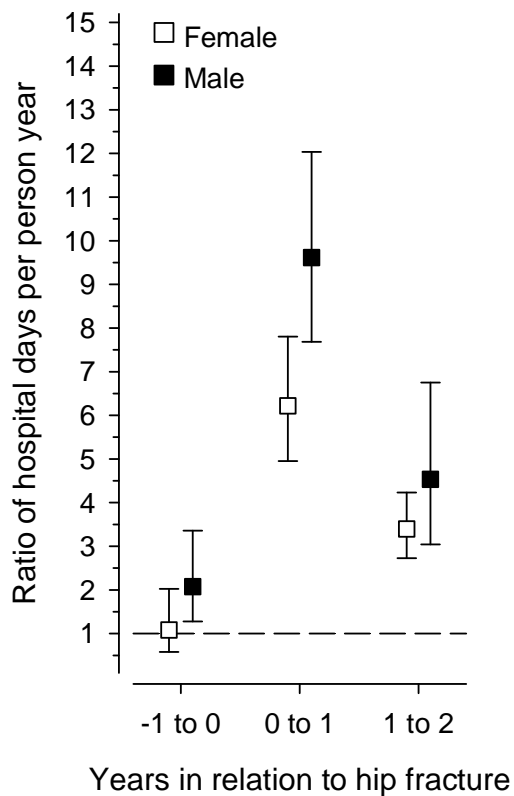


Figure 9. Ratio (age adjusted) of hospital days per person-year between the 70-year-old and older hip fracture patients (n=498) and general population in Central Finland. The hospital days are for the year before hip fracture (-1 to 0), and for the first (0 to 1) and second (1 to 2) year after hip fracture. The dotted line shows the hospital days in the general population and the whiskers the 95% confidence intervals.

5.5.4 Hospital days by the ICD-10 classes

In the prefracture year, the top three causes for hospital days in the hip fracture group were mental and behavioral disorders (F00-F99), diseases of the circulatory system (I00-I99), and injuries, poisonings and other consequences of external causes (S00-T98), resulting in 20.7%, 18.9% and 13.9% of all the hospital days, respectively (Table 11). As could be expected, in the first postfracture year, most hospital days (54.6%) in the hip fracture group were attributable to the S00-T98 class. In the second postfracture year, 25.1% of the hospital days were attributable to the F00-F99 diagnoses, 24.5% to the I00-I99 class, and 20.3% to the S00-T98 class. In the general population, the top three causes for hospital days in all the three follow-up years were I00-I99 (27.0 - 27.3% of all hospital days), F00-F99 (15.4 - 15.6%), and S00-T98 (8.3 - 8.5%).

Hospital days due to diseases of the digestive system (K00-K93) and the S00-T98 class were significantly more prevalent in the hip fracture group than in the general population. The age and gender adjusted RR was 4.03 (95% CI: 1.50 to 10.85) for the K00-K93 class and 2.03 (1.17 to 3.52) for the S00-T98 class. The RR for the subclass of injuries (S00-T14) was 2.29 (95% CI: 1.25 to 4.19).

In the first postfracture year, hospital days attributable to injuries peaked up in the hip fracture group, and exceeded multifold the days per py in the general population, RR = 53.69 (95% CI: 38.78 to 74.34). Furthermore, days due to several other diagnostic classes were also significantly more prevalent in the hip fracture group. The hospital days per py attributable to the F00-F99, G00-G99, I00-I99, J00-J99, N00-N99, and Z00-Z99 classes were three to six times more common in the hip fracture group than in the general population (Table 12).

In the second postfracture year, excess utilization of inpatient care was still seen in five diagnostic classes (S00-T98, F00-F99, G00-G99, I00-I99, and J00-99). The largest difference was in the number of hospital days attributable to injuries, RR = 8.54 (95% CI: 5.96 to 12.33).

There were opportunities to identify patients at high risk for hip fracture. As many as 279 (56.0%) of the future hip fracture patients had been hospitalized during the prefracture year, and a fall-related injury had been the first underlying diagnosis in 57 cases. In the 70+ population, altogether 810 (3.0%) person required inpatient care due to injurious falls.

Table 11. Hospital days by ICD-10 diagnostic classes in the hip fracture group (HF) and in the general population (GP).

ICD-10 class	Prefracture year		First postfracture year		Second postfracture year	
	HF n (%)	GP n (%)	HF n (%)	GP n (%)	HF n (%)	GP n (%)
All	11 458	304 863	40 244	297 468	16 242	288 012
A00-B99	169 (1.5)	5 647 (1.8)	275 (0.7)	5 443 (1.8)	104 (0.6)	5 333 (1.9)
C00-D48	445 (3.9)	23 472 (7.7)	784 (2.0)	22 942 (7.7)	191 (1.2)	22 140 (7.7)
D50-D89	182 (1.6)	1 785 (0.6)	96 (0.2)	1 749 (0.6)	33 (0.2)	1 719 (0.6)
E00-E90	285 (2.5)	7 609 (2.5)	35 (0.1)	7 532 (2.5)	356 (2.2)	7 455 (2.6)
F00-F99	2 377 (20.7)	46 863 (15.4)	4 550 (11.3)	46 029 (15.5)	4 085 (25.2)	44 924 (15.6)
G00-G99	566 (4.9)	21 614 (7.1)	2 008 (5.0)	21 317 (7.2)	1 613 (9.9)	20 236 (7.0)
H00-H59	14 (0.1)	1 821 (0.6)	14 (0.0)	1 752 (0.6)	3 (0.0)	1 700 (0.6)
H60-H95	7 (0.1)	209 (0.1)	0 (0.0)	196 (0.1)	0 (0.0)	192 (0.1)
I00-I99	2 168 (18.9)	82 291 (27.0)	5 612 (13.9)	80 617 (27.1)	3 980 (24.5)	78 638 (27.3)
J00-J99	916 (8.0)	21 882 (7.2)	2 605 (6.5)	21 365 (7.2)	1 180 (7.3)	20 611 (7.1)
K00-K93	987 (8.6)	9 958 (3.3)	187 (0.5)	9 601 (3.2)	138 (0.9)	9 049 (3.1)
L00-L99	47 (0.4)	1 820 (0.6)	83 (0.2)	1 747 (0.6)	22 (0.1)	1 591 (0.5)
M00-M99	681 (5.9)	18 313 (6.0)	375 (0.9)	17 591 (5.9)	380 (2.3)	17 024 (5.9)
N00-N99	357 (3.1)	10 071 (3.3)	561 (1.4)	9 889 (3.3)	249 (1.5)	9 287 (3.2)
Q00-Q99	0 (0.0)	98 (0.0)	0 (0.0)	98 (0.0)	0 (0.0)	95 (0.1)
R00-R99	514 (4.5)	15 910 (5.2)	239 (0.6)	15 501 (5.2)	257 (1.6)	15 257 (5.3)
S00-T98	1 589 (13.9)	25 916 (8.5)	21 980 (54.6)	24 604 (8.3)	3 295 (20.3)	23 834 (8.3)
<i>S00-T14</i>	<i>1 578 (13.8)</i>	<i>21 953 (7.2)</i>	<i>21 511 (53.4)</i>	<i>20 817 (7.0)</i>	<i>3 047 (18.7)</i>	<i>20 147 (7.0)</i>
Z00-Z99	154 (1.3)	9 584 (3.1)	840 (2.1)	9 496 (3.2)	356 (2.2)	8 927 (3.1)

Table 12. Hospital days per person-year (py) by ICD-10 diagnostic classes in the hip fracture (HF) group and general population (GP).

ICD-10 class	Prefracture year			First postfracture year			Second postfracture year		
	Days per py in HF group	Days per py in GP	RR [†] (95% CI)	Days per py in HF group	Days per py in GP	RR [†] (95% CI)	Days per py in HF group	Days per py in GP	RR [†] (95% CI)
A00-B99	0.25	0.23	1.08 (0.56 to 2.08)	0.59	0.22	2.62 (0.97 to 7.09)	0.26	0.20	1.29 (0.67 to 2.46)
C00-D48	0.86	1.06	0.81 (0.45 to 1.48)	2.11	0.95	2.21 (0.83 to 5.90)	0.61	0.87	0.70 (0.24 to 2.02)
D50-D89	0.26	0.07	3.55 (0.82 to 15.32)	0.16	0.06	2.54 (0.99 to 6.54)	0.07	0.06	1.10 (0.53 to 2.24)
E00-E90	0.35	0.30	1.18 (0.28 to 4.94)	0.07	0.31	0.23 (0.04 to 1.26)	0.97	0.32	3.07 (0.53 to 17.86)
F00-F99	3.09	1.92	1.61 (0.90 to 2.89)	8.63	1.92	4.49 (3.09 to 6.52)	9.56	1.83	5.23 (3.61 to 7.59)
G00-G99	0.98	1.01	0.96 (0.39 to 2.35)	4.83	0.92	5.24 (2.90 to 9.46)	4.53	0.84	5.36 (2.91 to 9.89)
H00-H59	0.02	0.06	0.37 (0.16 to 0.87)	0.03	0.06	0.55 (0.17 to 1.76)	0.01	0.05	0.16 (0.06 to 0.43)
H60-H95	0.01	0.01	1.18 (0.18 to 7.87)	0.00	0.01	0.00 (0.00 to 0.00)	0.00	0.01	0.00 (0.00 to 0.00)
I00-I99	3.48	3.94	0.88 (0.49 to 1.59)	12.90	3.72	3.46 (2.73 to 4.40)	11.30	3.50	3.23 (2.05 to 5.09)
J00-J99	1.65	1.11	1.48 (0.49 to 4.42)	6.95	1.07	6.53 (3.94 to 10.81)	3.88	1.02	3.82 (2.12 to 6.87)
K00-K93	1.75	0.43	4.03 (1.50 to 10.85)	0.41	0.39	1.08 (0.60 to 1.93)	0.37	0.34	1.07 (0.53 to 2.18)
L00-L99	0.09	0.08	1.10 (0.40 to 3.04)	0.21	0.07	3.12 (0.47 to 20.74)	0.07	0.07	1.06 (0.40 to 2.79)
M00-M99	0.96	0.75	1.27 (0.57 to 2.85)	0.71	0.68	1.04 (0.48 to 2.22)	0.87	0.63	1.38 (0.77 to 2.48)
N00-N99	0.53	0.48	1.12 (0.55 to 2.25)	1.24	0.46	2.68 (1.66 to 4.31)	0.65	0.40	1.63 (0.90 to 2.93)
R00-R99	1.00	0.71	1.40 (0.71 to 2.75)	0.49	0.67	0.73 (0.41 to 1.28)	0.66	0.63	0.05 (0.44 to 2.52)
S00-T98	2.42	1.19	2.03 (1.17 to 3.52)	51.46	1.09	47.05 (35.21 to 62.88)	8.48	1.04	8.16 (5.94 to 11.21)
<i>S00-T14</i>	<i>2.30</i>	<i>1.00</i>	<i>2.29 (1.25 to 4.19)</i>	<i>49.77</i>	<i>0.93</i>	<i>53.69 (38.78 to 74.34)</i>	<i>7.44</i>	<i>0.87</i>	<i>8.54 (5.96 to 12.33)</i>
Z00-Z99	0.29	0.47	0.61 (0.34 to 1.11)	2.25	0.43	5.22 (3.68 to 7.41)	1.16	0.40	2.91 (0.99 to 8.57)

[†] adjusted for age and gender

6. DISCUSSION

6.1 Medication use and risk of falls

Twenty-eight observational studies and one RCT were included in the systematic review (Study I). The primary outcome was a fall in 17 studies and a fall-related injury in 12 studies. Falls were monitored prospectively in 11 studies. A systematic classification of drugs was used in 11 studies, but still in many studies, drugs or drug groups were defined incompletely. Duration of therapy was addressed in eight studies and dosage in six studies. With respect to potential confounding factors, all the studies were controlled for age and gender. The confounding effect of one or more chronic conditions was assessed in two-thirds of the studies and concomitant use of other medications in half of the studies.

Based on their systematic review of original articles published from 1966 to 3/1996, Leipzig and colleagues were critical that the evidence linking drugs with falls in older people was based solely on observational data, with minimal adjustment for confounders, dosage, or duration of therapy (84,86). Though controlled trials are the gold standard for identifying the risks associated with drug use, few RCTs have been conducted since the review published by Leipzig et al. In this context, however, it must be noted that controlled clinical trials use often very narrow selection criteria and may, therefore, underestimate the true prevalence of drug-related adverse events. Using strict patient selection criteria may also restrict the generalizability of the findings. Compared to the previous literature (84,86), some improvement in controlling for confounders was seen in the studies of the present review. Nevertheless, assessment and control for confounding factors, and confounding by indication in particular, pose considerable challenges in designing epidemiological studies and analyzing the data (357). Users of a specific drug are likely to differ from nonusers, and confounding by indication makes it difficult to ascertain whether the relationship between falls and medication is due to the actual drug, or the indication for its use. Despite their limitations, observational studies are often the only option for assessing drug safety in larger scale, i.e. at population level, among older adults and in real clinical situations.

In the present systematic review, benzodiazepines increased the risk of falling in older people. The vast majority of the reviewed studies concerning this drug group

found a small to moderate, but consistent, association between the use of benzodiazepines and falls. Furthermore, the present meta-analysis showed that the use of benzodiazepines was also associated with an increased risk of hip fracture.

Adverse effects of benzodiazepines can contribute to falls in older adults. Benzodiazepines have negative effects on cognition, reaction time, gait, and balance (204). Furthermore, pharmacokinetics and -dynamics of these drugs change with age. The elimination half-life and duration of action is prolonged (83), and the concentration need to cause sedation decreases substantially with advanced age (358,359).

The present findings on benzodiazepines and falls are in concordance with those of Leipzig et al. (84). Four more recent studies (Table 3) have also reported that benzodiazepines increase the risk of falling (25,89,91,96). On the other hand, anxiolytics or hypnotics were not related to falls in three recent studies (93,94,97). With regard to confounding by indication, Avidan et al. reported that insomnia, but not hypnotic use, was associated with a greater risk of subsequent falls (94). Their study was based on a large US nursing home cohort in which the prevalence of hypnotic use was enviable low, 2.5% (94). Stone et al. measured sleeping time in a cohort of older women and found that short and fragmented sleep was associated with falls, independent of benzodiazepine use and other risk factors for falls (360). In these two studies the follow-up lasted for six to twelve months, but exposure to risks was assessed at the baseline only. Thus, it was not known whether or not either of the target variables (insomnia, drug use) was present at the time of falling. Nevertheless, it is plausible that sleeping problems and daytime tiredness may contribute to falling. Sleeping pills may offer a temporary relief, but they do not solve the problem, neither are they effective in long-term use nor free from adverse effects.

Antidepressant use was related to an increased risk of falls in the systematic review of Leipzig et al. (84). At that time, only one of the reviewed studies concerned SSRIs (85). Although it suggested that SSRIs may increase the risk of falls even more than the tricyclic antidepressants, the possibility of selection bias was speculated, i. e. SSRIs might have been preferentially prescribed to patients at high risk for falls. Thereafter several observational studies have reported that SSRIs are associated with an increased rate of falls (Study I, Figure 2). SSRIs and TCAs have similarities in their risk profiles through which they can contribute to falling. Both classes increase serotonin levels and can cause serotonin syndrome when used in higher doses or

concomitantly with other serotonergic drugs (361). They can also provoke inappropriate antidiuretic hormone secretion and hyponatremia (362,363). Though the cardiovascular safety of SSRIs is better than that of TCAs (364), SSRIs may exhibit cardiovascular depressant effects by inhibiting sodium and calcium channels (365).

With regard to confounding by indication, two observational studies have measured depressive symptoms at the time of falling, and found that antidepressants, SSRIs in particular, were independently associated with falls (97) and the association was stronger for the treatment than disease (366).

Antidepressants were also associated with a higher rate of hip fractures. In the present meta-analysis, the pooled risk for hip fractures was 1.82. Besides increasing the risk of falling, SSRIs may also have negative effects on bone metabolism and BMD (214,215).

There is evidence to suggest that antipsychotic drugs may be associated with falls in older people. Several studies confirming this association were presented in the present and previous systematic review (84). Older people tend to experience side-effects from antipsychotics more frequently and with greater severity than younger people, and drug's receptor binding characteristics determine largely the side-effects (367). Extrapyramidal symptoms due to dopaminergic-blocking are important and frequent adverse events of antipsychotics, and frail older people are more prone to such complications (368). In addition, antipsychotics have a number of other fall-contributing adverse effects including sedation, orthostatic hypotension, and anticholinergic effects such as blurred vision, cognitive impairment, and confusion (367). New atypical antipsychotics, such as risperidone, quetiapine and olanzapine, are associated with fewer side-effects, extrapyramidal symptoms in particular, than typical antipsychotics (369). In terms of falls, however, the documentation of their safety is still vague. Only two studies in the present systematic review concerned new atypical antipsychotics. Thereafter two studies have reported that new atypical medications were not associated with fewer falls than the older typical antipsychotics (25,93). This may be a matter of dosage. With increasing doses, the incidence of extrapyramidal adverse effects is higher and approaches that of the typical antipsychotics (368). Unfortunately, the studies referred above did not assess the impact of dosage on the risk of falling. Hence, further research is needed on the relative safety of new atypical antipsychotics in older people. Especially, when

prescribing antipsychotics for behavioral and psychological symptoms of dementia, physicians need to consider whether the benefits outweigh the risks (93).

With regard to cardiovascular drugs and falls, the present systematic review does not provide sound evidence to guide clinical practice. In most of the reviewed studies, no significant association was found between the use of cardiovascular drugs and falls. However, this does not mean that assessing an older patient's cardiovascular medications is unnecessary to prevent falls. On the contrary, in a recent falls prevention study, the effect of cardiovascular drug optimization was greater than that of psychotropic drug optimization (290). Especially, fallers with low blood pressure or orthostatic hypotension need to have a cardiovascular drug assessment.

Polypharmacy may increase the risk of falls. Leipzig et al. reported that older adults taking more than three or four medications were at increased risk of recurrent falls (86). Today's evidence based guidelines recommend several drugs for the treatment of a single condition, and comorbidity is frequently present as the population is steadily growing older. Hence, polypharmacy defined as use of more than three or four drugs covers nearly all our older people, and does not help to identify those at risk of falling. However, polypharmacy defined as use of six or more drugs and especially excessive polypharmacy (≥ 10 drugs) (370,371), can be seen as markers of increased fall risk. In a nursing home population, polypharmacy and excessive polypharmacy were associated with a four- to five-times increased risk of falls (372). The probability of drug interactions increases with an increasing number of medications, and polypharmacy often involves use of one or more psychotropic drugs (370). Further, polypharmacy can be a marker of existing but unrecognized health problems, such as poor disease control, progression of the underlying diseases, or new disease.

6.2 Incidence of hip fractures

In 2002-03, the population of the study area was 239 000 and 597 hip fractures occurred in the individuals living there. The hip fracture patients were predominantly women (70%) with a mean age of 82 years. Four fifths of the patients were living in their own homes or sheltered housing. The vast majority of fractures occurred indoors (79%), with low-energy mechanism (96%), and between six am and ten pm (78%). Cervical hip fractures constituted three fifths of all the fracture cases. The hip fracture

rates were higher for women than men. This discrepancy, however, was largely explained by age; women live longer and reach the “hip fracture age”.

In Central Finland between the years 1982-83 and 1992-93, the total number of hip fractures rose by 11% with no significant changes in the age-adjusted or age-specific hip fracture incidence (139). Between the years 1992-93 and 2002-03, the total number of hip fractures increased by 70%; for women the increase was 65% and for men 85%. Also the age-adjusted incidence of hip fractures increased, i.e. the rate was greater than expected by population aging. In the population aged 55+ years, the average age-adjusted increase was 36% for men and 25% for women. The gender- and age-specific changes were the greatest for men aged 75 to 84 years and women aged 85+ years.

There was also a small increase in the proportion of trochanteric and subtrochanteric fractures. Though most fractures still were cervical, their percentage decreased with age, and among the oldest patients the proportion of trochanteric and subtrochanteric fractures exceeded that of the cervical fractures. Compared to cervical hip fractures, trochanteric fractures are associated with more osteoporotic bone (373,374).

In the present study and the earlier study by Huusko et al. (139), the incidences were determined based on two-year hip fracture rates. The methodology of these two studies is similar and the comparability of findings should be good. These studies, however, are “cross sectional” rather than incidence trend analyses. Nevertheless, the age adjusted incidence rate of hip fractures was higher in the later period.

Kannus et al. have investigated nationwide hip fracture incidence trends in Finland over a long period of consecutive years (5,137). The incidence showed a steady increase between 1970 and 1997. In 1998 - 2004, leveling off and signs of declining incidence trend were observed particularly in women. The exact reasons for the observed trend break were unknown. The authors discussed that the cohort effect toward healthier older populations was one possible explanation. An increased average body weight could also be protective against hip fractures. Since the 1980's, BMI and prevalence of obesity have increased in all adult age groups of the Finns (375). A third possible explanation was improved functional ability of older people (376) and thereby reduced risk for falling and fractures. Healthier life style, e.g. exercise and non-smoking policy, may prevent falls and promote bone health. Also more specific actions to prevent and treat osteoporosis, such as use of calcium,

vitamin D, HRT and bone-specific antiresorptive drugs, could start to show their positive effects on the hip fracture risk (5). Last but not least, interventions to prevent falls, such as strength and balance training, reduction of psychotropic drugs, correction of visual impairment, modification of environmental hazards and use of gait stabilizing devices, could have been behind the positive development. The authors concluded, that the coming years will show whether the favorable trend in the incidence of hip fractures continues, and even if it does, the absolute number of hip fractures is still likely to increase because of the population aging.

In Central Finland, the hip fracture incidence rates have remained high during the recent years (138), and in 2002-03 the age adjusted incidence still exceeded the 10-year earlier level. Hence, more efforts are needed to implement and maintain the preventative strategies and interventions described above.

6.3 Second hip fractures

In order to assess the incidence of second hip fractures, 501 hip fracture patients aged ≥ 60 years were followed up at least for two years. The rate of second hip fractures was one per 20 person-years at the end of the first postfracture year and one per 12 py at two years. The age adjusted incidence of second hip fractures was similar for men and women. None of the characteristics measured at the time of first hip fracture was a significant predictor for the subsequent fracture, suggesting that the risk factors for the first and second hip fractures were largely the same. Even though psychotropic drugs are known to impair gait and balance and increase the risk of falling and hip fractures, their use became more common between the first and second hip fractures. Daily use of any psychotropic drug rose from 36% to 59%, and the concomitant use of two or more psychotropics doubled.

The first-year cumulative incidence of second hip fractures was 5.1% in the present study. Two population-based studies and one cohort study have reported lower rates: 1% (175) 3.8% (177) and 2.5% (182). However, differences in age, mortality and inclusion criteria may limit direct comparability of the incidence rates. Also secular changes may affect the incidence if the participants are enrolled over a long period of time, like in the study of Melton et al. (175) and in the Framingham study (182).

The present study confirmed the finding that the age adjusted incidence of second hip fractures is similar for both genders (177,178,179). We did not find predicting

factors for second hip fractures, but several risk factors have been found in other studies. Older age, cognitive impairment, lower bone density, impaired depth perception, impaired mobility, previous falls, dizziness and poor or fair self-perceived health have been associated with an increased risk for second hip fracture (226). High functional status has also been reported to be a risk factor for hip fracture recurrence (182). Better functional status improves survival and recovery after the initial fracture, but without any interventions, it may also represent increased opportunities for future falls and fractures.

The present study evaluated the use of psychotropic drugs, calcium and vitamin D supplements, and antiresorptive drugs in patients with sequential hip fractures. Use of psychotropic drugs increased substantially after the initial fracture, whereas osteoporosis was diagnosed in less than a fifth of the patients and treated even less frequently. As a limitation, the present study does not provide data on the medication use in patients who fractured their hips only once. Yet, the treatment of osteoporosis after hip fracture has been described in other studies. Studies from Canada, US and Finland reported undertreatment: 18 to 39% of patients received pharmacologic therapy for osteoporosis after hip fracture (377-379). Thus far, there are no studies on antiresorptive drugs in secondary prevention of hip fractures, probably because this kind of study is challenging to conduct. A sample size of 5000 would be needed to achieve adequate statistical power trial (380) and there might be problems with placebo controlled design. Zoledronic acid has been studied in 2127 patients with hip fracture (339). The reduction of second hip fractures was statistically non-significant, but the rate of new vertebral and peripheral fractures and also mortality decreased significantly. Good adherence to osteoporosis treatment is important, especially in the secondary prevention, and once yearly dosing may help to reach this goal.

The time frame between sequential hip fractures is relatively short. The risk for second hip fracture is highest within a few months after the initial fracture, and approximately a half of the fractures occur within one to two years (177,178). Thus, prevention of a new fracture event has to be started immediately and falls prevention is of particular importance. Early comprehensive assessment, skilled multidisciplinary care and rehabilitation, patient centered and individually tailored falls and fracture prevention, and safe discharge are recommended for the postoperative management of hip fracture patients (192,198). After hospitalization, continuity of care and

rehabilitation and long-term follow-up should be ensured. In this context, it means more than prescription drugs, domestic help, and meals on wheels.

6.4 Mortality after hip fracture

One-third of the ≥ 70 -year-old hip fracture patients died during the first postfracture year. The steepest decrease in survival was seen within the first month following the fracture. Nearly one-fourth of the first-year deaths occurred during the primary stay in the Central Finland Hospital. One-year mortality was three times higher in the hip fracture group than in the same-aged general population. Excess mortality was highest in the age group of 70-74 years and decreased towards the older age groups. This may reflect that morbidity differences between hip fracture patients and the general population were greater in the younger age-groups.

Huusko et al. reported that the first-year mortality after hip fracture remained unchanged between the early 1980's and early 1990's (243), neither did it change during the next decade. Death rates similar to ours have also been reported in the UK; in Oxford (1984-1998) and in Nottingham (1999-2003) the one-year death rates were 30.7% and 33%, respectively (245,250). The rate was lower, 19% at one year, in a study including community-dwelling older people only (248).

Compared with conventional care after hip fracture, better survival and functional outcome has been gained by centralized geriatric rehabilitation (244,381). Despite of these encouraging findings, such a care model was not in routine use in the Central Finland Health Care District. Excluding those who were discharged directly to their homes or died during their primary stay in the ward of traumatology ($n=61$), over 90% of the hip fracture patients were transferred to the primary care wards of their home municipalities. Probably a part of the early postoperative deaths could be prevented by improving the regimens of perioperative care and the availability of experienced staff, especially during weekends and holidays (382,383).

The standardized mortality ratio reflects excess mortality in relation to deaths in a given control population. A previous study with stringent inclusion criteria reported that hip fractures were not associated with significant excess mortality among patients older than 85 years when compared with the death rate in the general population (263). In the present study, the mortality rates in each age group were substantially

higher among the fracture patients than in the general population. Furthermore, it has been suggested that otherwise healthy and fit patients do not have increased mortality subsequent to hip fracture (384), neither do they sustain the fracture frequently; 2% of our patients had no chronic conditions.

In conclusion, mortality after hip fracture has remained almost unchanged during the last 20 years in Central Finland. One-third of older hip fracture patients die within the first year following the fracture, and nearly a half of the one-year deaths occurred within the first month postfracture. One-year mortality of hip fracture patients was three-times that of the same-aged general population. Excess mortality was dependent on age; it was highest among the youngest hip fracture patients and decreased linearly with advancing age.

6.5 Hospitalizations after hip fracture

Few studies (240) have addressed the possible impact of hip fracture on the utilization of inpatient care at a population level. This is probably due to the difficulties in gaining adequate data on hospitalizations covering entire populations. Fortunately, the Finnish nationwide hospital discharge register provides sufficiently comprehensive information on hospital episodes, i.e. the register covers all inpatient care episodes in hospitals and primary care wards, as well as patient's age, sex, place of residence, and the primary cause for hospitalization. In addition, the quality of the register data is monitored constantly and its validity, preciseness and usefulness for research purposes are known to be good (385-387).

In regard to hospitalizations among older people, cardiovascular diseases were the leading cause for bed days and accounted for one-fourth of all inpatient days in the 70+ population of Central Finland. Mental and behavioral disorders were the second leading cause and resulted in one of every six hospital days. Injuries, poisonings and certain other consequences of external causes were the third most important diagnostic class accounting for one in every 12 bed days. The vast majority of these days were due to injuries. Thus, measured by hospital days, injuries are a major public health concern among older people.

The effects of hip fracture on the utilization of inpatient care were assessed by evaluating hospital days in the hip fracture group and general population. Hospital days in the prefracture year were used as a measure of baseline comorbidity. The

difference in the inpatient care utilization was relatively small in the prefracture year; the number of age- and gender-adjusted hospital days per person-year was 30% higher for the future hip fracture patients than for the general population. In the first postfracture year the number of hospital days was nearly seven times higher in the hip fracture group than in the general population. In the second postfracture year, it was still 3.6-fold, despite the fact that the first-year mortality after hip fracture had been high and presumably concentrated on the frailest patients.

The utilization of inpatient care was also assessed by specific disease classes. In the prefracture year, the age-adjusted hospital days per py due to diseases of the digestive system and injuries were more prevalent in the hip fracture group than in the general population. It is possible that these conditions could predispose towards hip fracture. Diseases of the digestive system may cause malnutrition and low body weight, and previous falls and low-trauma fractures predict future fragility fractures, i.e. low body weight and a history of osteoporotic fractures are known risk factors for hip fracture (192, 198).

In the first postfracture year, the substantial excess of hospital days attributable to injuries represented predominantly initial hospitalizations for hip fractures. In Finnish studies, the average length of hospital stay for hip fracture has been six to seven weeks (230,231). Hospital days in the hip fracture group exceeded the population levels also in six other ICD-10 classes (Table 12). Rehospitalizations after hip fracture are common; 18% of patients were readmitted within 30 days after the initial discharge (236), and at six months, the readmission rate was 32% (237). Cardiac, neurological and chronic pulmonary diseases and infections (e.g. pneumonia, sepsis and urinary tract infections) were among the commonest causes for rehospitalizations (236,237).

In the second postfracture year, the days due to injuries were still over-represented in the hip fracture group. Hip fracture is a significant risk factor for subsequent fractures (388,389). The risk is highest immediately after the fracture and remains elevated for a lengthy period. In the second postfracture year, the hospital days due to mental and behavioral disorders and diseases of the nervous, circulatory and respiratory systems still exceeded the prefracture and population levels.

Hence, hip fracture was associated to significantly greater use of inpatient care that persisted at least for two years after the fracture event. An excess of hospital days was

seen in several diagnostic classes indicating that hip fracture as a major trauma can exacerbate existing comorbidities and launch a cascade of new impairments.

6.6 Clinical recommendations

More attention should be paid to the prevention of falls and fall-related fractures in older people. As population-level strategies, strength and balance training, sufficient intake of calcium and vitamin D, smoking cessation, and injury prevention campaigns should be promoted. All healthcare professionals who work with older people should know common risk factors for falls and commit themselves to screen for falls risk, at least simply by asking about falls. Those at high risk of falling, i.e. older people who present for medical attention because of a fall, report recurrent falls, or have gait or balance problems should receive comprehensive evaluation by a clinician with appropriate skills and experience. Specialist consultations should also be available.

Medication review is a part of the falls risk assessment. The Finnish Ministry of Social Affairs and Health recommends that every older individual with one or more chronic conditions have an annual comprehensive medical assessment including medication review. Falls risk assessment is compatible with this concept. An assessment must be followed by appropriate interventions. Individually tailored interventions delivered by a multidisciplinary team of health care professionals have been shown to be most effective.

There may be a tendency for physicians and their patients to perceive falls as secondary and non-medical issues. Overcoming this perception will require a change of attitudes. Falls in older people should be considered as markers of impaired health and functional status. Falls can also be drug related adverse events, and they are a warning sign for impending injuries. To prevent low-trauma fractures, assessment of osteoporosis risk is needed. The use of the Frax[®] tool may assist in screening and clinical decision making. Pharmacotherapy for osteoporosis has its place in the primary and secondary prevention of fractures, but pharmacotherapy alone is not sufficient. Pharmacotherapy should be combined with fall prevention strategies. The majority of peripheral fragility fractures are fall-induced, and fractures may still occur even though BMD T-scores are above -2.5 SD.

The high death rate and number of hospital days after hip fracture raise the question: could we do better? We have a good national practice guideline for

treatment of patients with hip fracture but the implementation is not sufficient. There is room for improvement in the perioperative management and postoperative care and rehabilitation of hip fracture patients. Currently, the postoperative care and rehabilitation of hip fracture patients is fragmented though these patients are critically ill and would need special attention. It may be unrealistic to expect that every primary care ward has the resources and specialist knowledge to treat these high-risk patients. Centralized, intensive and multidisciplinary postoperative care and rehabilitation might lead to better results, and even cost-benefits.

6.7 Future research

More information is needed about the effects of medication optimization on the risk of falls and fall-related fractures in older people. The medication optimization process should be structured and guided by research evidence or expert consensus statements. Furthermore, practical tools should be developed to facilitate and improve medication assessment in clinical practice.

The methods used in this study for assessing the incidence of hip fractures were rather laborious. More efforts should be directed towards improving the usability of routinely collected administrative data on hip fractures. The national discharge register is a valuable data source for monitoring hip fracture incidence, but further validation is needed to improve its accuracy and usability. The present incidence data could be used for such a validation project. Optimally, the impact of falls and fracture prevention programs could be monitored using register-based data. In addition to hip fractures, the incidence of other serious fall-related injuries should be easily monitorable.

Finally, it seems that our health care policymakers are not yet convinced that intensive care and rehabilitation of hip fracture patients could lead to better outcomes. Maybe this concerns also health care professionals. Therefore clinical intervention studies on the care of hip fracture patients should be promoted. These studies may investigate which patients benefit the most and what are the specific components and exact contents of successful rehabilitation. Clinical feasibility and implementability should be of special interest when designing intervention studies. Proper post-intervention follow-up and cost analysis should be promoted as well.

7. CONCLUSIONS

1. The systematic review of recently published studies showed that the current evidence on medication use and risk of falls is mainly based on observational studies, and many of them have methodological deficiencies. More randomized controlled trials are needed, and falls as an adverse effect should be included in the protocol of the clinical trials of medicines intended for elderly persons. CNS medicines, especially psychotropic drugs, are associated with an increased risk of falls in older people. In particular, the use of benzodiazepines or antidepressants, including SSRIs, was consistently associated with an increased risk of falls in older people. These drugs were also associated with a nearly two-fold risk for hip fracture.
2. The majority of patients with hip fracture were community-dwelling older women, and most of the hip fractures occurred indoors with a low-energy trauma mechanism, such as a fall on same level. The location of fracture was cervical in most cases, but the proportion of trochanteric and subtrochanteric hip fractures increased with age and exceeded that of the cervical fractures in the oldest old. The number of hip fractures almost doubled in Central Finland between the years 1992-93 and 2002-03. The incidence of hip fractures increased in both genders, and the accretion was more than could be explained merely by demographic changes.
3. The recurrence rate of hip fractures was rather high. The cumulative incidence of second hip fractures was 5% at one year after the initial fracture and 8% at two years. Among patients with sequential hip fractures, psychotropic drugs were commonly used even though they are known to impair gait and balance control and increase the risk of falling and fall-related fractures. The use of psychotropics increased after the first hip fracture. In contrast, the use of calcium, vitamin D and antiresorptive drugs was often overlooked in these high risk patients.
4. Mortality after hip fracture was high. One third of ≥ 70 -year-old hip fracture patients died within the first year following hip fracture. The death rate was

three-fold that of the same-aged general population. At two years after hip fracture the overall mortality was 42%, and as high as 55% in the male patients. The evaluation of hospitalizations in the 70+ population showed that hip fractures were also associated with a substantial increase in the utilization of inpatient care. Hospital days in several diagnostic classes increased and still exceeded both the prefracture and population levels in the second postfracture year. A hip fracture can far exceed the restricted reserve capacity of an older person and predispose to worsening of pre-existing comorbidities and the onset of new diseases.

8. SUMMARY IN FINNISH – SUOMENKIELINEN YHTEENVETO

Tutkimuksen lähtökohdat

Suurin osa ikääntyneiden tapaturmista syntyy kaatumisen seurauksena. Noin kolmannes kotona asuvista ja yli puolet laitoksissa asuvista yli 65-vuotiaista kaatuu vuosittain ainakin kerran. Kaatumisille altistavat monet ikääntymiseen ja sairauksiin liittyvät tekijät. Myös lääkkeiden aiheuttamat haitat voivat lisätä kaatumisvaaraa.

Kaatumisvammoista vakavimpia ovat reisiluun yläosan murtumat. Lonkkamurtumat lisäävät sairastavuutta ja kuolleisuutta sekä aiheuttavat toimintakyvyn laskua. Murtuman hoidosta ja toimintakyvyn heikkenemisestä aiheutuvat kustannukset ovat myös merkittäviä. Lonkkamurtumien ilmaantuvuus nousee iän myötä, joten väestön vanhetessa kaatumisten ja kaatumisiin liittyvien murtumien ehkäisyn merkitys korostuu entisestään.

Tavoitteet

Tämä väitöskirjatyö koostuu systemaattisesta kirjallisuuskatsauksesta ja lonkkamurtumien epidemiologiaa käsittelevästä väestötason tutkimuksesta. Systemaattisessa kirjallisuuskatsauksessa selvitettiin lääkkeiden käytön ja kaatumisten sekä lonkkamurtumien välistä yhteyttä ikääntyneillä ihmisillä. Epidemiologisen tutkimuksen tavoitteena oli lonkkamurtumien kokonaisilmaantuvuuden ja lonkan uusintamurtumien ilmaantuvuuden määrittäminen sekä lonkkamurtumien jälkeisen sairaalahoidon käytön ja kuolleisuuden selvittäminen keskisuomalaisessa väestössä.

Menetelmät

Lääkkeitä kaatumisten ja lonkkamurtumien vaaratekijöinä selvittäneen systemaattisen katsauksen kirjallisuushaku koski vuosina 1996-2004 julkaistuja englanninkielisiä alkuperäistutkimuksia. Valintakriteerit täyttäneet artikkelit analysoitiin tutkimuspopulaation, -asetelman, käytettyjen metodien, kohdelääkkeiden ja tulosten suhteen. Lonkkamurtumien ja bentsodiatsepiinien sekä masennuslääkkeiden käytön välistä yhteyttä selvittäneistä tutkimuksista tehtiin meta-analyysi.

Epidemiologinen työ koski Keski-Suomessa vuosina 2002 ja 2003 sattuneita lonkkamurtumia. Lonkkamurtumapotilaiden tunnistamiseen käytettiin Keski-Suomen keskussairaalan hoitojaksorekisteriä, leikkausyksikön tietokantaa ja päivystysleikkauslistoja. Lonkkamurtumadiagnoosin oikeellisuus ja murtumatyyppi varmistettiin sekä kliiniset tiedot kerättiin potilaiden sairauskertomuksista. Lonkkamurtumiksi luettiin reisiluun kaulan ja trokanteerisen sekä subtrokanteerisen alueen murtumat.

Potilaita seurattiin kuolemantapausten ja lonkan uusintamurtumien suhteen vuoden 2005 loppuun. Uusintamurtumapotilaiden ensimmäistä ja toista lonkkamurtumaa edeltävä lääkehoito kartoitettiin poikkileikkaustyyppisesti. Lonkkamurtumapotilaiden ja alueen väestön sairaalahoitopäivien käyttö ja hoitojaksojen päädiagnoosiryhmät selvitettiin valtakunnallisesta hoitoilmoitusrekisteristä.

Tulokset

Systemaattinen katsaus käsitti 29 alkuperäistutkimusta, joista vain yksi perustui satunnaistettuun ja kontrolloituun tutkimusasetelmaan. Tutkimusmenetelmissä ja sekoittavien tekijöiden hallinnassa todettiin puutteita, joskin ne olivat vähäisempiä kuin aiempaa kirjallisuutta analysoineessa katsauksessa oli havaittu. Useissa tutkimuksissa todettiin psyykenlääkkeiden käytön ja kaatumisvaaraan välinen yhteys. Yhtenäisintä tutkimusnäyttöä oli bentsodiatsepiinien ja masennuslääkkeiden osalta. Kaatumisten suhteen SSRI-ryhmän masennuslääkkeet eivät osoittautuneet trisyklisiä valmisteita turvallisemmiksi. Lonkkamurtumat olivat bentsodiatsepiinien ja masennuslääkkeiden käyttäjillä lähes kaksi kertaa yleisempiä kuin näitä lääkkeitä käyttämättömillä ikääntyneillä henkilöillä.

Vuosina 2002-2003 keskisuomalaisessa väestössä sattui 597 lonkkamurtumaa. Murtumien kokonaismäärä nousi 70 %:lla kymmenen vuoden takaiseen tilanteeseen nähden. Myös lonkkamurtumien ikävakioitu ilmaantuvuus suureni molemmilla sukupuolilla. Tyypillinen lonkkamurtumapotilas oli yli 80-vuotias kotona asuva nainen, ja yleisin lonkkamurtumaan johtava vammamekanismi oli kaatuminen sisätiloissa.

Lonkan uusintamurtumien kumulatiivinen ilmaantuvuus oli 5 % vuoden ja 8 % kahden vuoden kuluttua ensimmäisestä lonkkamurtumasta. Ensimmäisen murtuman yhteydessä määritetyistä muuttujista ei löytynyt toista lonkkamurtumaa ennustavia

tekijöitä. Samat vaaratekijät saattoivat näin ollen vaikuttaa sekä ensimmäisen että toisen lonkkamurtuman syntyyn. Psykykenlääkkeiden käyttö kuitenkin yleistyi ensimmäisen lonkkamurtuman jälkeen. Ensimmäisen lonkkamurtuman aikaan 36 % potilaista käytti jotain psykykenlääkettä. Toisen murtuman aikaan käyttäjiä oli 59 %. Bentsodiatsepiinit olivat yleisimmin käytetty psykykenlääkeryhmä. Osteoporoosilääkkeen, kalkin ja D-vitamiinin yhdistelmää toisen lonkkamurtuman saaneista potilaista käytti 9 %.

Yli 70-vuotiaiden lonkkamurtumapotilaiden kuolleisuus oli korkea. Kuukauden kuluttua lonkkamurtumasta 15 % potilaista oli kuollut ja vuoden kohdalla kuolleisuus oli 33 %. Murtumapotilaiden kuolleisuus oli kolminkertainen alueen samanikäisen väestön kuolleisuuteen verrattuna.

Murtumaa edeltävänä vuotena tulevat lonkkamurtumapotilaat käyttivät sairaalahoitopäiviä 30 % enemmän kuin samanikäinen väestö. Ensimmäisenä lonkkamurtuman jälkeisenä vuotena ero oli seitsenkertainen. Toisena lonkkamurtuman jälkeisenä vuotena lonkkamurtumapoitilaiden hoitopäivien määrä oli yli kolminkertainen väestöön nähden. Tapaturmasta johtuvien hoitopäivien lisäksi usean muun sairausryhmän hoitopäivät ylittivät väestön hoitopäivien käytön sekä ensimmäisenä että toisena murtuman jälkeisenä vuotena.

Päätelmät

Lonkkamurtuma on vakava tapaturma, joka usein ylittää ikääntyneen ihmisen reservikapasiteetin ja lisää sairastavuutta sekä kuolleisuutta merkittävästi. Aiemmistä tutkimuksista tiedetään, että lonkkamurtumapotilaiden ennustetta voidaan parantaa tehostetulla ja keskitetysti toteutetulla moniammatillisella hoidolla ja kuntoutuksella, vieläpä lisäämättä hoidosta koituvia kokonaiskustannuksia. Hajautetun hoidon malli oli kuitenkin edelleen vallitseva. Lyhyen perioperatiivisen hoitajakson jälkeen potilaat siirrettiin kotipaikkakuntiansa terveyskeskusten vuodeosastoille. Lonkkamurtumapotilaiden hoidossa ja kuntoutuksessa on parantamisen varaa. Murtumien ehkäisyä ajatellen kaatumisvaarassa olevien ikääntyneiden tunnistaminen ja aktiivinen vaaratekijöihin puuttuminen ovat avainasemassa. Säännöllinen lääkityksen arviointi on tärkeä osa tätä prosessia.

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ORIGINAL PUBLICATIONS I - IV

I

Hartikainen S, Lönnroos E, Louhivuori K.

Medication as a risk factor for falls: critical systematic review.

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II

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III

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IV

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