Hip fracture - Mortality and residual lifetime risk of fractures

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My von Friesendorff
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Abstract

Hip fracture is the most severe clinical manifestation of bone fragility, associated with multi-cause morbidity and high early mortality. Improved knowledge of long-term outcome is essential in developing future care and prevention of new fractures.

In this thesis, all hip fracture patients during 1984-1985 in Malmö, Sweden (766 women, 263 men) were followed within a remaining lifetime perspective to a maximum of 26 years and compared with a background population matched for age and sex.

At all ages and in both sexes, hip fracture patients had a higher mortality compared to the controls. Excess mortality was highest during the first year, but persisted for at least 20 years. The most common cause of death was cardiovascular disease, with a 50% risk increase in both female and male hip fracture patients.

Despite shorter survival, patients were more at risk of new fractures; most pronounced in the younger patients (<75 years). Almost half of all female and one third of male hip fracture patients suffered new fractures during their remaining lifetime. Women more often fractured on multiple occasions, while men suffered a single fracture. The mortality adjusted remaining lifetime risk of fractures was 85% in females and 62% in males. The most common subsequent fractures were those of the hip and vertebrae. Hip fracture patients were at higher risk of suffering yet another hip fracture.

These findings highlight the necessity of taking into consideration sex and age in hip fracture patients when determining how to best improve short and long term outcomes and prevention of subsequent fractures.

Key words: hip fracture, women, men, age, survival, mortality, subsequent fracture, fracture risk, residual lifetime, long term, cause of death

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Hip fracture

Mortality and residual lifetime risk of fractures

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The cover illustration shows a conventional X-ray of the pelvic region with an old intertrochanteric hip fracture operated on with a sliding hip screw on one side and a new untreated intertrochanteric hip fracture on the other side.

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Ju mer man tänker, desto mer inser man att det inte finns något enkelt svar.

Nalle Puh

To Ingrid and Jan, my parents

Contents

List of Publications

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

I. My von Friesendorff, Jack Besjakov, Kristina Åkesson. Long-term survival and fracture risk after hip fracture: A 22-year follow-up study in women. Journal of Bone and Mineral Research 2008;11:1832-41

II. My von Friesendorff, Fiona McGuigan, Jack Besjakov, Kristina Åkesson. Hip fracture in men – survival and subsequent fractures in a remaining lifetime perspective. Submitted.

III. My von Friesendorff, Fiona McGuigan, Cecilia Rogmark, Anthony D Woolf, Kristina Åkesson. Early and long-term mortality and cause of death after hip fracture – a case-control study over 22 years. Submitted.

IV. My von Friesendorff, Fiona McGuigan, Jan-Åke Nilsson, Anna H Holmberg, Kristina Åkesson. Lifetime risk of new fractures after hip fracture – a case-control study in 1029 hip fracture patients over 26 years. In manuscript.

Abbreviations

The following abbreviations, listed in alphabetic order, are used in this thesis:

BMD	Bone Mineral Density
BMI	Body Mass Index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DXA	Dual X-ray Absorptiometry
EpC	Centre for Epidemiology, National Board of Health and Welfare, Sweden
GI	Gastrointestinal disease
HR	Hazard ratio
ICD	International Classification of Diseases
QCT	Quantitative computed tomography
RR	Relative risk or Rate ratio
SCB	National Statistics Bureau, Sweden
SD	Standard deviation
T-score	Mean value of peak BMD in a population
WHO	World Health Organisation

1 Introduction

Osteoporosis and its clinical consequence of fracture constitute a major public health problem and which is expected to increase globally [1]. Hip fracture, the most devastating outcome of osteoporosis, is associated with increased mortality, morbidity and a high financial burden. The costs are due to the need for surgery, often requiring extended hospital stay; a high risk of post-op complications; and a need for extensive post-fracture care, rehabilitation and services from the social sector. In Sweden the first year cost of a hip fracture amounts to 140,000 SEK [2].

Hip fractures are common, and the knowledge base on epidemiology, aetiology and treatment has increased over the past decades. However, hip fracture patients are often considered as a single entity without fully taking into account that outcome might vary depending on sex and age at the time of sustaining the fracture. Overall women are most commonly studied, while men have received less attention despite the fact that the repercussions appear to be more serious for men than women. Further to this and recognising that age is perhaps the most important risk factor for hip fracture, the influence of age on short, intermediate and long term mortality and fracture outcomes have not been fully explored.

People who have sustained one fragility fracture have at least twice the risk of sustaining new fractures. Pharmacological treatment can reduce fracture risk, but are in general under-prescribed; however, they also require sufficient time to achieve their full effect. In order to optimise treatment options and to improve strategies for fracture prevention not only in the short term but also in the long term, there is a need for studies with an extended observation time with regards to subsequent fracture risk and mortality.

The aim of this thesis was to determine how sex and age contributes to the mortality and fracture outcomes of hip fracture patients in a remaining lifetime perspective.

2 Background

The skeleton provides protection to the internal organs and structure and in terms of mobility needs to be sufficiently light to allow rapid movement yet strong enough to avoid fractures. The skeleton consists of two types of bone: cortical and trabecular (also known as cancellous), of which cortical bone accounts for 80% of the total skeleton. In addition to its mechanical properties, bone has an endocrine function as the main reservoir for mineral homeostasis, and more recently it has been found to be involved in the regulation of energy metabolism [3].

The proportion of these two bone types differs depending on skeletal site, uniquely tailoring them to their particular role. Cortical bone is dense and resistant to bending making it suitable for its location in the shafts of long bones. It forms a protective outer layer around all the bones in the body. In contrast, trabecular bone is less dense and more elastic, and is mainly found in the metaphyseal regions and in vertebrae. It consists of a rigid network of thin calcified strands, known as trabeculae, which give maximum strength for minimum weight.

Bone is metabolically active and responsive to changes in its environment; however, the overall turnover rate is low compared to other tissues and estimated at 10% per year. Trabecular bone, because of its large surface area has a higher turnover rate (20-25%), compared to cortical bone (3-5%) [4]. Maintaining skeletal integrity relies on a balance between bone formation and bone resorption. Childhood and adolescence is marked by general skeletal growth as well as an increase in bone density. In young adults bone mass is stable due to the tight coupling of bone formation and resorption, which allows continual renewal and repair of the skeleton. Peak bone mass is considered to be reached between 20-30 years of age. Subsequently, there is a gradual reduction in bone mass with advancing age, and in women this loss is accelerated after menopause [5, 6]. Figure 2.1 illustrates the structural differences between normal and osteoporotic bone, which contribute to skeletal fragility.

Osteoporosis

Definition of osteoporosis

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and increased risk of fracture [7].

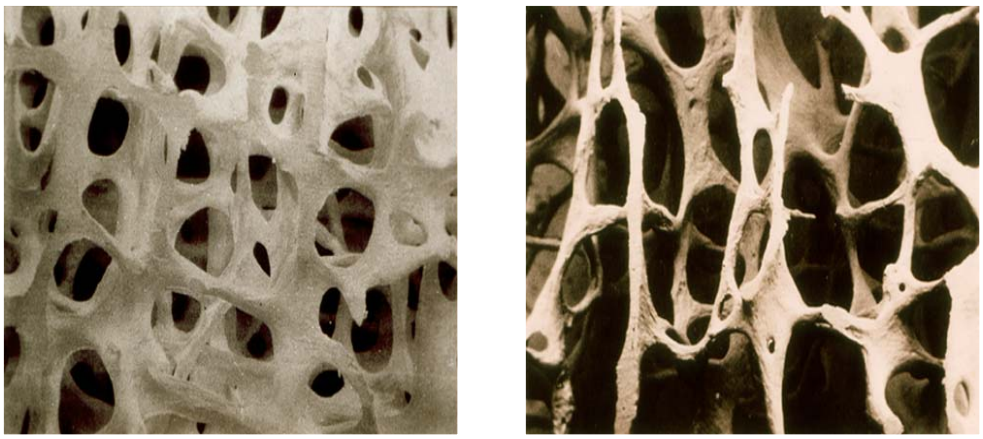


Figure 2.1 Normal (left) and osteoporotic (right) trabecular bone.
(International Osteoporosis Foundation www.iofbonehealth.org)

Diagnosis and diagnostic methods

Osteoporosis was historically a clinical diagnosis made by the presence of fragility fractures, but since the mid 1990's the World Health Organisation (WHO) has established a criterion for the diagnosis of osteoporosis whereby bone mineral density (BMD) is quantified by dual X-ray absorptiometry (DXA). Diagnosis is based on a standard deviation (SD) change from the mean in BMD of young adults in the same population [8]. BMD is measured at the lumbar spine or hip, where a density within one SD from the value of young adults (T-score) is considered normal Osteopenia is defined as BMD between 1 and 2.5 SD lower than the mean and osteoporosis is defined as BMD below 2.5 SD. Severe or manifest osteoporosis is defined by the presence of one or more fragility fractures in addition to BMD less than 2.5 SD.

Many techniques have been developed to measure bone mass. The most validated of which is DXA. A non-invasive technique using a small X-ray dosage, combining two different energy X-rays which allows differentiation of bone mineral and soft tissue. Available measures include bone mineral content (BMC, g) and areal BMD (aBMD, g/cm^2) which is an approximation of the true volumetric density [9]. Almost any skeletal site can be measured, but measurements of the hip or spine are preferred for diagnosing osteoporosis, estimating fracture risk and monitoring the efficacy of

pharmacological therapies. DXA is generally considered to be the golden standard in terms of BMD assessment.

Quantitative ultrasound (QUS) allows the study of bone properties which contribute to bone quality such as bone mass and bone micro-architecture. Only peripheral sites can be measured, most commonly the heel [10]. QUS appears to predict hip fracture at a similar level as DXA [11] and correlates quite will with BMD at peripheral sites but not sufficiently well with BMD at central sites [12]. Hence its use as a tool for measurement is limited, despite its low cost, being portable and not involving radiation. Furthermore, it has not been validated for monitoring therapy.

Quantitative computed tomography (QCT) has an advantage over DXA in that it can measure three dimensional volumetric BMD (vBMD) and discriminate between trabecular and cortical bone. However, QCT uses higher doses of radiation and is more expensive than DXA [13], thereby making it unsuitable for routine BMD assessment or monitoring of treatment.

Epidemiology of osteoporosis and fracture

Osteoporosis becomes more common with advancing age. The burden of osteoporosis throughout the world is estimated to increase [1, 14]. Already, one in three women and one in eight men above age 50 have osteoporosis [15]. Women are at a higher risk of developing osteoporosis, where the beginning of the risk increase coincides with the withdrawal of endogenous estrogen at menopause. Another contributing factor to the discrepancy between the genders is the longer survival overall in women compared to men.

The age and sex specific incidence of extremity fractures show a bimodal curve, the first peak occurring in adolescence and the second in older age. During adolescence, fracture incidence is almost doubled in young men compared to young women and usually results from trauma such as sports and leisure time activities, road traffic accidents or falling from larger heights. The second peak, in older age, starts around age 50 in women but not until 70 years in men [16-18]. In these ages, the majority of fractures are related to osteoporosis, typically occurring at the hip, pelvis, proximal humerus, forearm and vertebra [17, 19] (Figure 2.2).

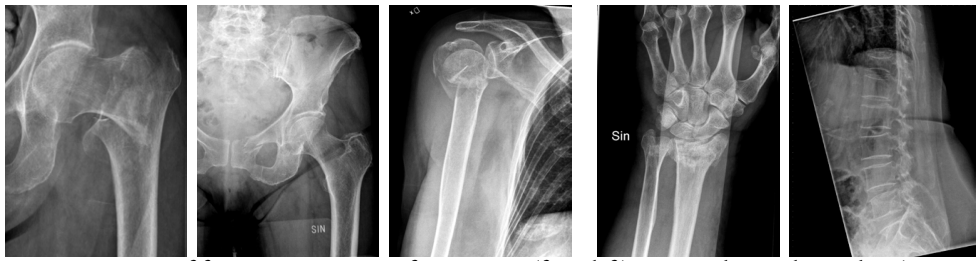


Figure 2.2 X-rays of frequent osteoporotic fracture sites (from left): intertrochateric hip, pelvic (superior ramus), proximal humerus, distal radius and vertebrae.

Hip fracture

Hip fracture, which increases exponentially with age, is the most devastating of the osteoporotic fractures and is associated with high short term mortality, increased morbidity and increased costs for the patient and society [1, 14]. The incidence is estimated to increase world wide especially in developing countries [1, 14] although recent studies from Sweden and North America have shown a plateau in incidence rates [20-24].

The incidence of osteoporosis and hip fracture varies considerably between different populations, with Scandinavia having the highest incidence of hip fractures in the world. In Sweden approximately 70,000 osteoporosis related fractures occur annually of which 18,000 are hip fractures [25]. The majority of those suffering hip fractures, three quarters, are women, while in Norway a relatively higher incidence of hip fracture is seen in men [14, 26, 27]. The peak incidence of hip fracture occurs at different ages in women and men and reflects the gender specific differences in life-span. Hip fractures may be defined as femoral neck fracture (ICD10; S72.0) or inter/sub-trochanteric femoral fracture (ICD10; S72.1-S72.2) (Figure 2.3).

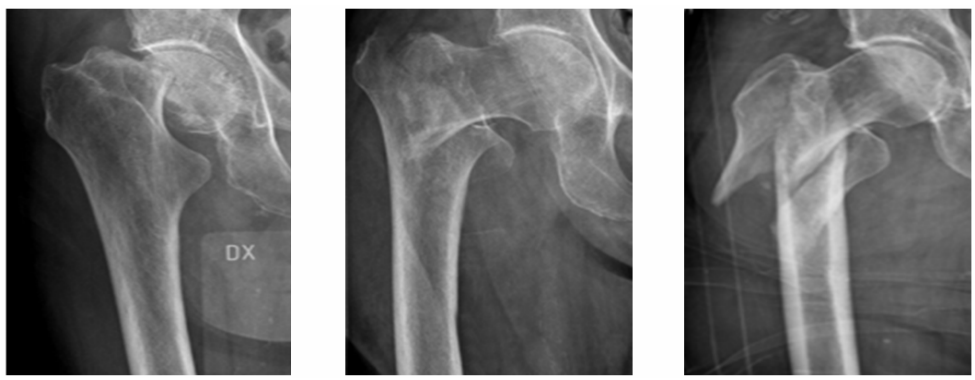


Figure 2.3 X-rays of the three different types of hip fracture (from left): femoral neck, intertrochanteric and subtrochanteric.

Other fragility fractures

Distal forearm fractures usually result from a high energy trauma earlier in life or a typical low energy trauma later in life. Low energy trauma distal forearm fractures related to osteoporosis usually appear 10-15 years earlier in age than low energy trauma hip fractures [28]. Distal forearm fractures are not associated with increased mortality [29] but may be an early indication of increased risk of future hip fracture in both women and men [28, 30]. Proximal humerus fractures have the same fracture pattern as distal forearm fractures with an early and a late peak corresponding to early high and later low energy trauma [31].

The incidence of vertebral fractures or vertebral deformities increases with age, but are more common in men than women between the ages of 50-59, although the incidence in women increases thereafter. Current estimates suggest that in Europe, one in eight men and women over the age of 50 have sustained a vertebral deformity [32]. Clinical vertebral compression fractures come to awareness because of the co-occurrence of pain. In contrast, vertebral fractures can also be asymptomatic, often sustained from simple actions such as lifting a smaller weight or bending, and the patient may be totally unaware of their presence or the event giving rise to them. It is estimated that only one third of all vertebral fractures come to clinical attention [33], yet the use of a simple measuring tape to identify height loss would likely improve the identification of these patients since they are at high risk of additional fractures.

Risk factors for osteoporosis and fracture

In addition to age and sex, a large number of medical, pharmacological, lifestyle and genetic factors are associated with low bone mass and fracture risk. Risk factors may be divided into those dependent and those independent of bone mass. They may relate to the attainment of peak bone mass or to the rate at which bone is lost; or they may relate for example to the risk of falling. Predisposing factors for bone mass and fracture may overlap or be specific to each. Risk factors can also be classified as modifiable and non-modifiable. Modifiable risk factors such as physical activity and diet are interesting from the perspective of intervention strategies. Table 2.1 outlines a number of established risk factors, some of which are dealt with in more detail below.

Increased weight is strongly associated with higher BMD, which in turn is associated with lower fracture risk. This is in part explained by oestrogen production in peripheral adipose tissue as well as the anabolic effect of load-bearing on the skeleton. The physical protection of extra padding when falling also plays a role in injury prevention. Tobacco smoking has been associated with low weight, low BMD and fracture risk in both women and men [34-36]. Tobacco smoking itself also has a negative affect on bone cells leading to reduced bone quality [37-39]. Physical activity affects the bone directly through response to mechanical loading, and indirectly via muscle activity. Physical activity is positively associated with increased bone mass in

young people [40, 41] but its bone effects in the elderly are controversial however, its positive effect on balance, coordination and propensity to fall is probably essential [42-44].

Table 2.1. Risk factors for osteoporosis and fracture	
General factors	Age Sex Low body weight Previous fragility fracture Ethnicity
Lifestyle factors	Diet & nutrition (calcium, vitamin D) Physical activity Smoking Excessive alcohol intake
Bone related	Low bone mass Hip geometry
Genetic	History of maternal hip fracture
Secondary causes	Endocrine disorders (hypogonadism, hyperparathyroidism, diabetes) Connective tissue disorders (osteogenesis imperfecta) Malignant disease Drugs (glucocorticoids, heparin) Various (alcoholism, anorexia, malabsorption)
Fall related	Hazardous environment Neuromuscular disorders Visual impairment Cognitive impairment Fall mechanics Medication

Most fragility fractures with the exception of vertebral fractures relate to a fall. Studies on fall frequency suggest annual falls of 30% in those 65 years and 50% in those above 80 years [45, 46], with an estimated 1-14% of falls leading to fracture [47-49]. Falls are influenced by intrinsic factors i.e. neuromuscular control, balance, cognitive impairment and visual acuity and extrinsic factors i.e. slippery floors, obstructions and bad lightning. Fall mechanics also play important roles, for example the energy in the fall, the energy absorbed by internal padding (soft tissue) or external padding (hip protectors) and the way of falling.

Risk of new fractures

Several studies have shown that a low energy fracture in a middle aged person predisposes to further new fractures [50, 51]. This is confirmed by evidence from meta-analysis and a review report which suggest that this applies to both men and

women and to different age groups [52, 53]. The extent of fracture risk is, however, dependent on a number of factors including type of prior fracture, duration of follow-up, sex, age and perhaps even difference in average lifetime in different countries. Furthermore, assessment of the 'relative risk' of sustaining a new fracture is affected by whether comparisons are made between fracture patients or a control population. For this reason, it is often difficult to make comparisons between the various published studies and therefore fully evaluate the real risk of sustaining a new fracture. This is particularly true with respect to hip fracture patients and their future fracture outcome. There are relatively few studies, and often these studies have a low sample size or the number of fracture events is low, the follow-up times vary considerably and rarely are the individuals followed-up for a sufficiently long period to fully evaluate the consequence on new fractures. Further to this, long term estimates of fracture risk are, although providing important information, often based on statistical modelling [54-57] rather than on actual observation over a long time period.

Mortality and osteoporotic fractures

It is well established that hip fracture patients have a high early mortality, with approximately 20-30% of patients dying within the first year. Excess mortality directly attributable to the fracture itself is estimated at 17%-32% depending on age [58-60]. Most studies agree that men have a higher mortality compared to women and this appears to be valid in both the short term and for as much as five years after the hip fracture is sustained [29, 60-65]. The importance of this lies in the fact that although men in general are younger than women when they suffer their hip fracture, they are clearly more frail than women which affects their outcome. Only a few studies have followed hip fracture patients for more than 5 years, and unfortunately among the published data, there is a lack of uniformity with regards to study design and analysis, for example reporting relative risks in different time spans, between men and women, in different age groups or the use of presumably healthier control groups [64, 66-68]. This renders it difficult to establish the true risk of mortality after hip fracture [69].

Fractures at other sites such as the vertebrae, pelvis and proximal humerus are also associated with increased mortality [29, 31, 70-72]. Vertebral fracture leads to a gradual increase rather than the high early mortality as seen with fractures at the hip. Compared to the general population, mortality is increased for up to two decades [29, 73].

Co-morbidities and pre-fracture functional status play a varying role in contributing to fracture risk and to mortality associated with fracture [64, 66, 68, 70, 71, 74]. Conditions known to contribute to hip fracture risk include diabetes [75-77], neurological diseases such as Parkinsons' [78-80], stroke [81] and cardiovascular disease [82].

Prevention of fracture

Effective pharmacological agents are available for treatment of osteoporosis and preventions of fractures [83, 84]. Antiresorptive agents such as bisphosphonates [13, 84-87], selective estrogen receptor modulators (SERMs) [88], estrogens [89, 90], calcitonin [91] inhibit osteoclast action and reduce bone resorption, however with variable efficacy in terms of fracture reduction. None of these are able to restore bone structure. By contrast, anabolic agents such as PTH stimulate osteoblasts and bone formation, thus directly increasing bone mass [92, 93]. Additionally, strontium ranelate appears to have dual function, even if the anti-resorptive effect predominates [94]. Regardless of the chosen treatment, there is an inevitable delay between initiation of treatment and onset of effect. This is related to the fact that compared to other tissues, bone turnover is a much slower process. There may also be problems with compliance due to the regimen of administration and side effects. Recently it has also been shown that a new bisphosphonate, zoledronic acid, developed for fracture prevention may also decrease hip fracture associated mortality [95]. Despite the availability of these medications, osteoporosis and fracture patients are still under-treated [96-98].

In older individuals, prevention of falls is of major importance to fracture prevention. Removing obstacles from the home environment and the use of hip protectors to reduce the impact of trauma are all improvements which may have an immediate effect although they don't offer 24 hour protection. Balance and coordination training can also rapidly reduce the propensity to fall [47, 99, 100].
In addition to this, measures to maintain the best possible health status in persons otherwise at risk, should reduce both fracture and the adverse consequences of fracture. Such a strategy includes optimised treatment of co-morbidities, reduction of excess medication and ensuring that a balanced nutritional status is maintained.

3 Aims of the Thesis

The general aim of this thesis is to evaluate the influence of age and sex on mortality and subsequent fracture risk after hip fracture in a remaining lifetime perspective.

The specific aims for the study were

I. To describe the long-term survival, subsequent fractures and musculoskeletal trauma as consequence of age in men and women after hip fracture.

II. To describe mortality and cause of death in men and women after hip fracture in comparison to age- and sex-matched controls from the background population.

III. To evaluate excess mortality in hip fracture patients in the short, intermediate and long-term compared to the background population.

IV. To evaluate short- and long-term subsequent fracture risk after hip fracture in men and women compared to age- and sex-matched controls from the background population.

V. To describe differences in subsequent fracture pattern between men and women with hip fracture and age- and sex-matched controls from the background population.

4 Subjects and Methods

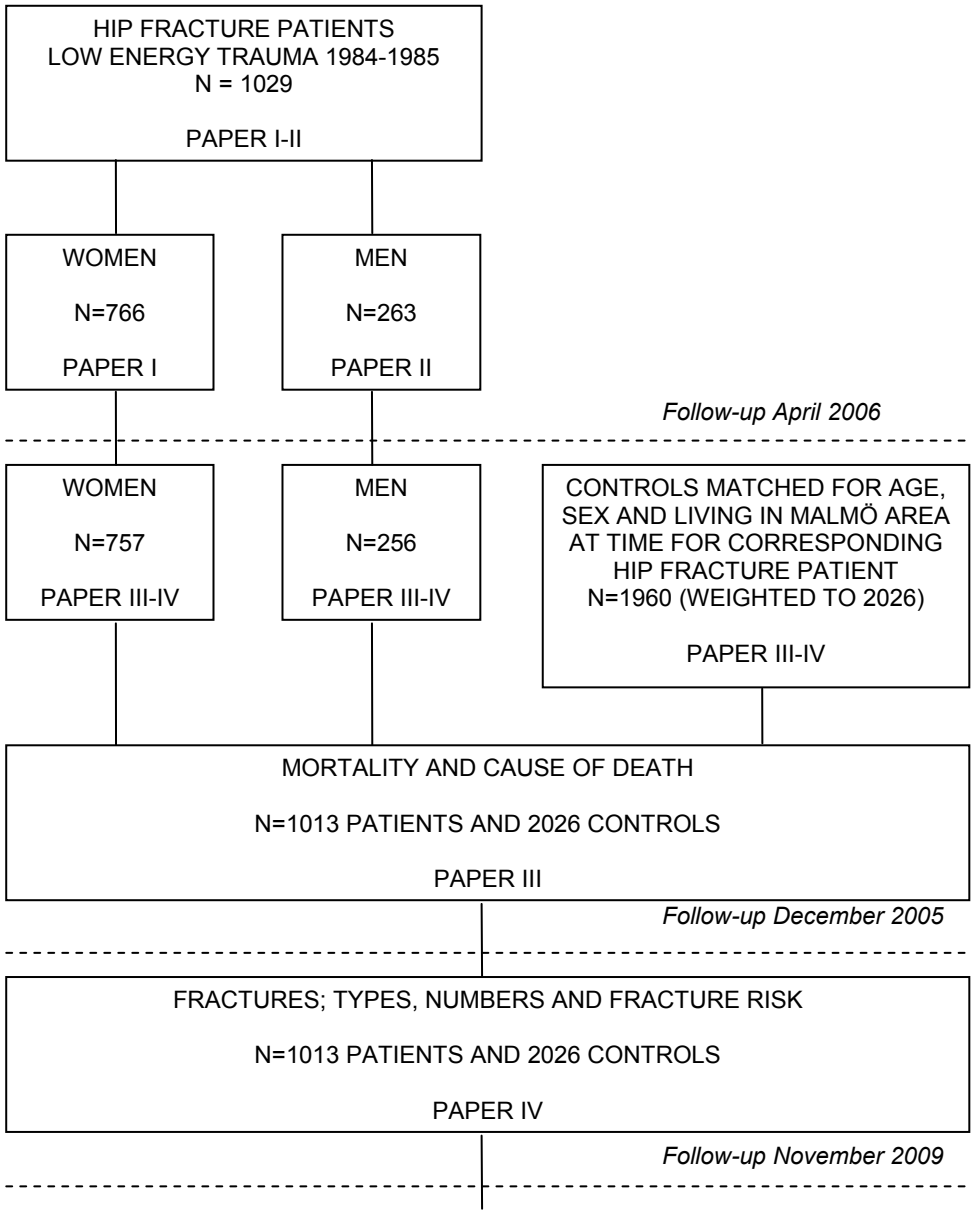
All hip fracture patients, both female and male, suffering a hip fracture during two consecutive years 1984-1985 in the city of Malmö, Sweden, were identified through the database at the Department of Radiology Malmö, Skåne University Hospital. The department has saved the radiographic records and X-rays since the beginning of last century. It is serving the department of Orthopaedics, which is the only unit treating adult fractures in a catchment area of approximately 260 000 inhabitants [101].

In this thesis, all adult patients presenting with a hip fracture from low energy trauma and sustained after the age of 20 years, were included. Hip fractures due to high energy trauma and pathological fractures of any cause were excluded. Hip fracture was defined as a fracture of the proximal femur from femoral neck (intracapsular) to the subtrochanteric region (corresponding to ICD10 codes S72.0-S72.2). Information relating to the index hip fracture was cross-validated with the surgical register and medical charts. In addition, the hip fracture cases were compared with age- and sex-matched controls from the background population. The inclusion date for the participant was defined as the date of the index hip fracture among the patients during the two year inclusion period and the same date was also the inclusion date for the corresponding controls.

Hip fracture cohort

In all, 1029 patients suffered an index hip fracture during the inclusion years, 766 women and 263 men. Women and men are reported separately in **Paper I-II**. After exclusion of 16 cases for whom matching controls could not be identified, analyses were performed and reported on 1013 patients, 757 women and 256 men in **Paper III-VI** (Figure 4.1). Their mean age was 80 years and 74 years at time of index hip fracture, in women and men, respectively. The age distribution among patients is shown in Figure 4.2.

Figure 4.1 Flowchart of study



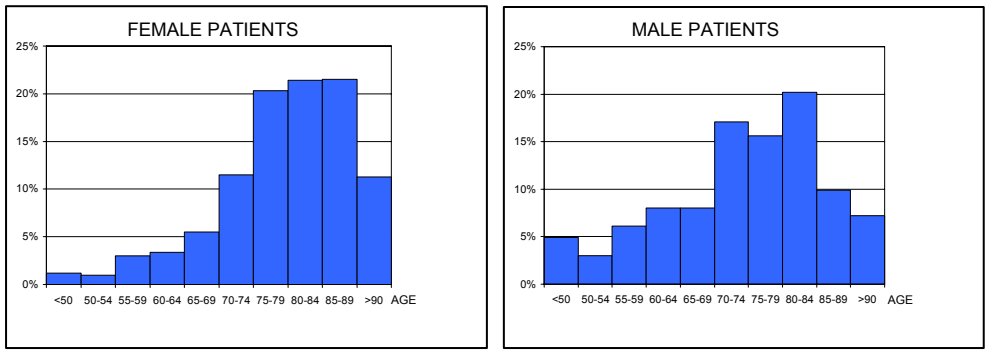


Figure 4.2 Age distribution in 5 year age-bands from <50 to ≥90 years as percentage of total number.

Control cohort

For each included hip fracture patient (case), two controls were randomly selected from the National Statistics Bureau (SCB), Sweden and matched by sex and age (year and month). All controls were alive and resident in the catchment area on the date of the corresponding index hip fracture. Each control was linked to a specific case using the random sampling technique and then returned to the general sample. In those cases where only one control (n=66) could be found, the weight of this control was doubled. In total, 1960 controls (weighted to 2026) were obtained and matched to the 1013 index hip fracture cases (Figure 4.1).

Assessment of new fracture

From the index hip fracture/inclusion date and thereafter, every trauma event resulting in an X-ray of a skeletal structure or region was recorded. The following information was documented: date, type of trauma, number of structures examined, and if fracture; type of fractures. Spinal radiograms performed because of clinically suspected vertebral fractures were also included. Only new fractures occurring after the inclusion date were included. All musculoskeletal radiographic investigations occurring from the inclusion date were individually assessed for each patient, and data were exclusively collected by one person.

Co-existing fracture, meaning a fracture at another site, caused by the same trauma event and occurring simultaneously with the index hip fracture, was also recorded. In addition, hip fractures having occurred before the index hip fracture was registered. In **Paper IV** the different fracture types were categorized according to each specific skeletal structure and reported according to major fracture groups; hip, pelvis, shoulder, wrist, clinical vertebral fractures and "other" (Appendix Table 4.1).

Patients and controls were followed for new fractures, using the records at the department of radiology until death or April 2006 yielding a maximum of 22 years of follow-up (**Paper I-II**). In **Paper IV** the study was extended until November 2009, giving a maximum of 26 years of follow-up (Figure 4.1).

Assessment of musculoskeletal trauma

All X-ray investigations of the musculoskeletal region because of trauma were evaluated in patients and controls (**Paper I-II and IV**). The impact of the trauma was recorded for all X-rays in the same way as when evaluating the index hip fracture (high or low energy trauma or pathological fracture). If an X-ray investigation did not reveal any fracture, it was defined as a musculoskeletal trauma event. Hence such a trauma event was severe enough to warrant referral to a physician and further to a musculoskeletal X-ray investigation. The trauma event was used as an approximation of a musculoskeletal injury, most likely a fall. Repeated X-rays from the same trauma event were only referred to once.

Mortality date and cause of death

Using the unique 10-digit personal identification number allotted to every Swedish citizen, date of death (**Paper I-IV**) and cause of death (**Paper III**) for each individual hip fracture patient and control were obtained from the Centre for Epidemiology (EpC), National Board of Health and Welfare, Sweden. The causes of death were coded according to the International Classification of Diseases (ICD), 8th through 10th versions. The underlying cause of death was used, since it is validated and used as an international standard by WHO. In Sweden the underlying cause of death is validated by the EpC and more than 99% of all Swedish subjects receive a diagnosis [102]. We reported cause of death according to major disease categories - the codes for these and related sub-groups are given in Appendix Table 4.2. In **Paper III** patients and controls were followed until the time at which the latest data from Swedish Cause of Death register were available, i.e. December 2005, providing a maximum 22 year follow-up.

5 Statistical Methods

Descriptive data are presented as mean and standard deviation (SD) or median with range [range]. Baseline data are reported in 5-year age-bands, with those below 50 year reported as one age-band. Additionally, all subjects were stratified into three age-groups: below 75 years, 75-84 years and above 85 years at inclusion date (index hip fracture). Data in hip fracture patients and controls are presented by sex and in age-stratified groups or overall. Student's independent t-test was used to identify differences in mean age between groups. Cox proportional hazard regression was used to adjust for age differences. Chi-square test was used to test differences in proportions between groups.

Survival and excess mortality

Survival following the index hip fracture is presented in absolute numbers and quantified using survival function estimates by the Kaplan-Meier method. Differences in survival are further tested using log-rank test (or Gerhan-Wilcoxon test) (**Paper I-II**) including the individual case-control-match (**Paper III-IV**). Follow-up started on the date of the index hip fracture/inclusion date and continued until "date of death" (complete event) or "being alive at the end of follow up" (censoring event).

Excess mortality is also reported in relative risk (rate ratio) during follow up with 95% confidence interval (CI) (**Paper III**). As a complementary analysis, Cox Proportional Hazard Regression analysis was used to quantify excess mortality differences in sex and specific age-groups or overall. Mortality risk is presented as Hazard Ratio (HR) with 95% CI at 1-, 5- and 10 years. Statistically, time-points above 10 years could not be tested by the Cox model, since median survival was less than 10 years in all age-groups (<75, 75-84, ≥85 years) except amongst the youngest women. Therefore, the assumptions of proportional hazard were not fulfilled, and mortality rate until end of follow-up is presented as rate ratio (RR) with 95% CI (Paper III).

Cause of death

Incidence of specific causes of death are presented as percentage and shown separately for sex and age-groups, patients and controls (**Paper III**). In order to compare patients and controls, rate ratios (RR) are calculated with 95% CI. To illustrate the time

aspect on causes of death between patients and controls, Kaplan Meier Survival plots were constructed. In these analyses, however, it is not valid to perform statistical differentiation analysis using log rank test, since the unique matching is invalidated if the matched patient and control have not died from the same condition. Relative risks are presented as risk ratios, which equates to the risk for patients to die from a certain cause compared to controls and takes into consideration time at death in person-years.

New fractures

New fractures after the index hip fracture/inclusion are presented in absolute numbers; as first fracture and total number of fractures during follow-up. Fracture risk after the date of inclusion was quantified using survival function estimates by the Kaplan-Meier method. Follow-up continued until "date of first new fracture" (complete event) or "being free of new fractures at the end of follow up" (censoring event) (**Paper I-II**). When adjusting for mortality "date of death" was added as a censor (**Paper I-II, IV**). Differences in fracture risk between age–groups were tested using the log-rank test or Gerhan-Wilcoxon test (**Paper I-II**). In the case- control study, differences in fracture risk were tested using log-rank-test with unique case-control-match (**Paper IV**).

To quantify fracture risk, fracture incidence is reported as rate per 1000 person years, for first new fracture and the total number of fractures. Relative risk (RR) was used to compare fracture incidence between hip fracture patients and controls (**Paper IV**).

For statistical analysis SPSS, version 17.0 (SPSS Inc) and Statistica software release 7.1 (StatSoft Inc.) were used. The level of significance was set at $p < 0.05$.

Ethics

Study I-IV all received ethical approval from the Institutional Review Board, Lund University, Lund, Sweden. All collected data were treated confidentially.

6 Results

Paper I

Long-term survival and fracture risk after hip fracture: A 22-year follow-up study in women

Research Question

(1) What is the influence of age on long-term survival in female hip fracture patients? (2) How many subsequent fractures occur and in what proportion? (3) What is the residual lifetime and the 10-yr fracture risk in women after hip fracture? (4) How does musculoskeletal trauma (requiring hospital attention) relate to subsequent fracture?

Subjects and Methods

This study included all women (n=766) suffering a hip fracture due to low energy trauma during 1984-1985 in Malmö, Sweden (the hip fracture cohort). The patients were prospectively followed until death or for 22 years with regards to survival, new fractures and musculoskeletal trauma.

Results

At the time of the hip fracture, the mean age was 80 ± 10 years [range 32–99], with 42% of the fractures occurring in those between 75 and 85 years of age (Figure 4.2). After 22-years 94% had died, hence most women were followed for the remainder of their lives. Survival, which is equivalent to the time at risk of sustaining a new fracture, was 79% at 1 year, dropping to 48% at 5 years and 33% at 10 years. The short term survival, i.e. one year, was approximately 13% lower with increasing age-group; <75, 75–84 and ≥85 years (93%, 79% and 66%, respectively).

After the index hip fracture, 342 women (45%) suffered at least one new fracture. A total of 768 subsequent fractures were registered at 715 occasions (mean of 2.3, range [1–11] fractures/woman). Of the fracture occasions, 15% occurred within the first year, 27% within 2 years, and 73% within 5 years of follow-up.

Using stratification by age-groups to evaluate the risk of new fractures, the mortality-adjusted risk was similar up to 4 years and the unadjusted risk up to 2 years after the

index hip fracture. The mortality-adjusted risk was higher in age-group 75-84 years compared to those below 75 years, while it was not possible to include the oldest in the evaluation because of their high early mortality. The overall 10-yr fracture risk was 40%, which after adjustment for mortality increased to 65%. The unadjusted residual lifetime fracture risk was 45% and the mortality-adjusted risk 86%.

In 6 out of 10 female hip fracture patients seeking hospital care for musculoskeletal trauma, the X-ray investigations verified a fracture.

Conclusions

Almost one half of all women with a hip fracture suffer new fractures during their remaining lifetime. As is shown in this study, subsequent fracture risk is highly dependent on age at the time of hip fracture and on survival both in the short and long term. Unadjusted risk values underestimate the 10 year and life-time risk of fracture.

Paper II

Men with hip fracture – survival and subsequent fractures in a remaining lifetime perspective

Research Question

(1) How does age at the time of the index hip fracture influence long-term survival in male hip fracture patients? (2) How many new fractures are sustained after a hip fracture and how does this relate to age at index hip fracture in male hip fracture patients? (3) What are the residual lifetime and the 10-year fracture risk? (4) How does musculoskeletal trauma relate to fracture risk?

Subjects and Methods

This study includes all men (n=263) in the hip fracture cohort whose fracture occurred 1984-85. The male patients were prospectively followed until death or for 22 years, with survival and new fractures as the main outcome variables.

Results

At the time of the hip fracture, the mean age was 74 ±12 years [range 33-101]. Age distribution is shown in Figure 4.2. At 22 years, the overall mortality was 93% hence most were followed for their remaining lifetime. Overall, survival was 68% at one year, 60% at 2 years and 38% at 5 years. Stratified by age-group, survival at 10 years was 39% in those <75years, dropping to just 7% in men aged 75-84 years. None of the patients ≥85 years were still alive after 10 years.

After the index hip fracture at least one new fracture was identified in 28% (74/263) of the male patients; 131 fractures (mean 1.8, range [1-7] fractures/person). Of these fractures, 16% (21/131) had occurred within the first year and 69% (90/131) within 5 years. For the entire cohort, the 10-year unadjusted risk of new fracture was 25%, and the mortality-adjusted risk 46%. The 5-year unadjusted risk was 21% which was almost the same as the 10-year risk. Residual lifetime risk of new fracture was 28%, equivalent to 62% mortality-adjusted risk. Men below 75 years of age at the time of the index hip fracture were at greatest risk of new fractures (p=0.007).

X-ray investigations because of musculoskeletal trauma were frequent in these patients and 1 in 2 investigations verified a new fracture.

Conclusions

In male hip fracture patients, the time at risk of a new fracture is highly dependent on age when sustaining the hip fracture and on subsequent survival. Almost one third of all men with hip fracture suffer new fractures during their remaining lifetime, with most occurring in those relatively younger, while the oldest die, reducing their time at risk. In men with hip fracture, it appears most relevant to use 5-year risk estimates rather than 10-year risks, since longer time frames only applies to those who are younger.

Paper III

Early and long-term mortality and cause of death after hip fracture – a case control study over 22 years

Research Question

(1) To what extent does excess mortality relate to age and observation time, for women and men with hip fracture in comparison to the background population? (2) To what extent does cause of death differ between women and men with hip fracture patients compared to controls and over time?

Subjects and Methods

This study includes the hip fracture cohort, both men and women (n=1013) with the exception of those for whom no matching controls could be found. The fracture patients are compared to the control cohort consisting of duplicate age- and sex-matched women and men, all living in the same city, at time of the index hip fracture/inclusion date (n=2026).

Results

After 22 years, mortality was 94% in the hip fracture patients compared to 88% in the controls. The high mortality after hip fracture was apparent when stratifying for sex and age; the median survival among female hip fracture patients was 4.9 yrs (95% CI 4.4-5.4) and among males 3.7 yrs (95% CI 2.7-4.7), equating to a median loss of 2.9 and 3.7 life-years in female and male patients respectively, compared to controls ($p<0.001$). Similarly, the age effects on median survival are obvious when comparing age-groups (<75, 75-84 and ≥85 yrs); the differences in median survival between female patients and controls were 6.3 yrs, 3.2 yrs and 1.9 yrs in each age-group, respectively and 8.5 yrs, 2.7 yrs and 2.3 yrs in men ($p<0.001$). In the short term, within the first year after the index hip fracture, mortality was substantially increased both female and male patients regardless of age (RR range 3.7-8.9). Excess mortality persisted over the entire duration of the study (RR range 1.5-2.6).

The most common causes of death in absolute numbers were cardiovascular disease (CVD), cancer and pneumonia in both cases and controls, women and men. The risk of dying from CVD was increased by 45-50% in female and male hip fracture patients. In women after hip fracture, musculoskeletal trauma, gastro-intestinal disease and neurological disease showed a two-folded increase as causes of death (RR range1.9-2.6). In male hip fracture patients, excess mortality was three-fold from neurological diseases, musculoskeletal trauma, pneumonia and chronic obstructive pulmonary disease (COPD) as causes of death (RR range 3.1-4.3).

Conclusions

All cause mortality differed between female and male hip fracture patients in the short, intermediate and long term, but also in comparison to the background population. Mortality was overall highest in male hip fracture patients. The most common cause of death for patients and controls was cardiovascular disease, with hip fracture patients displaying an up to 50% increased risk compared to controls.

Paper IV

Lifetime risk of new fracture after hip fracture - a case-control study in 1029 hip fracture patients over 26 years

Research Question

(1) What is the remaining lifetime incidence of new fractures in men and women after hip fracture compared to controls from the background population? (2) How many new fractures and what types of new fractures do hip fracture patients suffer according to age and sex, compared to background population? (3) What is the remaining lifetime mortality-adjusted fracture risk in hip fracture patients and background population?

Subjects and Methods

This study includes the same hip fracture and control cohorts as Paper III. The subjects were followed until death or November 2009, i.e. almost 26 years for new fractures and long term influence of mortality on fracture risk, analysed by sex and age.

Results

At the end of follow-up 4% of the hip fracture patients compared to 9% of the controls were still alive and at risk. In women, at least one new fracture occurred in 45% of both female hip fracture patients and their controls, while 30% vs 23% occurred in male patients and controls. Of those who sustained fractures, it was more common among women to sustain new fractures on more than one occasion (patients 57%/controls 46%) than among men (patients 38%/controls 40%).

While the absolute risk of new fractures was higher in women than in men, the relative risk was higher in male hip fracture patients than in female patients compared to their respective matched controls (RR 2.5 (95% CI 2.0-3.1) vs 1.6 (95% CI 1.5-1.8)). However, when stratifying for age, the relative risk was only increased in those below age 85. The 10-year mortality-adjusted fracture risk in female hip fracture patients was 65% compared to 47% in controls. The 5-year mortality-adjusted fracture risk in male hip fracture patients was 37% compared to 15% in controls.

The most common fractures were those of the hip and vertebrae in both patients and controls. The risk of a new hip fracture was evident in female patients below age 85 (RR range 1.4-1.9), while the risk in the oldest was similar to that of controls. Male hip fracture patients, regardless of age, had a doubled risk of new hip fractures (RR 2.1). Female hip fracture patients had an increased risk of subsequent vertebral fractures, most pronounced in the younger age-groups (RR range 1.7-2.5). Vertebral fractures were more common in male controls in absolute numbers; however, when including time at risk into the estimate, the risk was similar to that of the patients.

Conclusions

All hip fracture patients have a reduced time at risk because of excess mortality which is most pronounced during the first years post-fracture. Nevertheless, hip fracture patients below 85 years of age have an increased risk of subsequent fractures during their remaining lifetime compared the fracture risk in a matched control population. The risk of subsequent fractures is influenced by age and sex, which emphasize the importance of stratification.

7 General Discussion

Introduction

This study provides a detailed analysis of the short, intermediate and long term consequences after hip fracture in terms of mortality and risk of subsequent fracture. Because of the extended time-frame, it is relevant to discuss in terms of true mortality in a remaining lifetime perspective, a perspective rarely used in other reports. The reported outcomes are not projections based on statistical estimates, which could lead to over-estimation of subsequent fracture frequency, particularly among older individuals, if mortality rates are not taken into consideration. The hip fracture patients were compared with age- and sex-matched controls from the background population in the same catchment area and all analyses were performed stratifying for sex and age related effects.

The findings from the study highlight that excess mortality and fracture risk after hip fracture is very different between the sexes and within age-groups compared to background population, trends that have not been picked up as clearly by the studies published to date, due to analyses being performed without as rigorous age- and sex stratification.

Hip fracture

This study evaluates hip fractures from the femoral neck to the subtrochanteric region. The literature is not uniform in the fractures selected for study. Some include only femoral neck fractures, others only intertrochanteric fractures while some based on register data have included all femoral, including diaphyseal fractures which are not considered typically osteoporotic [62].

This study includes only hip fractures due to low energy trauma. Although there have been suggestions that when excluding high energy trauma, there is a risk of also excluding some osteoporotic patients [103]. For this study we consider high energy trauma cases to represent a different subset, which while worthy of study is not the primary interest of the study. Additionally, the inclusion of all adult fractures, a rather high proportion of younger individuals would have high energy fractures unrelated to fragile bone. Unlike some studies which were unable to evaluate the trauma impact and therefore included high energy trauma fractures [104] the unique system

operated by the radiology department and the manual re-checking against medical charts enabled us to refine patient selection. Similarly, patients with a cancer diagnosis were not excluded solely on the basis of a previous diagnosis; however, we did exclude all pathological fractures. Since cancer is common in the elderly and exclusion of these individuals has otherwise the potential to overlook a large number of non-pathological fractures [105]. It would also influence/bias mortality estimates and patterns of subsequent fracture.

Mortality and excess mortality

Many studies have reported on hip fracture patients in the short term after the hip fracture and it is well established that mortality rates within the first year are extortionately high. This study confirms that for both men and women early mortality is high, but goes further to show that for women, mortality is approximately 10% lower than in men at 1 year and as long as 5 years after the hip fracture. Thereafter, and up to 22 years the mortality rates for men and women converge, explained by the fact that it is predominantly the younger patients who survive.

Overall, as one would expect, the absolute mortality was higher in the oldest individuals. This trend, illustrated in Figure 7.1 was most pronounced at one year in the oldest men, which was disproportionately high. We also showed that men between the ages of 75 and 84 had rates of death equivalent to women who were 10 years older. For younger (<75 years) hip fracture patients, both men and women, the majority (~90%) will survive beyond the first year, thereafter dropping to 54% by 10 years and 19% by 22 years (Figure 7.1). When you consider that the proportion of those men above the age of 75 years who survived beyond 5 years was less than 20%, while for women it was almost double this, the implications for fracture prediction using algorithms such as FRAX are very important. Predicting 10 year risk of fracture, although suitable for women, is relatively meaningless in men above age 75 since so few survive [106].

It is necessary to determine the natural or expected rate of mortality in the background population, to put this information into context. It also enables delineation of the contribution to mortality from the hip fracture itself (estimated to decrease survival by almost 2 years [107]) compared to other unrelated causes [108]. With this information it is possible to demonstrate where the focus of efforts for fracture prevention should be, not just among hip fracture patients but in the general population.

Despite the importance of this knowledge, we are aware of only three studies comparable with ours [29, 59, 104]. While Farahmand found that the relative risk of death after 1-year was higher in the youngest age groups, we did not observe this and the overall 1-year mortality was also almost half of what we observed (22%). These

results may reflect differences in the cohorts (their patients were in general younger) and the methods of analysis. Another report also reported a trend with a higher relative risk of death in the younger patients however this study did not present confidence intervals and p-values or report the mean age for men and women separately, therefore it is somewhat difficult to make direct comparisons with the study we performed [29]. It is possible that this result stems from the fracture patients below the age of 50 included in our study which could skew the observations since mortality at one year would be quite low compared to other age groups. Only in the Norwegian cohort studied was the one year absolute mortality (overall, in the sexes and age-groups) comparable with the observations from our study, although the relative risks at one year were comparably lower than in our and the other studies [104]. The reason for which is unclear.

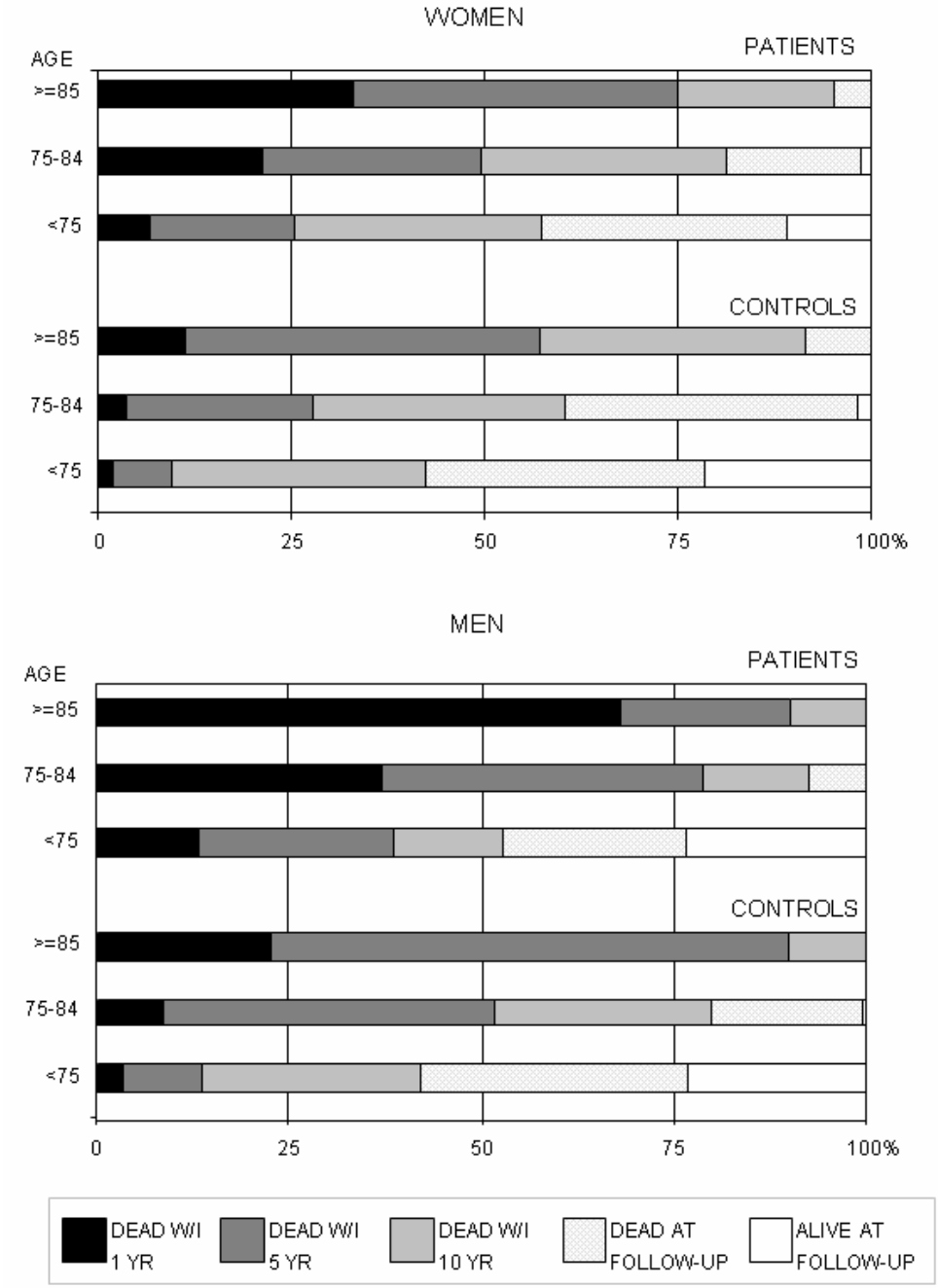
Mortality in general is higher in patients than controls. Despite the oldest male controls having lower mortality than the same age patients at 1 year, by 5 years the mortality rates are very similar, the controls having caught up (Figure 7.1). A similar trend is seen in the women although it takes an extra 5 years to catch up and reach equivalent levels of mortality. The importance of performing analyses stratified by sex and age are illustrated by the results we obtained. There are differences in mortality between all of the stratified categories (i.e. men, women, patients, controls and ages).

In most countries women have a longer average lifetime than men, exemplified in this study in which the average lifetime (at the inclusion period) for Swedish men was 74 compared to 80 years for women. This means that in the background population mortality rates between men and women of the same age will be markedly different [62, 109]. With this in mind, comparisons between men and women are of questionable value. The ages of patients included in the published literature also varies considerably: some include patients above age 50 years [59, 110, 111], 60 years [105, 109, 112, 113] or 65 years of age [114-116], assuming that these patients are most likely to suffer hip fracture due to osteoporosis and low energy trauma.

Cause of death

Although several studies report on co-morbidities exists, few addressing hip fracture patients and cause of death have been published [62, 64, 66, 68, 117], therefore there are a number of unanswered questions: do these patients die of trauma related reasons, particular those who die soon after the hip fracture? Are these patients more frail in the first place? Do they suffer other causes of death compared to controls?

Figure 7.1 Mortality among hip fracture patients and controls, until the end of the study, stratified by age-groups. Proportion dead at different time points during the observation period (up to 22 years).



We found that while the major causes of death were remarkably similar between patients and controls, the relative risk of dying from one of these diseases was higher among hip fracture patients than their controls, with the exception of cancer, possibly because longevity is associated with increased cancer incidence. Both male and female patients had a higher relative risk of CVD. A recent study by Sennerby reported an increased risk of suffering a hip fracture with CVD [82], which suggests that there are converging aetiologies for these diseases. Pulmonary related disease was a bigger problem in men, leading one to speculate that a larger proportion of the male patients smoked [75]. As shown in other studies, endocrine diseases are also a leading cause of death [75, 76].

In this study we employed the underlying cause of death in accordance with the recommendations of the international consensus by the WHO. The cause of death register in Sweden has been validated and in less than 1% the cause of death is missing [102].

New fractures

Currently available reports addressing the issue of subsequent fracture after hip fracture often focus on recurrent hip fractures but not on subsequent fractures of all types and those who do report only on a comparatively few hip fracture cases or low numbers of fractures [50, 55, 56]. The importance of knowing what types of fractures that are likely to occur in the aftermath of a hip fracture and also in what time frame they can be expected lies in the fact that, some fractures e.g. vertebral are easier to prevent with medication than others. Medications also have a delay in time-to-effect which has to be taken into consideration. As it is known that fractures within one year are common, they can best be prevented by the use of immediate acting interventions e.g. hip protectors and removal of environmental hazards.

Figure 7.2 illustrates the proportion of hip fracture patients, in 5-year age-bands, with and without new fractures at the end of the study. The proportion who fractured within one year is also marked. In all age-bands of women, the incidence of a new fracture was remarkably consistent and approximately 15% of all new fractures occurred within 12 months of the index hip fracture. By 5 years, one third of all women had fractured. In all age groups of men, approximately 23% of all patients who had a fracture sustained it within the first year, and almost all of those who suffered a new fracture had sustained it within 5 years.

Figure 7.2 Proportion of hip fracture patients with and without new fractures at the end of the study (22 years) in 5-year age-groups

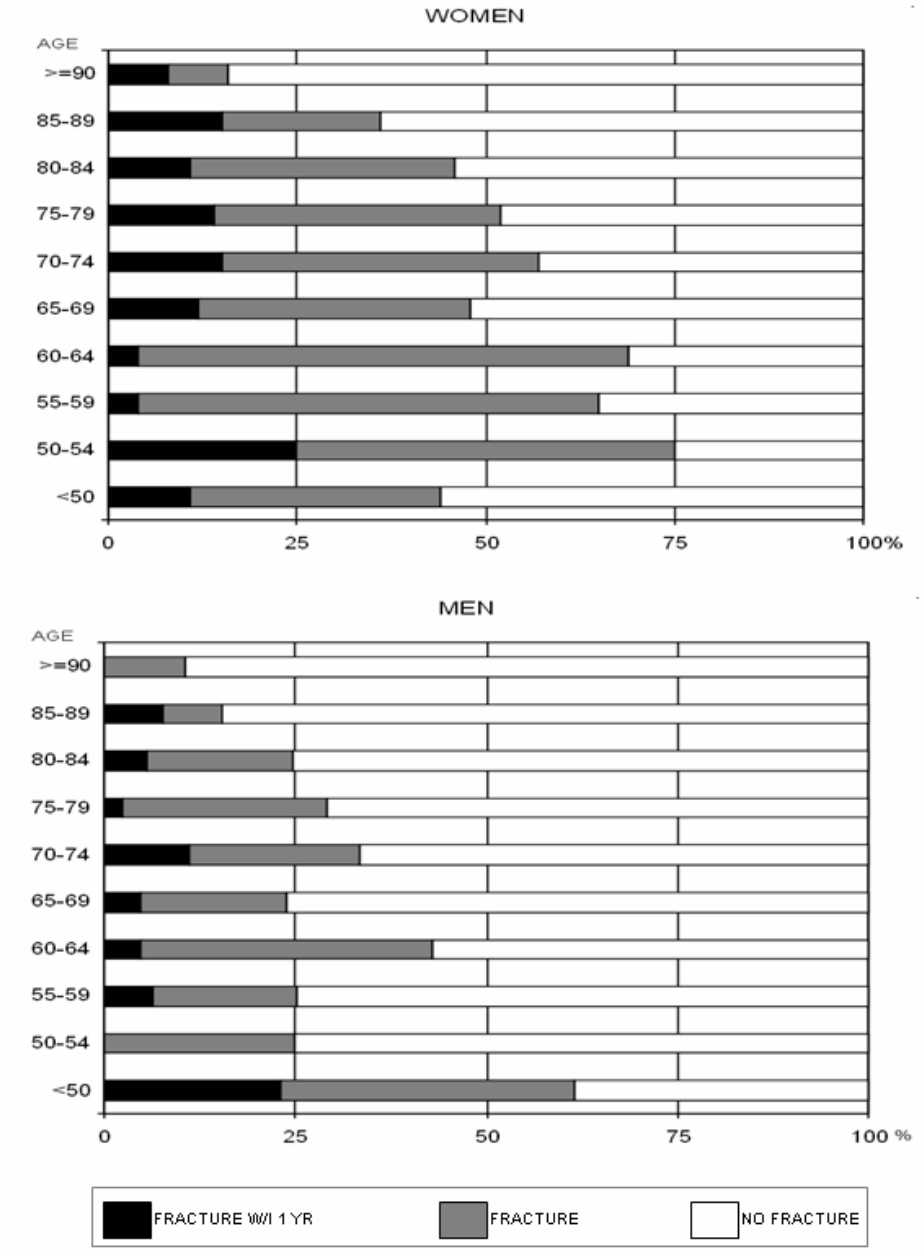


Figure 7.3 instead shows the fractures in the different age-groups, highlighting the cumulative proportion of fractures occurring also at long term; 5, 10 and 26 years. Interestingly, we showed that women who fracture, do so on multiple occasions compared to men who are more likely to suffer only a single fracture incident. Women in this study had almost double the fracture incidence than men, which is in keeping with the current knowledge that, for women, the highest subsequent fracture risk occurs after hip fracture while in men it occurs after vertebral fractures [24, 50, 55-57, 115, 118].

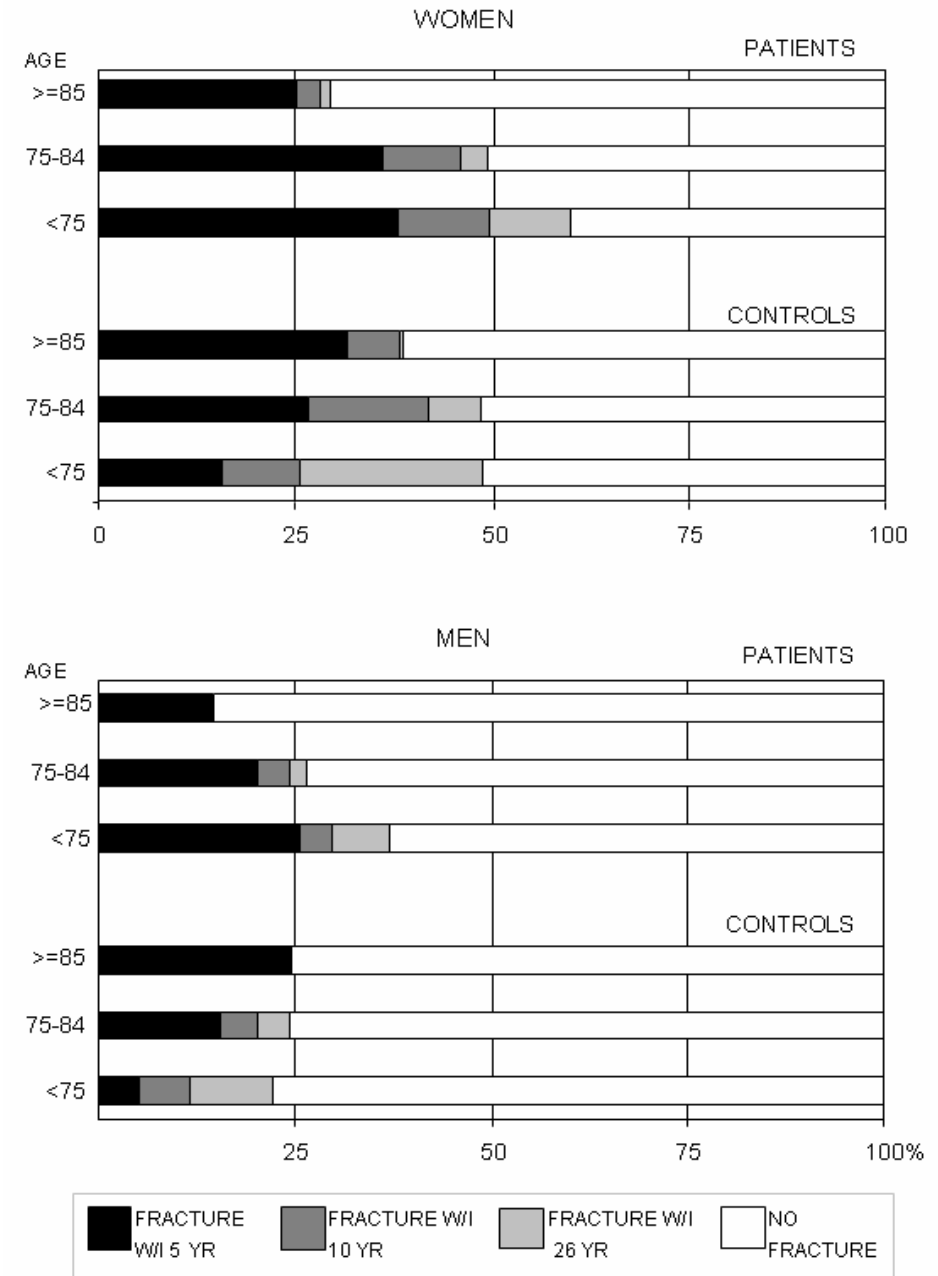
The most common types of subsequent fracture were at the hip and spine in both patients and controls, highlighting that further serious osteoporotic fractures are extremely likely to occur [24, 57, 115, 119, 120]. Furthermore, since both fracture types are described to be associated with increased mortality and morbidity [58-60, 65], treating or preventing these fractures has implications beyond the interest of the orthopaedic department.

Fracture risk

It has already been established that if a low energy fracture is sustained, then further fractures are more likely and this is already obvious in middle age [50, 51]. Translating our findings into assessment of fracture risk in the population at large, we can say the following: For a woman who has already had a hip fracture, it means that in her remaining lifetime she is almost 50% more likely to sustain at least one subsequent fracture. If she survives the first hip fracture, her risk of having another fracture increases substantially over time, reaching 65% at 10 years and 85% by 20 years. This also means that younger women, who are likely to survive longer, are also extremely likely to fracture again during their lifetime. For a man who has already had a hip fracture, it means that in his remaining lifetime he is almost 28% more likely to sustain a fracture, but this is likely to be at a single occasion. If he survives the first hip fracture, his risk of having another fracture also increases substantially over time, substantially reaching 36% at 5 years and 46% by 10 years. The fracture risk is lower than in women, partly due to high mortality among males.

The risk of a subsequent hip fracture was increased in patients generally and almost doubled in patients who were younger than 85 years. Risk factors for a second hip fracture in women are among others, low weight, low BMD, weight-loss [57, 115]. The largest increase was in male patients [71, 121].

Figure 7.3 Proportion of hip fracture patients and controls with new fractures at 5, 10, and 26 years, stratified by age-groups



We have shown that survival i.e. time at risk is important in estimating future fracture risk. Low survival among the oldest (>85years) acts as a competing event with fracture. This in addition to the high fracture incidence also observed in the oldest controls, especially in women, partly explains why fracture risk in hip fracture patients above age 85 is similar to the background population.

Musculoskeletal trauma

In this study we showed that almost every second radiographic investigation from a musculoskeletal trauma event led to a fracture in both men and women, suggesting that these patients are fall-prone. This information is of valuable socioeconomic interest, even if a fracture is not sustained the trauma injury often requires hospitalisation for pain management. Analysis of the type of trauma which resulted in the individual receiving medical attention reveals that almost all traumas in these patients are due to a low energy impact. The fractures sustained could have been prevented by pharmacological interventions.

Strengths and Limitations

The study design used offers advantages over register studies which although larger are often unable to determine with certainty the level of trauma (high/low energy), the side fractured (left/right) or when exactly the fracture occurred (new recent/repeated old). Estimates and exclusions are often made and verification of correct coding by the physician is not always possible. In Sweden, all citizens get a unique identification number which makes it possible to separate and identify patients, in a way which may not be possible in other countries.

This study includes a control group very closely matched to the patient population, which is not the case in all studies. In some studies they make comparisons with the general population selected from national statistical registers, overlooking the fact that individuals in different parts of the country could have different average lifetime and a completely different environment regarding nutrition, risk factors for fracture in addition to a different genetic background. In other studies exclusion criteria differ e.g. controls without prior fracture, in which case hip fracture patients are being compared with a population much healthier than the 'general population'.

This thesis utilised the unique archive at Malmö University Hospital where medical charts and X-rays have been saved since the beginning of last century, making it ideal for epidemiological research. Malmö city has also, until recently, had the advantage of having only one emergency hospital taking care of all emergency fractures and also treating all fracture follow-ups, thereby minimizing the possibility of missing any fracture [101]. While many studies rely on self reported fractures from

interviews/questionnaires our data rely on fracture assessments from one department of radiology. Even if a patient fractured elsewhere in Sweden or abroad it is most likely that the follow-up occurred in Malmö and therefore the fracture is captured. If anything the fracture numbers are under-estimated rather than the opposite.

There are a number of inherent difficulties associated in studying hip fracture patients. In many of the reported studies, women constitute the majority of the study cohort and hence drive the findings. When hip fracture patients are followed only in the short term, the majority of old patients who have a high early mortality drive the findings. If hip fracture patients are followed in long term without stratifying for age and sex, the younger individuals, especially women, will drive the findings. By following almost all hip fracture patients in a residual life time perspective, stratifying for age and sex and also performing analyses at different time points we were able to minimise the pitfalls mentioned above and obtain a true estimation of fracture occurrence and risk.

Several limitations to our study have to be acknowledged. In long term follow-up studies there is the possibility that results may be affected by secular changes over the years. The average lifetime for men and women in Sweden has increased during the observation period from 74 to 79 years in men and from 80 to 83 years in women, however these changes ought to affect cases and controls equally and are minimised by the short 2 year inclusion period that was employed. The mean age of sustaining a hip fracture in Sweden has increased proportionately to the average lifetime.

When interpreting the results, one has to be aware that treatment of medical conditions as well as surgical techniques has altered. In Sweden today, 56% of femoral neck hip fractures receive a primary hip replacement compared to just 2% in the mid 1980's, the inclusion date of our cohort [122]. There are to our knowledge no studies that show changes in mortality rate because of this alteration in surgical methods, although multiple studies suggest decreased morbidity [123-125]. The increased incidence of hip replacement could influence the pattern of subsequent fractures. One might expect an increase of fractures close the hip replacement implant rather than other femoral fractures. We can only speculate if the improved mobility following hip replacement results in more or less new fractures or different types of fracture. Similarly we can only speculate whether the few patients in our study who had their pins and plates removed due to discomfort could contribute to repeated hip fracture.

Finally, diagnosis of the cause of death has also undergone some changes over the course of the study. At the outset of the study the autopsy frequency in Sweden was 45%, for men and 35% for women but dropped to 19% for men and 9% for women by the end [102]. Therefore there is the possibility of some inaccuracies in the received cause of death information. Another limitation is the lack of detailed medical information since co-existing diseases can contribute both to the occurrence of a first

fracture, mortality and subsequent fracture risk. This information would have been of value since it is well recognized that co-morbidity may have pronounced effects on all aspects.

Prevention of new fractures: clinical implications

By showing the importance of age and sex on post-fracture survival and subsequent fracture risk, the clinical implication should be that both are factored in when establishing fracture prevention programs. However, the immediate measures should focus on optimised care from the fracture event through surgery and post-operative management. This is indeed also occurring, and hip fracture patients are fast-tracked through the emergency care to surgery. This also includes ensuring that the patient has received best possible preparations for surgery, factors that all contribute to post-fracture outcome. During the rehabilitation phase, prevention of future fractures should be included and best results are obtained by systematic approaches [49, 126, 127].

At its simplest level, fall prevention can be removal of hazards in the household and local environment and avoidance of multi-drug use with side effects on balance. Physiotherapy and exercise improve muscle strength and balance therefore theoretically may reduce falls, if not fractures [47, 100]. There are medications available, some with wider implications than just bone, reducing mortality rates and treating cardiovascular disease and atherosclerosis [95, 120, 128]. Given this knowledge, the under-treatment of osteoporosis is depressing [98, 129].

But the ultimate aim is to prevent fractures occurring in the first place, therefore clinicians from all disciplines and general practitioners should be fully educated in the risk factors for fracture within their speciality which includes referral for BMD assessment.

Future perspectives

Although we have addressed several important questions in this thesis, questions remain and new are added. Our findings are based on patients recruited during the mid 1980's, but given the improvements in surgical methods and medical care having occurred since then, a remaining question is if this has had any implications on long term mortality and subsequent fracture risk. This includes the effect of aging populations and the possibility that the mean age at hip fracture increases even further. However, the findings also emphasis that fracture prevention programs are necessary and when initiated their efficacy must be evaluated in order to ensure the effect on subsequent fractures; on time to fracture and on types of subsequent fractures for cost-effectiveness. There has been a clear reluctance to introduce fracture

prevention program and issues remain; who will be responsible for introducing such programs and who will be responsible for continued management, treatment and compliance.

8 Conclusions

In this thesis the following conclusions were reached for patients with hip fracture in a remaining lifetime perspective

- All hip fracture patients, both men and women and in each age-group, have an excess mortality compared to the background population. This is evident at all time points but highest during the first year, and persisting over 20 years.

- Almost half of all women with hip fracture suffer subsequent fractures.

- Almost one third of all men with hip fracture suffer subsequent fractures.

- Hip fracture patients below 75 years, both men and women, are at greatest risk of suffering subsequent fractures because of a longer time at risk, whereas those who are older, above 85 years, do not have a risk increase because of their high mortality.

- Hip fracture patients, men and women, have a greater risk of new fractures than their corresponding controls from the background population, evident in all but the oldest, those above 85 years.

- Hip and vertebral fracture, are the most common subsequent fractures in men and women with hip fracture as well as among controls.

- The most common cause of death was cardiovascular diseases, with a significant relative risk increase in hip fracture patients. The risk of dying from pneumonia, neurological and musculoskeletal trauma was also higher.

- Strategies to prevent subsequent fractures in hip fracture patients need to consider age, sex and the high risk mortality.

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10 Populärvetenskaplig sammanfattning

Osteoporos (benskörhet) innebär att såväl bentätheten som skelettets hållfasthet minskar, vilket leder till ökad risk att få frakturer (benbrott). Osteoporos är en folksjukdom, där frakturerna medför stora kostnader såväl för individen som för samhället. De frakturer som räknas som osteoporosfrakturer är i första hand de som drabbar höft, bäcken, axel, handled och kota. De som redan haft en osteoporosfraktur har en dubbelt så hög risk att få flera frakturer även vid lindrigt våld. Av frakturerna är höftfrakturen den som ger störst konsekvenser för den drabbade. Tre av fyra höftfrakturpatienter är kvinnor där majoriteten är gamla, ofta med andra komplicerande sjukdomar. Trots att det idag finns behandling mot osteoporos som effektivt kan minska risken för fraktur, är det få frakturpatienter som får förskrivet dessa mediciner. Detta innebär att osteoporos är både underdiagnostiserat och underbehandlat.

Syftet med studierna i denna avhandling är att identifiera skillnader i överlevnad på kort och lång sikt efter en höftfraktur och kvantifiera risken för nya frakturer i förhållande till ålder och kön. I studien ingår alla patienter, 766 kvinnor och 263 män, som drabbades av en höftfraktur i Malmö 1984/85 p.g.a. en lågenergiskada, d.v.s. att de snubblat eller fallit på golvet eller motsvarande. Dessa patienter jämförs med kontrollpersoner ur normalbefolkningen.

I avhandlingens första del beskrivs de kvinnliga höftfrakturpatienterna, som följdes i 22 år. Medelåldern var 80 år när de drabbades av höftfrakturen och nästan alla följdes livet ut. Endast 1 av 20 var kvar i livet vid uppföljningens slut. Redan inom ett år hade 1 av 5 dött, hälften var döda inom fem år och efter tio år fanns bara 1 av 4 kvar i livet. Knappt hälften av kvinnorna drabbades av nya frakturer under sin återstående livstid, i genomsnitt två nya frakturer. Risken att drabbas av nya frakturer var störst hos de yngre kvinnorna. För varje år en kvinna överlevde efter höftfrakturen ökade risken och vid uppföljningens slut hade nästan alla (85%) drabbats av minst en ny fraktur.

I avhandlingens andra del beskrivs de manliga höftfrakturpatienterna. Dessa

var yngre när de drabbades av sin höftfraktur, medelålder 76 år, och hade en högre tidig dödlighet. Av män med höftfraktur dog var tredje inom ett år och 6 av 10 inom fem år. Efter tio år var bara var femte man kvar i livet. Dödligheten var mest påtaglig hos männen över 85 år, där hälften dog redan inom 3 månader. Knappt en tredjedel drabbades av nya frakturer. Flest nya frakturer fick de män som var mellan 75-84 år där 4 av 10 drabbades, medan den långsiktiga risken var störst hos de yngre männen – precis som hos kvinnorna, eftersom dessa överlevde längre.

I nästa arbete tas reda på i hur stor utsträckning höftfrakturpatienterna skiljer sig från normalbefolkningen, när det gäller dödlighet och dödsorsak, i en jämförelse mellan alla höftfrakturpatienter och ålders- och könsmatchade kontrollpersoner. En högre dödlighet sågs under hela studieperioden hos både manliga och kvinnliga höftfrakturpatienter jämfört med kontroller, likaså inom varje åldersgrupp (under 75 år, 75-84 år, över 85 år). Relativt sett var dödligheten högst hos de yngre männen, de under 75 år. Den vanligaste dödsorsaken var hjärt-kärlsjukdom. Om man tog hänsyn till när dödsfallen inträffade, så hade både manliga och kvinnliga höft-frakturpatienter cirka 50% ökad risk att dö i hjärt-kärlsjukdomar jämfört med kontrollpersonerna.

I sista arbetet analyseras om höftfrakturpatienter har större risk att få nya frakturer jämfört med kontrollpersonerna. Nya frakturer inträffar hos närmare hälften av alla kvinnor, både höftfrakturpatienter och kontrollpersoner, och hos en tredjedel av de manliga höftfraktur-patienterna jämfört med var fjärde av de manliga kontrollpersonerna. Både kvinnliga och manliga höftfraktur-patienter hade en ökad risk över tid att drabbas av nya frakturer jämfört med kontrollpopulationen, förutom hos de allra äldsta (över 85 år). De höftfrakturpatienter som var relativt sett yngre när de drabbades av höftfrakturen, hade högre risk att drabbas av nya frakturer. De vanligaste nya frakturerna var höft-fraktur och kotfraktur hos både patienter och kontroller.

Sammanfattningsvis så har höft-frakturpatienter en ökad dödlighet och en ökad frakturrisk i förhållande till jämförbara personer i normal-befolkningen. Dessa studier visar att det är stora skillnader mellan kvinnor och män över tid, skillnader som dessutom är starkt åldersberoende. Denna kunskap har betydelse, inte minst för hur man lägger upp framtida åtgärder för att förebygga nya frakturer hos höftfraktur-patienter.

11 References

1. Cooper, C., G. Campion, and L.J. Melton, 3rd, *Hip fractures in the elderly: a world-wide projection.* Osteoporos Int, 1992. **2**(6): p. 285-9.
2. Borgstrom, F., et al., *At what hip fracture risk is it cost-effective to treat? International intervention thresholds for the treatment of osteoporosis.* Osteoporos Int, 2006. **17**(10): p. 1459-71.
3. Lee, N.K., et al., *Endocrine regulation of energy metabolism by the skeleton.* Cell, 2007. **130**(3): p. 456-69.
4. Downey, P.A. and M.I. Siegel, *Bone biology and the clinical implications for osteoporosis.* Phys Ther, 2006. **86**(1): p. 77-91.
5. Riggs, B.L., et al., *Rates of bone loss in the appendicular and axial skeletons of women. Evidence of substantial vertebral bone loss before menopause.* J Clin Invest, 1986. 77(5): p. 1487-91.
6. Walker-Bone, K., E. Dennison, and C. Cooper, *Epidemiology of osteoporosis.* Rheum Dis Clin North Am, 2001. **27**(1): p. 1-18.
7. *Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis.* Am J Med, 1993. **94**(6): p. 646-50.
8. *Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group.* World Health Organ Tech Rep Ser, 1994. **843**: p. 1-129.
9. *Prevention and management of osteoporosis.* World Health Organ Tech Rep Ser, 2003. **921**: p. 1-164, back cover.
10. Gluer, C.C. and R. Barkmann, *Quantitative ultrasound: use in the detection of fractures and in the assessment of bone composition.* Curr Osteoporos Rep, 2003. **1**(3): p. 98-104.
11. Stewart, A., V. Kumar, and D.M. Reid, *Long-term fracture prediction by DXA and QUS: a 10-year prospective study.* J Bone Miner Res, 2006. **21**(3): p. 413-8.
12. Garnero, P., et al., *Markers of bone resorption predict hip fracture in elderly women: the EPIDOS Prospective Study.* J Bone Miner Res, 1996. **11**(10): p. 1531-8.

13. Black, D.M., et al., *Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group.* Lancet, 1996. **348**(9041): p. 1535-41.
14. Melton, L.J., 3rd, *Hip fractures: a worldwide problem today and tomorrow.* Bone, 1993. **14 Suppl 1**: p. S1-8.
15. Tarantino, U., et al., *Incidence of fragility fractures.* Aging Clin Exp Res, 2007. **19**(4 Suppl): p. 7-11.
16. Garraway, W.M., et al., *Limb fractures in a defined population. II. Orthopedic treatment and utilization of health care.* Mayo Clin Proc, 1979. **54**(11): p. 708-13.
17. Cooper, C., *Epidemiology of osteoporosis.* Osteoporos Int, 1999. **9 Suppl 2**: p. S2-8.
18. Melton, L.J., 3rd, C.S. Crowson, and W.M. O'Fallon, *Fracture incidence in Olmsted County, Minnesota: comparison of urban with rural rates and changes in urban rates over time.* Osteoporos Int, 1999. **9**(1): p. 29-37.
19. Obrant, K.J., et al., *Increasing age-adjusted risk of fragility fractures: a sign of increasing osteoporosis in successive generations?* Calcif Tissue Int, 1989. **44**(3): p. 157-67.
20. Brauer, C.A., et al., *Incidence and mortality of hip fractures in the United States.* JAMA, 2009. **302**(14): p. 1573-9.
21. Leslie, W.D., et al., *Trends in hip fracture rates in Canada.* JAMA, 2009. **302**(8): p. 883-9.
22. Rogmark, C., et al., *Incidence of hip fractures in Malmo, Sweden, 1992-1995. A trend-break.* Acta Orthop Scand, 1999. **70**(1): p. 19-22.
23. Ahlborg, H.G., et al., *Prevalence of osteoporosis and incidence of hip fracture in women - secular trends over 30 years.* BMC Musculoskelet Disord. **11**(1): p. 48.
24. Melton, L.J., 3rd, et al., *Secular trends in hip fracture incidence and recurrence.* Osteoporos Int, 2009. **20**(5): p. 687-94.
25. SBU, *Osteoporosis -prevention, diagnostik och behandling*. 2003.
26. Kanis, J.A., et al., *International variations in hip fracture probabilities: implications for risk assessment.* J Bone Miner Res, 2002. **17**(7): p. 1237-44.
27. Lofthus, C.M., et al., *Epidemiology of hip fractures in Oslo, Norway.* Bone, 2001. **29**(5): p. 413-8.
28. Mallmin, H., et al., *Fracture of the distal forearm as a forecaster of subsequent hip fracture: a population-based cohort study with 24 years of follow-up.* Calcif Tissue Int, 1993. **52**(4): p. 269-72.

29. Johnell, O., et al., *Mortality after osteoporotic fractures.* Osteoporos Int, 2004. **15**(1): p. 38-42.
30. Haentjens, P., et al., *Evidence from data searches and life-table analyses for gender-related differences in absolute risk of hip fracture after Colles' or spine fracture: Colles' fracture as an early and sensitive marker of skeletal fragility in white men.* J Bone Miner Res, 2004. **19**(12): p. 1933-44.
31. Olsson, C., A. Nordquist, and C.J. Petersson, *Long-term outcome of a proximal humerus fracture predicted after 1 year: a 13-year prospective population-based follow-up study of 47 patients.* Acta Orthop, 2005. **76**(3): p. 397-402.
32. O'Neill, T.W., et al., *The prevalence of vertebral deformity in european men and women: the European Vertebral Osteoporosis Study.* J Bone Miner Res, 1996. **11**(7): p. 1010-8.
33. *Incidence of vertebral fracture in europe: results from the European Prospective Osteoporosis Study (EPOS).* J Bone Miner Res, 2002. **17**(4): p. 716-24.
34. Baron, J.A., et al., *Cigarette smoking, alcohol consumption, and risk of hip fracture in women.* Arch Intern Med, 2001. **161**(7): p. 983-8.
35. Olofsson, H., et al., *Smoking and the risk of fracture in older men.* J Bone Miner Res, 2005. **20**(7): p. 1208-15.
36. Gerdhem, P. and K.J. Obrant, *Effects of cigarette-smoking on bone mass as assessed by dual-energy X-ray absorptiometry and ultrasound.* Osteoporos Int, 2002. **13**(12): p. 932-6.
37. Liu, X., et al., *Cigarette smoke extract inhibits chemotaxis and collagen gel contraction mediated by human bone marrow osteoprogenitor cells and osteoblast-like cells.* Osteoporos Int, 2003. **14**(3): p. 235-42.
38. Nguyen, T.V., et al., *Lifestyle factors and bone density in the elderly: implications for osteoporosis prevention.* J Bone Miner Res, 1994. **9**(9): p. 1339-46.
39. Ward, K.D. and R.C. Klesges, *A meta-analysis of the effects of cigarette smoking on bone mineral density.* Calcif Tissue Int, 2001. **68**(5): p. 259-70.
40. Valdimarsson, O., et al., *Daily physical education in the school curriculum in prepubertal girls during 1 year is followed by an increase in bone mineral accrual and bone width--data from the prospective controlled Malmo pediatric osteoporosis prevention study.* Calcif Tissue Int, 2006. **78**(2): p. 65-71.

41. Alwis, G., et al., *A 2-year school-based exercise programme in pre-pubertal boys induces skeletal benefits in lumbar spine.* Acta Paediatr, 2008. **97**(11): p. 1564-71.
42. Gerdhem, P., et al., *Influence of muscle strength, physical activity and weight on bone mass in a population-based sample of 1004 elderly women.* Osteoporos Int, 2003. **14**(9): p. 768-72.
43. Farahmand, B.Y., et al., *Physical activity and hip fracture: a population-based case-control study. Swedish Hip Fracture Study Group.* Int J Epidemiol, 2000. **29**(2): p. 308-14.
44. Gerdhem, P., et al., *Association between 25-hydroxy vitamin D levels, physical activity, muscle strength and fractures in the prospective population-based OPRA Study of Elderly Women.* Osteoporos Int, 2005. **16**(11): p. 1425-31.
45. Blake, A.J., et al., *Falls by elderly people at home: prevalence and associated factors.* Age Ageing, 1988. **17**(6): p. 365-72.
46. Tinetti, M.E., M. Speechley, and S.F. Ginter, *Risk factors for falls among elderly persons living in the community.* N Engl J Med, 1988. **319**(26): p. 1701-7.
47. Gillespie, L., *Preventing falls in elderly people.* BMJ, 2004. **328**(7441): p. 653-4.
48. Grenier-Sennelier, C., et al., *Designing adverse event prevention programs using quality management methods: the case of falls in hospital.* Int J Qual Health Care, 2002. **14**(5): p. 419-26.
49. Haines, T.P., et al., *Effectiveness of targeted falls prevention programme in subacute hospital setting: randomised controlled trial.* BMJ, 2004. **328**(7441): p. 676.
50. Center, J.R., et al., *Risk of subsequent fracture after low-trauma fracture in men and women.* JAMA, 2007. **297**(4): p. 387-94.
51. Robinson, C.M., et al., *Refractures in patients at least forty-five years old. a prospective analysis of twenty-two thousand and sixty patients.* J Bone Joint Surg Am, 2002. **84-A**(9): p. 1528-33.
52. Kanis, J.A., et al., *A meta-analysis of previous fracture and subsequent fracture risk.* Bone, 2004. **35**(2): p. 375-82.
53. Klotzbuecher, C.M., et al., *Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis.* J Bone Miner Res, 2000. **15**(4): p. 721-39.
54. Lippuner, K., et al., *Remaining lifetime and absolute 10-year probabilities of osteoporotic fracture in Swiss men and women.* Osteoporos Int, 2009. **20**(7): p. 1131-40.

55. Nguyen, N.D., et al., *Residual lifetime risk of fractures in women and men.* J Bone Miner Res, 2007. **22**(6): p. 781-8.
56. Bliuc, D., et al., *Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women.* JAMA, 2009. **301**(5): p. 513-21.
57. Ryg, J., et al., *Hip fracture patients at risk of second hip fracture: a nationwide population-based cohort study of 169,145 cases during 1977-2001.* J Bone Miner Res, 2009. **24**(7): p. 1299-307.
58. Empana, J.P., P. Dargent-Molina, and G. Breart, *Effect of hip fracture on mortality in elderly women: the EPIDOS prospective study.* J Am Geriatr Soc, 2004. **52**(5): p. 685-90.
59. Farahmand, B.Y., et al., *Survival after hip fracture.* Osteoporos Int, 2005. **16**(12): p. 1583-90.
60. Kanis, J.A., et al., *The components of excess mortality after hip fracture.* Bone, 2003. **32**(5): p. 468-73.
61. Giversen, I.M., *Time trends of mortality after first hip fractures.* Osteoporos Int, 2007. **18**(6): p. 721-32.
62. Kannegaard, P.N., et al., *Excess mortality in men compared with women following a hip fracture. National analysis of comedications, comorbidity and survival.* Age Ageing, 2010. **39**(2): p. 203-9.
63. Rapp, K., et al., *Hip fractures in institutionalized elderly people: incidence rates and excess mortality.* J Bone Miner Res, 2008. **23**(11): p. 1825-31.
64. Vestergaard, P., L. Rejnmark, and L. Mosekilde, *Increased mortality in patients with a hip fracture-effect of pre-morbid conditions and post-fracture complications.* Osteoporos Int, 2007. **18**(12): p. 1583-93.
65. Cooper, C., et al., *Population-based study of survival after osteoporotic fractures.* Am J Epidemiol, 1993. **137**(9): p. 1001-5.
66. Roche, J.J., et al., *Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study.* BMJ, 2005. **331**(7529): p. 1374.
67. Schroder, H.M. and M. Erlandsen, *Age and sex as determinants of mortality after hip fracture: 3,895 patients followed for 2.5-18.5 years.* J Orthop Trauma, 1993. 7(6): p. 525-31.
68. Wehren, L.E., et al., *Gender differences in mortality after hip fracture: the role of infection.* J Bone Miner Res, 2003. **18**(12): p. 2231-7.
69. Abrahamsen, B., et al., *Excess mortality following hip fracture: a systematic epidemiological review.* Osteoporos Int, 2009. **20**(10): p. 1633-50.

70. Browner, W.S., et al., *Mortality following fractures in older women. The study of osteoporotic fractures.* Arch Intern Med, 1996. **156**(14): p. 1521-5.
71. Cauley, J.A., et al., *Risk of mortality following clinical fractures.* Osteoporos Int, 2000. **11**(7): p. 556-61.
72. Kado, D.M., et al., *Incident vertebral fractures and mortality in older women: a prospective study.* Osteoporos Int, 2003. **14**(7): p. 589-94.
73. Hasserius, R., et al., *Long-term morbidity and mortality after a clinically diagnosed vertebral fracture in the elderly--a 12- and 22-year follow-up of 257 patients.* Calcif Tissue Int, 2005. **76**(4): p. 235-42.
74. Kenzora, J.E., et al., *Hip fracture mortality. Relation to age, treatment, preoperative illness, time of surgery, and complications.* Clin Orthop, 1984(186): p. 45-56.
75. Holmberg, A.H., et al., *Risk factors for hip fractures in a middle-aged population: a study of 33,000 men and women.* Osteoporos Int, 2005. **16**(12): p. 2185-94.
76. Lipscombe, L.L. and J.E. Hux, *Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995-2005: a population-based study.* Lancet, 2007. **369**(9563): p. 750-6.
77. Melton, L.J., 3rd, et al., *Fracture risk in type 2 diabetes: update of a population-based study.* J Bone Miner Res, 2008. **23**(8): p. 1334-42.
78. Melton, L.J., 3rd, et al., *Fracture risk after the diagnosis of Parkinson's disease: Influence of concomitant dementia.* Mov Disord, 2006. **21**(9): p. 1361-7.
79. Genever, R.W., T.W. Downes, and P. Medcalf, *Fracture rates in Parkinson's disease compared with age- and gender-matched controls: a retrospective cohort study.* Age Ageing, 2005. **34**(1): p. 21-4.
80. Johnell, O., et al., *Fracture risk in patients with parkinsonism: a population-based study in Olmsted County, Minnesota.* Age Ageing, 1992. **21**(1): p. 32-8.
81. Ramnemark, A., et al., *Stroke, a major and increasing risk factor for femoral neck fracture.* Stroke, 2000. **31**(7): p. 1572-7.
82. Sennerby, U., et al., *Cardiovascular diseases and risk of hip fracture.* JAMA, 2009. **302**(15): p. 1666-73.
83. MacLean, C., et al., *Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis.* Ann Intern Med, 2008. **148**(3): p. 197-213.
84. Wells, G., et al., *Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women.* Cochrane Database Syst Rev, 2008(1): p. CD004523.

85. Cummings, S.R., et al., *Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial.* JAMA, 1998. **280**(24): p. 2077-82.
86. McClung, M.R., et al., *Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group.* N Engl J Med, 2001. **344**(5): p. 333-40.
87. Reginster, J., et al., *Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group.* Osteoporos Int, 2000. **11**(1): p. 83-91.
88. Ettinger, B., et al., *Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators.* JAMA, 1999. **282**(7): p. 637-45.
89. Torgerson, D.J. and S.E. Bell-Syer, *Hormone replacement therapy and prevention of vertebral fractures: a meta-analysis of randomised trials.* BMC Musculoskelet Disord, 2001. **2**: p. 7.
90. Torgerson, D.J. and S.E. Bell-Syer, *Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials.* JAMA, 2001. **285**(22): p. 2891-7.
91. Chesnut, C.H., 3rd, et al., *A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group.* Am J Med, 2000. **109**(4): p. 267-76.
92. Greenspan, S.L., et al., *Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial.* Ann Intern Med, 2007. **146**(5): p. 326-39.
93. Neer, R.M., et al., *Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis.* N Engl J Med, 2001. **344**(19): p. 1434-41.
94. Reginster, J.Y., et al., *Effects of long-term strontium ranelate treatment on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis: Results of a five-year, randomized, placebo-controlled trial.* Arthritis Rheum, 2008. **58**(6): p. 1687-95.
95. Lyles, K.W., et al., *Zoledronic acid and clinical fractures and mortality after hip fracture.* N Engl J Med, 2007. **357**(18): p. 1799-809.

96. Kiebzak, G.M., et al., *Undertreatment of osteoporosis in men with hip fracture.* Arch Intern Med, 2002. **162**(19): p. 2217-22.
97. Giangregorio, L., et al., *Fragility fractures and the osteoporosis care gap: an international phenomenon.* Semin Arthritis Rheum, 2006. **35**(5): p. 293-305.
98. Rabenda, V., et al., *Low incidence of anti-osteoporosis treatment after hip fracture.* J Bone Joint Surg Am, 2008. **90**(10): p. 2142-8.
99. Kronhed, A.C. and M. Moller, *Effects of physical exercise on bone mass, balance skill and aerobic capacity in women and men with low bone mineral density, after one year of training--a prospective study.* Scand J Med Sci Sports, 1998. **8**(5 Pt 1): p. 290-8.
100. Chang, J.T., et al., *Interventions for the prevention of falls in older adults: systematic review and meta-analysis of randomised clinical trials.* BMJ, 2004. **328**(7441): p. 680.
101. Jonsson, B., et al., *Remembering fractures: fracture registration and proband recall in southern Sweden.* J Epidemiol Community Health, 1994. **48**(5): p. 489-90.
102. The National Board of Health and Welfare CENTRE FOR EPIDEMIOLOGY, S., *Causes of death*. 2006: The National Board of Health and Welfare, Sweden.
103. Mackey, D.C., et al., *High-trauma fractures and low bone mineral density in older women and men.* Jama, 2007. **298**(20): p. 2381-8.
104. Forsen, L., et al., *Survival after hip fracture: short- and long-term excess mortality according to age and gender.* Osteoporos Int, 1999. **10**(1): p. 73-8.
105. Center, J.R., et al., *Mortality after all major types of osteoporotic fracture in men and women: an observational study.* Lancet, 1999. **353**(9156): p. 878-82.
106. Kanis, J.A., et al., *FRAX and the assessment of fracture probability in men and women from the UK.* Osteoporos Int, 2008. **19**(4): p. 385-97.
107. Braithwaite, R.S., N.F. Col, and J.B. Wong, *Estimating hip fracture morbidity, mortality and costs.* J Am Geriatr Soc, 2003. **51**(3): p. 364-70.
108. Poor, G., et al., *Determinants of reduced survival following hip fractures in men.* Clin Orthop Relat Res, 1995(319): p. 260-5.
109. Fransen, M., et al., *Excess mortality or institutionalization after hip fracture: men are at greater risk than women.* J Am Geriatr Soc, 2002. **50**(4): p. 685-90.

110. Parker, M.J., et al., *Hip fracture rehabilitation -- a comparison of two centres.* Injury, 2002. **33**(1): p. 7-11.
111. Todd, C.J., et al., *Differences in mortality after fracture of hip: the east Anglian audit.* BMJ, 1995. **310**(6984): p. 904-8.
112. Nguyen, N.D., et al., *Identification of high-risk individuals for hip fracture: a 14-year prospective study.* J Bone Miner Res, 2005. **20**(11): p. 1921-8.
113. Jones, G., et al., *Symptomatic fracture incidence in elderly men and women: the Dubbo Osteoporosis Epidemiology Study (DOES).* Osteoporos Int, 1994. **4**(5): p. 277-82.
114. Browner, W.S., et al., *Non-trauma mortality in elderly women with low bone mineral density. Study of Osteoporotic Fractures Research Group.* Lancet, 1991. **338**(8763): p. 355-8.
115. Chapurlat, R.D., et al., *Incidence and risk factors for a second hip fracture in elderly women. The Study of Osteoporotic Fractures.* Osteoporos Int, 2003. **14**(2): p. 130-6.
116. Richmond, J., et al., *Mortality risk after hip fracture.* J Orthop Trauma, 2003. **17**(1): p. 53-6.
117. Boereboom, F.T., J.A. Raymakers, and S.A. Duursma, *Mortality and causes of death after hip fractures in The Netherlands.* Neth J Med, 1992. **41**(1-2): p. 4-10.
118. Nymark, T., et al., *Short time-frame from first to second hip fracture in the Funen County Hip Fracture Study.* Osteoporos Int, 2006. **17**(9): p. 1353-7.
119. Berry, S.D., et al., *Second hip fracture in older men and women: the Framingham Study.* Arch Intern Med, 2007. **167**(18): p. 1971-6.
120. Cree, M.W., A.G. Juby, and K.C. Carriere, *Mortality and morbidity associated with osteoporosis drug treatment following hip fracture.* Osteoporos Int, 2003. **14**(9): p. 722-7.
121. Boston, D.A., *Bilateral fractures of the femoral neck.* Injury, 1982. **14**(3): p. 207-10.
122. Socialstyrelsen, S.K.o.L., *Öppna jämförelser av hälso- och sjukvårdens kvalitet och effektivitet.* 2009: Socialstyrelsen, Sveriges Kommuner och Landsting.
123. Tidermark, J., et al., *Internal fixation compared with total hip replacement for displaced femoral neck fractures in the elderly. A randomised, controlled trial.* J Bone Joint Surg Br, 2003. **85**(3): p. 380-8.

124. Leonardsson, O., et al., *Long-term follow-up of replacement compared with internal fixation for displaced femoral neck fractures: results at ten years in a randomised study of 450 patients.* J Bone Joint Surg Br. **92**(3): p. 406-12.
125. Roden, M., M. Schon, and H. Fredin, *Treatment of displaced femoral neck fractures: a randomized minimum 5-year follow-up study of screws and bipolar hemiprostheses in 100 patients.* Acta Orthop Scand, 2003. **74**(1): p. 42-4.
126. Bogoch, E.R., et al., *Effective initiation of osteoporosis diagnosis and treatment for patients with a fragility fracture in an orthopaedic environment.* J Bone Joint Surg Am, 2006. **88**(1): p. 25-34.
127. McLellan, A.R., et al., *The fracture liaison service: success of a program for the evaluation and management of patients with osteoporotic fracture.* Osteoporos Int, 2003. **14**(12): p. 1028-34.
128. Persy, V. and P. D'Haese, *Vascular calcification and bone disease: the calcification paradox.* Trends Mol Med, 2009. **15**(9): p. 405-16.
129. Luthje, P., et al., *Undertreatment of osteoporosis following hip fracture in the elderly.* Arch Gerontol Geriatr, 2009. **49**(1): p. 153-7.

12 Appendix

Appendix Table 4.1 Categorization of fractures in **Paper IV**

Fracture Site	**Description**	**Comparable ICD codes**
Hip	Fractures of the femoral neck to subtrochanteric fractures. Excludes isolated fractures of the major/minor trochanter.	10: S72.0-S72.2
Pelvis	Fractures of the pelvis.	10: S32.2 - S32.8
Shoulder	Fractures of the proximal humerus and scapula. Excludes clavicle and isolated tuberculum major/minor fractures.	10: S42.1 - S42.2
Forearm	Fractures of the distal radius and ulna. Excludes diaphyseal and proximal forearm fractures and metacarpal fractures.	10: S52.5-S52.6, S52.8
Vertebral	Vertebral fractures.	10: S12.2, S22.0, S32.0
Other	All other fractures.	

Appendix Table 4.2a: ICD Codes for major causes of death – major groups in **Paper III**

Coding of major causes of death	
Infectious disease	ICD 10 – A00-B99, ICD 9 and 8 – 000-136 and 460-486
Cancer	ICD10 – C00-D48 excludes D10-D36, ICD 9 and 8 – 140-239
Endocrinological diseases	ICD 10 – E00-E90, ICD 9 and 8 – 240-279
Psychiatric diseases	ICD 10 – F00-F99, ICD 9 and 8 – 290-319 (excludes 290)
Neurological disease	ICD 10 – G00-G99, ICD 9 and 8 – 320-358 and 290
Cardiovascular disease	ICD10 – I00-I99, ICD9 and 8 – 390-459
Chronic obstructive pulmonary disease	ICD 10 – J40-J47, ICD 9 and 8 – 490-496
Pneumonia and upper respiratory tract infection	ICD 10 - J00-J22, ICD 9 and 8 – 460-466 and 480-486
Digestive system diseases	ICD 10 – K00-K93, ICD 9 and 8 – 520-577
Musculoskeletal disorders, excluding trauma	ICD 10 – M00-M99, ICD 9 and 8 – 710-738
Genitourinary diseases	ICD 10 – N00-N99 excludes N60-N64, ICD 9 and 8 – 580-629 excludes 610-611
External causes	ICD 10 – S00-T98 and V01-Y98, ICD 9 and 8 – 800-999
Trauma, musculoskeletal	ICD 10 – S00-S99 and T00-T14, ICD 9 and 8 – 800-959
Other diseases	Remaining ICD codes

Appendix Table 4.2b: ICD Codes for major causes of death – sub-groups in **Paper III**

Coding of causes of death according to sub-groups	
Breast cancer	ICD 10 – C50, ICD 9 and 8 – 174
Lung cancer	ICD 10 – C34, ICD 9 and 8 – 162
Prostate cancer	ICD 10 – C61, ICD 9 and 8 – 185
Digestive system cancer	ICD 10 – C15-C26, ICD 9 and 8 – 150-159
Diabetes Mellitus	ICD 10 – E10-E14, ICD 9 and 8 – 250
Dementia	ICD 10 – F1-F3 and G30, IUC 9 and 8 – 290
Alcohol related diseases	ICD 10 – F10 and G31.2, ICD 9 and 8 – 291 and 303
Coronary heart disease	ICD 10 – I20-I25, ICD9 and 8 – 410-414
Stroke	ICD 10 – I60-I69, ICD 9 and 8 – 430-438
Urinary tract infection	ICD 10 – N10, N12, N13.6, N15, N30, N34 and N39.0, ICD 9 and 8 – 590 and 595
Road traffic accidents	ICD 10 – V01-V99, ICD 10 – E807-E846
Falls	ICD 10 – W00-W19, ICD 9 and 8 – E880-E888
Suicide	ICD 10 – X60-X84, ICD 9 and 8 – E950-E959

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