Hip Fracture Incidence and Prevalence of Osteoporosis in Sweden in Recent Decades

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Hip Fracture Incidence and Prevalence of Osteoporosis in Sweden in Recent Decades

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The real voyage of discovery consists not in seeking new landscapes,
but in having new eyes.

Marcel Proust

Contents

List of papers

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

I *Stable hip fracture incidence and bone mineral density – A study of Swedish urban and rural women 1987–2002* (Rosengren B, Ahlborg H, Gärdsell P, Sernbo I, Daly R, Nilsson J-Å, Karlsson M). Accepted for publication in Acta Orthopaedica.

II *No Changes in Hip Fracture Incidence or Bone Mineral Density in Swedish Urban and Rural Men 1987–2002* (Rosengren B, Ahlborg H, Gärdsell P, Sernbo I, Daly R, Nilsson J-Å, Karlsson M). Submitted

III *Prevalence of Osteoporosis and Incidence of Hip Fracture in Women – Secular Trends Over 30 Years* (Ahlborg H, Rosengren B, Järvinen T, Rogmark C, Nilsson J-Å, Sernbo I, Karlsson M). Accepted for publication in BMC Musculoskeletal Disorders.

IV *Secular Trends in Swedish Nationwide Hip Fractures 1987–2002 – Results of Birth Cohort and Period Effects* (Rosengren B, Ahlborg H, Mellström D, Nilsson J-Å, Björk J, Karlsson M). Submitted

Aims

The aims of this thesis were to evaluate:

- Secular trends in urban and rural Swedish men and women regarding the number of hip fractures, hip fracture incidence and their relationship to changes in risk factors, mainly BMD and osteoporosis, and changes in demographics.

- Nationwide secular trends in the number of hip fractures and hip fracture incidence including possible period and cohort effects.

- Secular changes in BMD and prevalence of osteoporosis and incidence of hip fracture in the city of Malmö, Sweden, with possible expectations for the future.

Introduction

Bone

Bone is a mineral connective tissue that serves three main functions: (i) support for muscle and tendons; (ii) protection for vital organs and hemopoetic tissue; and (iii) mineral reservoir especially for calcium, magnesium and phosphate. Bone consists of approximately 75% inorganic components, 20% organic components and 5% water. The abundant inorganic component consists mainly of an analog of the naturally occurring mineral hydoxyapatite [$Ca_{10}(PO_4)_6(OH)_2$]. Of the organic components, 98% are collagen fibers and the remaining 2% bone cells. There are three main types of bone cells, of which 90–95% are osteocytes, thought to sense and mediate the effects of mechanical load, 4–6% bone-forming osteoblasts, and 1–2% bone-resorbing osteoclasts. The external portion of a bone consists of a dense calcified tissue called cortical bone, while the inside is formed of the same tissue components arranged in a trabecular network and is referred to as cancellous or trabecular bone.

As stated more than fifty years ago: "The stability and immutability of dry bones and their persistence for centuries, and even millions of years after the soft tissues have turned to dust, give us a false impression of bone during life. Its fixity after death is in sharp contrast to its ceaseless activity during life"(Cooke 1955). Bone is a living organ constantly reshaping and reinforcing damaged structures throughout life by a continuous process of resorption and formation called remodeling. About 10% of the total bone tissue is remodeled annually, with a higher 20–25% proportion in trabecular bone than the 3–5% proportion in cortical bone. Trabecular bone is thus more susceptible than cortical bone to changes affecting bone cells. The process of remodeling takes place in a cluster of activated cells referred to as the bone remodeling unit (BRU). The units, consisting of osteoblasts and osteoclasts and their precursors, are located mainly on the surface of trabecular bone and within the Haversian canals in cortical bone. After activation the remodeling sequence starts with resorption of bone by osteoclasts. The resulting resorption pit is

then filled by osteoblasts with unmineralized bone matrix called osteoid and is finally mineralized.

Bone strength and fracture

Bone strength is a multimodal term with no clear definition. Obviously it concerns the mechanical strength of bone to withstand an outer force. This strength is dependent on many factors (Table 1) and Bone Mineral Density (BMD) encompasses only some of these factors, but is at present the most readily available entity for clinical evaluation of bone strength. Main determinants of fracture risk are presented in Figure 1.

Factors influencing bone strength
Structural properties
Bone macro architecture (geometry)
Bone micro architecture (both trabecular and cortical)
Material properties
Matrix and mineral composition
Degree of mineralization
Micro damage accumulation
Bone turnover

Table 1

When a force is applied to a bone it is absorbed and stored in the bone by the act of bone deformation. When the force is lower than the yield point of the bone, the bone will resume its original shape after the release of the force. Any force greater than the yield point will cause micro damage and plastic deformation of the bone (i.e. the bone will not resume its original shape after the force has been released). Continuing to increase the force will eventually reach the breaking strength of the bone and a fracture will occur and the bone will separate into two or more fragments.

Fractures caused by a small force (low energy) occur if the bone strength is weak while high-energy fractures occur no matter what the bone strength is. It has been accepted that falls from low height, i.e. from standing, result in low-energy trauma while a traffic accident in 100 km/h gives a high-energy trauma. In line with the above reasoning, it cannot be excluded that some high-energy fractures occur in individuals with low bone strength. Fractures resulting from low-energy trauma are usually called fragility fractures and include fractures of

the hip, wrist, vertebrae, shoulder and pelvis. This thesis considers only the most adverse and most frequently examined of these: the hip fracture.

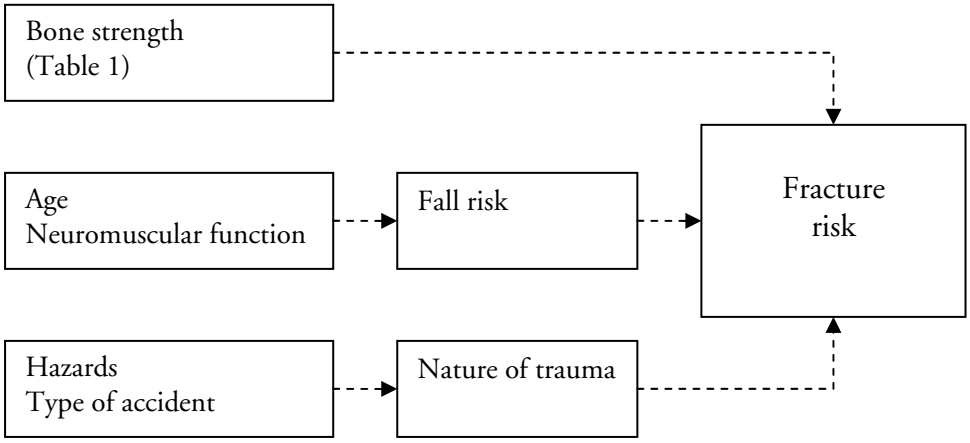

Figure 1

Hip fracture

The hip fracture is said to have first been recognized by Ambroise Paré in 1634. In 1824 Sir Astley Cooper made the important distinction between the two major types of hip fractures (Cooper 1842), (i) the intra-capsular, with the potential of affecting the vascular supply of the femoral head, and (ii) the extra-capsular.

Definition

The incidence of fractures is bimodal, with peaks in childhood and in old age. During younger ages a fracture is usually preceded by a substantial trauma. In older ages bone strength is decreased and the trauma preceding a fracture is often minor, such as falling from standing height. The remaining lifetime risk of any fragility fracture at age 50 in Malmö, Sweden, has been estimated as 46% in women and 22% and in men, and for hip fracture, generally considered the worst fragility fracture, 23% in women and 11% in men (Kanis et al. 2000). Probably due to the shifts in demographic distribution in society, improved health care and increased expected survival, the average age of hip fracture patients has increased since the 1960s at a rate of about 1 year of age per 5-year calendar period (Haleem et al. 2008).

A fracture of the proximal part of the femur is referred to as a hip fracture. Three main categories are defined based on the anatomical location of the fracture line; (a) cervical (medial to the intertrochanteric line), (b) intertrochanteric and (c) subtrochanteric (distal to the intertrochanteric line and up to 5 cm distal to the lesser trochanter) (Figure 2). Each subtype can be further categorized according to special classifications for optimal surgical treatment. With few exceptions all hip fractures are treated surgically (current general classification and treatment regime from Malmö, Sweden, are presented in Table 2).

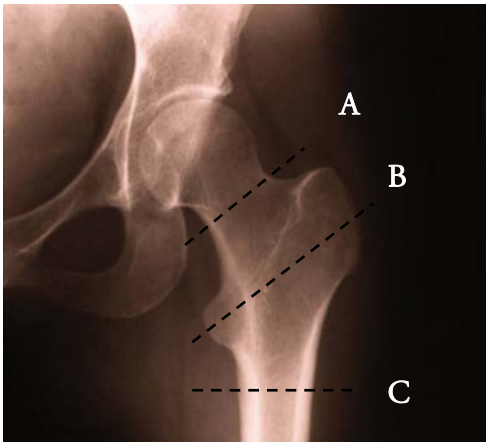

Figure 2

Main outlines of present general classification and treatment regimes of hip fractures in Malmö, Sweden

Fracture type	Surgical treatment method
Cervical (A)	
Undisplaced	LIH nails
Displaced in young individuals (<70 years)	LIH nails
Displaced in healthy elderly (70–80 years)	Total arthroplasty (THA)
Displaced in morbid or elderly (>80 years)	Hemi-arthroplasty
Trochanteric fracture (B)	
Stable	Plate with compression screw
Unstable	Sliding plate with compression screw
Subtrochanteric fracture (C)	
	Sliding plate with compression screw or Intramedullar nail

Table 2

Epidemiology, secular trends and projections for the future

The majority of hip fractures occur after a fall from a low height (Gallagher et al. 1980). There are reports of a seasonal variation with increased incidence in winter although most hip fractures occur indoor and are not the result of a fall on snow or ice (Jacobsen et al. 1995, Jacobsen et al. 1991). Hip fracture incidence increases exponentially with age (Kanis et al. 2000); 90% of hip fractures occur after the age of 50 (Gallagher et al. 1980) and 80% affect women (Gallagher et al. 1980). In ages above 50 the male to female ratio is between 1:2 and 1:4 (Gullberg et al. 1993, Leslie et al. 2009). Racial differences are obvious, with a higher risk in Caucasians than non-Caucasians (Silverman et al. 1988, Fang et al. 2004, Farmer et al. 1984). Differences are seen between countries (in Europe 7-fold (Johnell et al. 1992)) as well as within countries (Kaastad et al. 1998, Sanders et al. 2002, Sernbo et al. 1988, Mannius et al. 1987, Jonsson et al. 1992, Melton et al. 1999, Chevalley et al. 2002).

Osteoporosis and its ultimate consequence, hip fractures are known to have occurred in ancient Egypt (1990–1786 B.C.) (Dequeker et al. 1997). During most of the last century both the number and the incidence of hip fractures have mostly been inferred to have increased, but recent studies report a leveling off or even a decrease in hip fracture incidence (Rogmark et al. 1999, Melton et al. 1996, Melton et al. 2009, Kannus et al. 2006, Jaglal et al. 2005, Nymark et al. 2006, Lofman et al. 2002, Chevalley et al. 2007, Icks et al. 2008, Leslie et al. 2009, Abrahamsen et al. 2010). Future changes in age structure in society, especially in the number of individuals aged ≥65 years, which has been anticipated to double in Europe and sextuple in Asia from 1990 to 2050 (Cooper et al. 1992, Cummings et al. 2002), have led to projections of dramatically increasing numbers of hip fractures in the future (from 1.7 million in 1990 to 6.3 million worldwide in 2050) and a probable shift of geographical dominance in the number of hip fractures from Europe and North America to Asia and South America (Cooper et al. 1992).

Costs and requirements for society

Recently there have been an estimated 70 000 annual osteoporosis-related fractures in Sweden (SBU 2003) and annual costs of MSEK 5 639 (Borgstrom et al. 2007), which is about 3.2% of the total nationwide health care costs. Already in 1996 the number of hospital-bed days due to osteoporotic fracture in Sweden was estimated to be more than 600 000, a number in between those for stroke and ischemic heart disease (Johnell et al. 2005). Worldwide hip

fracture costs have been estimated at $34 800 million in 1990, increasing to $131 000 million in 2050 (Johnell 1997). The future thus will require a major allocation of hip fracture care resources, including reorganization and expansion of hospitals and operation theaters as well as social disability services.

Osteoporosis and other risk factors for fragility fractures

Osteoporosis is a silent disease. You often don't know that you have got it until your get the symptom – a fracture.

The relationship between age, loss of bone quality and certain fractures was identified in 1824 by Sir Astley Cooper (Cooper 1842). The term osteoporosis was initially used to describe the porosity of senile human bone in histological specimens. Osteoporosis is currently defined as "a disease characterized by low bone mass, micro architectural deterioration of the bone tissue leading to enhanced bone fragility and as a consequence increased fracture risk" (Anonymous 1991) An operational definition based on bone mass and previous fragility fracture was produced by an expert group of the WHO (WHO 1994), a definition that is widely accepted today (Table 3). This operational definition only partly encompasses the two concepts used earlier: (i) individuals with fractures (making prediction impossible) and (ii) individuals with increased fracture risk (when not including other risk factors than BMD and previous fracture). The measurement of BMD, however, has at least as good ability to predict fracture risk as the ability of cholesterol to predict heart disease or blood pressure to predict stroke risk (Kanis et al. 2005). With decreasing BMD there is a continuous increase in fragility fracture risk without any clear cut-off values, with each standard deviation decrease in BMD (as measured by DXA) implying a 1.5- to 3-fold risk of fragility fracture. When BMD is measured in the hip, there is a corresponding 2.6-fold risk of hip fracture (Marshall et al. 1996).

Normal bone mineral density (BMD), osteopenia, osteoporosis, and established osteoporosis as defined by the World Health Organization

Diagnostic category	*Definition*	*BMD T-score*
Normal bone mass	BMD <1 standard deviation below the average young adult value	>–1
Osteopenia	BMD 1 to 2.5 standard deviations below the average young adult value	–1 to –2.5
Osteoporosis	BMD >2.5 standard deviations below the average young adult value	<–2.5
Severe osteoporosis or Established osteoporosis	BMD >2.5 standard deviations below the average young adult value and at least one osteoporotic fracture	<–2.5

Table 3

There are, however, many other risk factors for fragility fracture (Table 4) and tools have been developed to encompass these too, together with estimates of 5- or 10-year fragility fracture probabilities derived from major international or national studies. The Fracture Index is a simple self-administered questionnaire which estimates 5-year fracture probability (Black et al. 2001) while a web-based clinical risk assessment tool (FRAX) has been developed by WHO to estimate country-specific 10-year fracture probability. The risk factors assessed in the FRAX model are sex, age, weight, height, glucocorticoid use, smoking, prior fracture, family history of fracture, rheumatoid arthritis and excess alcohol consumption with or without BMD measurements (Kanis et al. 2005). No consensus regarding the optimal probability threshold for treatment exists, though, which makes clinical use somewhat difficult.

Risk factors for osteoporosis and fragility fracture

Age	Nutrition	Ethnicity
Gender	BMI/weight/height	Nursing home resident
BMD	Alcohol/smoking/caffeine	Organ transplantation
Heredity	Physical inactivity	Premature menopause
Skeletal geometry	Falls	Vitamin D deficiency
Prior fracture	Immobility	Malapsorbtion
Sedative medication	Glucocorticoids	Malignancy

Table 4

Pathogenesis of osteoporosis

In early life bone size and BMD increase through a process called modeling. In early adulthood, between the ages of 18 and 30, the highest bone mass in life is reached, referred to as peak bone mass (PBM). PBM is higher in men than in women, probably due to the later onset and longer duration of puberty in boys compared to girls. After PBM is attained, bone mass is fairly stable until menopause, when female sex hormone levels drop and result in a subsequent loss of BMD the following 5 or 10 years (Ahlborg et al. 2003). Bone turnover in osteoporotic individuals can be decreased, normal or even elevated, but imbalance between formation, which is usually decreased, and resorption always seems to be present (Eriksen et al. 1990). If a specific cause of osteoporosis is present (such as endocrine, metabolic, gastrointestinal or renal disorders and certain drug treatment) it is referred to as secondary, otherwise the term primary osteoporosis is used.

Assessment of bone mineral density

DXA (Dual energy X-ray Absorptiometry)

DXA was introduced in 1987 and is currently considered the golden standard for measurements of bone mass and the basis for the diagnosis of osteoporosis. The technique uses two X-ray energies transmitted through the body, which are attenuated differently by soft tissue and bone, making evaluation of the central skeleton possible (Mazess et al. 1989). The most studied regions are the hip and spine, but peripheral limb evaluation of the forearm or calcaneus is also possible.

SPA (Single photon absorptiometry)/DPA (Dual photon absorptiometry)

SPA was the first practical technique for determination of areal bone density using a radioactive isotope and was available in the 1960s (Nauclér et al. 1974). The method relies on the assumption that the thickness of the soft tissue in the area of measurement is constant, ensured by a cuff of the same density as the soft tissue, usually filled with water. Hence only appendicular parts of the skeleton, most often the forearm or the calcaneus, can be analyzed. The detector moves across the fixed limb and registers the mineral content of the bone by comparing it with the surrounding water and soft tissue. The SPA technique was replaced by DXA, but studies have shown good correlation

between the two (Karlsson et al. 1993) as well as good fracture prediction with SPA (Cummings et al. 1993, Marshall et al. 1996, Stone et al. 2003). DPA was a further development of SPA enabling evaluation of central parts of the skeleton such as the spine and hip, but it too has been replaced by DXA.

QUS (Quantitative ultrasound)

In quantitative ultrasound a signal from 100 kHz to 2 MHz is transmitted through appendicular bone, most often the calcaneus. Derived parameters are speed of sound (SOS) (Heaney et al. 1989) and bone ultrasound attenuation (BUA) (Langton et al. 1984). The parameters are considered to reflect not only bone mineral content but also bone microarchitecture, elasticity and strength.

QCT (Quantitative computer tomography)

QCT evaluates the actual volumetric bone density of the selected area by the use of standard CT scanners with optional protocols (Alvarez et al. 1976). Specific analysis of trabecular bone, bone cortex, bone size and bone shape in the area of interest are possible. Smaller systems for analyses of peripheral QCT (pQCT) in the forearm or the lower leg are available, and recently apparatuses for high-resolution pQCT (HR-pQCT) have been introduced, making evaluation of specific trabecular and cortical microarchitecture and bone loss possible.

Outcome

Mortality

Following a hip fracture, mortality rates are increased 2–4-fold (Farahmand et al. 2005, Forsen et al. 1999), more pronounced in men than women and with evident geographic variations (Haleem et al. 2008). The one-year and five-year mortality figures after a hip fracture has been described as being around 35% and 60% in men, while the corresponding figures for women are 20% and 55% (Vestergaard et al. 2007, Forsen et al. 1999, Johnell et al. 2004, Sernbo et al. 1993). The increased mortality rates seem only partly attributable to the fracture, surgery and complications, but more so to pre-fracture morbidities (Johnell et al. 2004). The main predictors of death are age, mental status, comorbidity and functional impairment (Poor et al. 1995, Alegre-Lopez et al. 2005, Sernbo et al. 1993).

Morbidity

A hip fracture is a terrible event for the individual, with deterioration of walking ability, impairment of independence as well as psychological expectations of rapid deterioration and death. It has been shown that 80% of women aged ≥75 years would prefer death to a bad hip fracture with loss of independence and quality of life (Salkeld et al. 2000). Outcome after hip fracture depends on a number of variables, not only age but also pre-fracture morbidity and social network. Apart from any direct medical complications (such as pneumonia, urinary tract infection or the more rare pressure ulcer), impaired independence and walking ability are the most common disabilities. One year after hip fracture, reports show that 60% of patients are in need of assistance for activities of daily living, 80% are unable to perform simple operational activities (such as shopping, house cleaning or getting to places out of walking distance) (United States. Congress. Office of Technology Assessment. 1994) and fewer than 50% regained their pre-fracture walking ability (Sernbo et al. 1993). A major initial decrease in average quality of life and well-being (both subjectively and objectively evaluated) has been shown with a regain after a couple of months but remaining impaired after one and five years (United States. Congress. Office of Technology Assessment. 1994, Randell et al. 2000, Tosteson et al. 2001).

Prevention of hip fractures

A number of non-pharmacological interventions have been proposed to decrease hip fracture risk including fall prevention, exercise and hip protectors. Fall prevention programs alone have not as yet been shown to reduce hip fracture risk, but exercise, especially walking (Feskanich et al. 2002) as well as multimodal approaches for nursing home residents (Jensen et al. 2002) have been inferred to reduce hip fracture risk. Ambiguous evidence on the efficacy of hip protectors has been presented. Lifestyle factors such as cigarette smoking and alcohol consumption are known risk factors for hip fracture, but a decrease or cessation of use has not been shown to decrease hip fracture risk. Lower hip fracture risk in previous smokers as compared to current smokers has, however, been reported (Vestergaard et al. 2003).

Analyses of hip fracture risk reduction by pharmacological treatment have mostly included only individuals with osteoporosis. A risk reduction for hip fractures of 26–53% has been shown for alendronate (Wells et al. 2008),

risedronate (Wells et al. 2008), strontium ranelate (Reginster et al. 2008) and zoledronic acid (Black et al. 2007)in individuals with osteoporosis and of 40% for Denosumab, a new monoclonal antibody for a receptor activation protein (RANK-L) in a recent phase III study (Cummings et al. 2009). No risk reduction has been shown for etidronate (Wells et al. 2008), ibandronate (Recker et al. 2004), pamidronate (Brumsen et al. 2002) or recombimbinant human parathyroid hormone (PTH)(Greenspan et al. 2007) and data for vitamin K are ambiguous (Rejnmark et al. 2006, Cockayne et al. 2006). For patients not selected on the basis of osteoporosis, a risk reduction of 13% has been shown for calcium and vitamin D supplementation (Tang et al. 2007) and a reduction of 18% for vitamin D supplementation alone (Bischoff-Ferrari et al. 2009) although debated (DIPART-Group).

Material and methods

Paper I

(a) BMD and other risk factors for fragility fracture

The study population consisted of 474 Caucasian women, born in 1908 (aged 80), 1918 (aged 70), 1928 (aged 60), 1938 (aged 50) and 1948 (aged 40) and living in the city of Malmö in Sweden, and 275 age-matched Caucasian women living in the rural municipality of Sjöbo in Sweden, who were randomly selected in 1988 from the National Population Records and were invited to participate in a study, evaluating bone mineral density BMD (g/cm^2) by SPA (as described below) lifestyle and neuromuscular function (as described below) (Gardsell et al. 1991). A total 328 of the invited urban women (69% participation rate) and 231 of the invited rural women (84% participation rate) attended the baseline measurements undertaken in 1988/1989. All participants were invited to a follow-up measurement in 1998/1999. Fifty-five of the urban women and 38 of the rural women had died and 95 of the urban women and 72 of the rural women had relocated during the study period or declined further participation. The second measurement was attended by 178 urban women and 121 rural women, aged 60–90 at follow-up. Based on these measurements we defined 4 samples of women aged 50–80 years at measurement: (i) urban women measured in 1988/1989 (n=257), (ii) urban women measured in 1998/1999 (n=171), (iii) rural women measured in 1988/1989 (n=180) and (iv) rural women measured 1998/1999 (n=118).

(b) Hip fractures

For fracture evaluation we included the female population aged ≥50 years 1987–2002 in (i) the city of Malmö, representing an urban region, and (ii) 9 municipalities near the village of Sjöbo (Sjöbo, Tomelilla, Simrishamn, Bromölla, Skurup, Hörby, Höör, Ystad and Osby), representing a rural region. Hip fracture data for the respective regions were obtained from the register of the National Board of Health and Welfare, as described below.

Paper II

(a) BMD and other risk factors for fragility fracture

The study population consisted of 306 Caucasian men, born in 1908 (aged 80), 1918 (aged 70), 1928 (aged 60), 1938 (aged 50) and living in the city of Malmö, and 201 age-matched Caucasian men living in the rural municipality of Sjöbo, who were randomly selected from the National Population Records in 1988 and invited to participate in a study, evaluating bone mineral density BMD (g/cm^2) by SPA (as described below) lifestyle and neuromuscular function (as described below) (Gardsell et al. 1991). A total 242 of the invited urban men (79% participation rate) and 160 of the invited rural men (80% participation rate) attended the baseline measurements undertaken in 1988/1989. All participants were invited to a follow-up measurement in 1998/1999. Ninety-seven of the urban men and 51 of the rural men had died and 66 of the urban men and 36 of the rural men had relocated during the study period or declined further participation. The second measurement was attended by 79 urban men and 73 rural men, aged 60–90 at follow-up. Based on these measurements we defined four samples of men aged 60–80 years at each measurement: (i) urban men measured 1988/1989 (n=202), (ii) urban men measured 1998/1999 (n=75), (iii) rural men measured 1988/1989 (n=121) and (iv) rural men measured 1998/1999 (n=69).

(b) Hip fractures

For fracture evaluation we included the male population age ≥60 years 1987–2002 in (i) the city of Malmö, representing an urban region and (ii) 9 municipalities near the county village of Sjöbo (Sjöbo, Tomelilla, Simrishamn, Bromölla, Skurup, Hörby, Höör, Ystad and Osby), representing a rural region. Hip fractures data for the respective regions were obtained from the register of the National Board of Health and Welfare, as described below.

Paper III

(a) BMD

The study population consisted of 456 women measured at our centre during three different time periods: (1) 106 women measured 1970–1974 (Westlin 1974); (2) 175 women measured 1987–1993 (Karlsson et al. 1993, Duppe et al. 1992); and (3) 178 women measured 1998–1999 (Paper I) as shown in Figure 3. The third sample was population-based and the other two were recruited by non-randomized invitation. In all three cohorts, subjects were without known metabolic disease or other conditions known or suspected to

interact with bone mineral density. BMD measurements were made by SPA, with definitions of osteoporosis as described below.

(b) Hip fractures

All fractures of the proximal femur (hip fractures) in women aged ≥50 years living in the city of Malmö, in 1967–68, 1974–75(Nilsson et al. 1978), 1980–85(Johnell et al. 1984), 1987–95(Gullberg et al. 1993, Rogmark et al. 1999) and 1999–2001(Rogmark 2003), were identified and verified in the records of the Department of Diagnostic Radiology and the Department of Orthopedic Surgery, Skåne University Hospital, Malmö, Sweden.

Paper IV

Hip fracture data for men and women aged ≥50 years in Sweden 1987–2002 were obtained from the register of the National Board of Health and Welfare as described below.

Protocol for hip fracture data extraction from the register of the National Board of Health and Welfare

In papers I, II and IV hip fracture data were obtained from the official register of the National Board of Health and Welfare, which includes all patients discharged from hospital in Sweden classified according to treated disease and surgical procedure. We selected patients classified with an acute proximal femoral fracture each year by the diagnosis code ICD9 820x, ICD10, S720, S721 or S722 in the diagnosis code fields (Table 5) and with a relevant surgical procedure for proximal femur fracture by the operation code ICD9 841,82x or ICD10 NFB, NFJ in the operation code fields (Table 5).

BMD measurements by SPA

Bone mineral density (BMD, mg/cm^2) was measured in the forearm at 6 cm proximal to the ulnar styloid process by single-photon absorptiometry (SPA). The technique includes a rectilinear scan across the radius and ulna, with the radiation source (241 Am) and detector moving simultaneously, according to a previously described method (Nauclér et al. 1974). The precision of the method, measured as the week-to-week variation over one year, estimated by standardized phantom data, amounted to less than 1%. The same densitometer was used throughout the studies but because of replacement of the radiation source in 1980, the values obtained thereafter in Paper III were

adjusted with the use of phantom data. The coefficient of variation was 1–2% when evaluated by the phantom and 4% when evaluated by repeated measurement after the repositioning of the arm in 20 subjects. The long-term drift of the densitometer was 0.1%/year (95% CI –0.2, 0.4), evaluated by a standardized phantom every second week.

Osteoporosis

Osteoporosis was defined by WHO criteria (Table 3) as a BMD value lower than 2.5 SD below the mean of a young reference population (WHO 1994). T-score was defined as the actual BMD value in relation to the mean and SD of a cohort of healthy young individuals. The values for defining both osteoporosis and T-score were derived from a non-population-based sample of 38 healthy women aged 20–39 years measured at the forearm in 1971 using the same equipment as in the present study, with a mean BMD (SD) of 542 (76) mg/cm^2.

Evaluation of lifestyle and neuromuscular function

Medical history, including the presence of chronic diseases (diabetes mellitus, heart disease, lung disease, stroke, thyroid disease, epilepsy, rheumatic disease, and Parkinson's disease), use of certain medications (corticosteroids, thyroid, diabetic (including insulin)), smoking habits (non-smoker, former smoker or current smoker), alcohol consumption, disability, dizziness (no, every week, every day), falling (never, occasionally, 1–2 times/month, weekly) and subjective health (good, fairly good, poor, very poor) were evaluated in all participants and for women also the use of oral contraceptives (never vs. current or former) and estrogen therapy (never vs. current or former), age at menarche and menopause and history of oophorectomy, using the same questionnaire at both measurements. Participants were classified as having chronic disease(s) or medication use if they answered "yes" to any of the diseases or medications listed above. For those who reported not being teetotalers the average intake of beer, wine, and hard liquor was used to estimate grams of alcohol consumed per week. Disability was defined as having difficulty performing common activities of daily living and was assessed by asking participants whether they required outside assistance to perform daily activities (e.g., shopping, dishwashing, cleaning, personal hygiene), or could not manage activities such as shopping, dressing, making their bed or going to the toilet. If they answered "yes" to any of these questions, they were classified as physically disabled. Menopause was defined as occurring 1 year

after the last menstrual period or at the time of oophorectomy. Weight and height were determined in 1988/1989 by a questionnaire and in 1998/1999 by measurements with an electronic scale and a standard height meter, and the values were used for calculation of BMI. Gait velocity and balance were objectively evaluated as previously described (Ringsberg et al. 1998).

Cohorts used for BMD collection in women (Papers I and III)

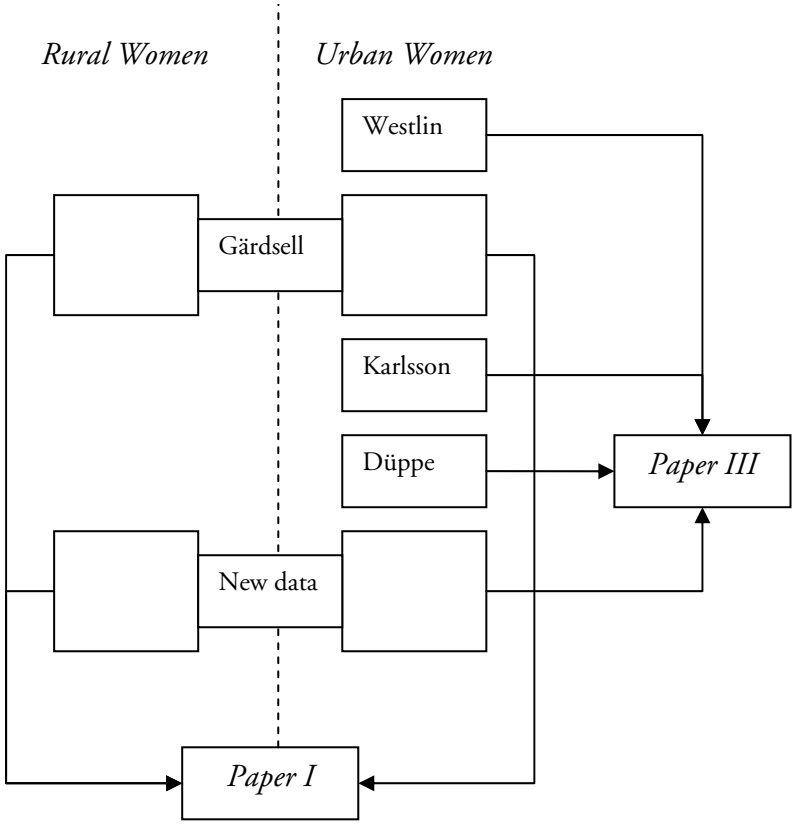

Figure 3

Summary of papers

Paper I

Stable Hip Fracture Incidence and Bone Mineral Density – A Study of Swedish Urban and Rural Women 1987–2002

Introduction: The aim of this observational study was to investigate Swedish urban and rural women to see (i) whether there has been a secular decrease in hip fracture incidence during the last decade and (ii) whether secular changes in hip fracture incidence could be attributed to secular changes in bone mass or other risk factors.
Results: There were no differences in age-adjusted hip fracture incidence or bone mass, but in some other risk factors found when analyzing all women, rural women or urban women separately from 1988/1989 to 1998/1999.
Conclusions: Since no secular differences in bone mass or changes in age-adjusted hip fracture incidence were evident, changes in the other investigated risk factors for hip fractures such as gait velocity and balance evident either are of minor importance or are counteracted by changes in other risk factors.

Paper II

No Changes in Hip Fracture Incidence or Bone Mineral Density in Swedish Urban and Rural Men 1987–2002

Introduction: The aim of this observational study was to investigate Swedish urban and rural men to see (i) whether there has been a secular decrease in hip fracture incidence during the last decade and (ii) whether secular changes in hip fracture incidence could be attributed to secular changes in bone mass or other risk factors.
Results: There were no differences in age-adjusted hip fracture incidence or bone mass but in some other risk factors found when analyzing all men, rural men or urban men separately from 1988/1989 to 1998/1999.
Conclusions: Since no secular differences in bone mass or changes in age-adjusted hip fracture incidence were evident, changes in the other investigated

risk factors for hip fractures such as gait velocity and balance either are of minor importance or are counteracted by changes in other risk factors.

Paper III

Prevalence of Osteoporosis and Incidence of Hip Fracture in Women – Secular Trends Over 30 Years

Introduction: This study aimed to characterize secular patterns in the prevalence of osteoporosis and the incidence of hip fracture within the same female target population during the last three decades of the former century.
Results: There was no significant difference in the age-adjusted prevalence of osteoporosis during the evaluated period. The crude incidence of hip fracture in the target population increased by 110% from 1967 to 2001 whereas the age-adjusted incidence was stable.
Conclusions: The increased number of hip fracture in elderly women is more likely to be attributable to demographic changes in the population than to secular increase in the prevalence of osteoporosis.

Paper IV

Secular Trends in Swedish Nationwide Hip Fractures 1987–2002 – Results of Birth Cohort and Period Effects

Introduction: Using central national data this ecological study aimed to evaluate (i) whether a decrease in age-standardized hip fracture incidence was evident also in Sweden, (ii) whether there were any changes in the annual number of hip fractures and (iii) whether the changes were due to period and/or cohort effects.
Results: Before 1996 the age-standardized hip fracture incidence was stable and the annual number of hip fractures increased. After 1996 both the age-standardized hip fracture incidence and the number of hip fractures decreased. There were both minor period as well as major cohort effects during this period, so that women born 1889–96 had substantially higher hip fracture risk than women born 1945–52.
Conclusions: Our findings indicate that new projections on the burden of hip fractures must be calculated.

General discussion

Difficulties in deriving data for epidemiological hip fracture research

Ultimately one would like to select all patients with an acute sustained hip fracture, and only those, from a register including all patients and all relevant information for the planned study. However, for a variety of reasons this is not currently possible for nationwide data in Sweden but has been done in cohorts in smaller regions in several countries (Nymark et al. 2006, Melton et al. 1996, Chang et al. 2004), including Sweden (Gullberg et al. 1993). Efforts to set up specific hip fracture registers are under way in several countries and show promising results. The Swedish national hip fracture register (Rikshöft) at present accounts for only 69% of hip fractures in Sweden but collects a wide variety of data, not only care processes and outcome but also quality of life and other variables.

There is no common definition of the entity of hip fracture in epidemiological studies. Some authors include all fractures of the femur (also femoral shaft and distal femoral fractures) while others include all, or combinations of, the three main types of hip fractures (cervical, trochanteric and subtrochanteric fractures) and yet others include only patients who have undergone specific surgical procedures (for example hip arthroplasty). The sources used for data collection also vary, each marred by its own disadvantages. Manual review of medical records and X-ray films can, if correctly done, be considered the golden standard, but this is very time-consuming, especially for lager cohorts. Compared to this, data retrieval from registers (local or national) are generally considered less valid. Although with substantial variation between countries (Schwartz et al. 1999) the use of national discharge registers is nevertheless, with the known limitations, generally accepted as the basis for research.

Few studies have examined the validity of data sources for epidemiological hip fracture research. In a subsample of patients with hip fracture (treated with arthroplasty) evaluation of summarized medical and surgical information (face sheet) as compared to medical records showed inconsistencies in about

10–15% of patients (Fox et al. 1998), mainly concerning surgical procedure classification and complications. A study from Sweden (Zetterberg 1989) compared data derived from ICD codes in discharge registers to a manual review of surgical and radiographic records and found twice the number of hip fractures in the discharge database. In Norway a study comparing the manual method to local discharge registers and a national register found evidence of underestimation (46%) as well as overestimation (17–19%) (Lofthus et al. 2005) using register data. To exemplify difficulties in data extraction and interpretation from national discharge registers, it is worth mentioning the scientific debate concerning the secular development of hip fracture incidence in New Zealand. Two research groups using the same data set (national discharge register) found opposing results; one found a trend of a decrease (Fielden et al. 2001), at least in women, while the other, with allegedly stricter inclusion criteria, found an increase of hip fracture incidence (Stephenson et al. 2003); this has been further discussed by others together with the identification of possible pitfalls (Langley et al. 2002, Brophy et al. 2006).

Different algorithms can be used for data extraction from the discharge register. There are always errors in registers and risk of bias in the data extraction process. There are two main approaches to the problem of inclusion bias. The main goal is to include either (i) all patients with the sought diagnosis (and accept the inclusion of some patients without it) or (ii) only patients with the sought diagnosis (and accept missing some patients with it).
In our algorithm only patients having both a diagnosis of hip fracture and a relevant surgical procedure for hip fracture (Table 5) in the same inpatient record in the discharge register are included. Other algorithms have been suggested (Gedeborg et al. 2008) and a consensus is strongly advocated in order to obtain comparability between different results (Brophy et al. 2006).

DIAGNOSIS CODES

ICD9
820x Fracture of proximal femur
- 820.A Transcervical fracture, closed
- 820.B Transcervical fracture, open
- 820.C Pertrochanteric fracture, closed
  - Intertrochanteric
  - Subtrochanteric
  - Trochanteric NOS
- 820.D Pertrochanteric fracture, open
- 820.W Unspecified part of proximal femur, closed
  - Hip fracture NOS
  - Proximal femur NOS
- 820.X Unspecified part of proximal femur, open

ICD10
S72 Fracture of femur
- S720 Cervical fracture
  - S72.00 closed
  - S7201 open
- S721 Pertrochanteric fracture
  - S72.00 closed
  - S7201 open
- S723 Subtrochanteric fracture
  - S72.00 closed
  - S7201 open

SURGICAL PROCEDURE CODES

ICD9

841	Arthroplasty of the hip
82x	Fracture Procedures

ICD10

NFBxx	Arthroplasty of the hip
NFJxx	Fracture Procedures

Table 5

Our extraction process cannot be verified in nationwide data from Sweden but examining our results from Malmö (Papers I and II), with hip fracture data derived from central registers (using the extraction procedure described above), in comparison with data from manually verified medical records or X-ray films and records (Paper III) seems to show reasonable concordance (Figure 4). Our data derived from the central registers (Papers I and II) are quite similar to the results in Paper III after 1992 with an average annual difference of 0.5% (both before and after 1996, when a change in code classification took place) but seem to underestimate the number of hip fractures before that year by an average of 15% annually. Re-examining the data extraction process used by the authors of the respective articles on which paper III is based revealed some differences. While the results before 1992 are based on the X-ray archives and X-ray records alone (Gullberg et al. 1993), after that year they are based on computer-based clinical records and operating room reports (Rogmark et al. 1999, Rogmark 2003) without left or right indexation, making classification of bilateral hip fractures or a following hip fracture the same calendar year impossible after 1992 in the same manner as in our extraction protocol. In a recent Danish study 9% of patients sustaining a hip fracture sustain another during the following year (Ryg et al. 2009) but since our window of examination is one calendar year the figure is not fully transferable to our data. The fraction of patients with a hip fracture not undergoing surgery for various reasons could be anticipated to be very small, and the remaining difference could be referred to misclassifications either in the central registers or in the archives or records of the X-ray department in Malmö. Since the data from the central registers are anonymous, the true reason for the discrepancies cannot be further examined.

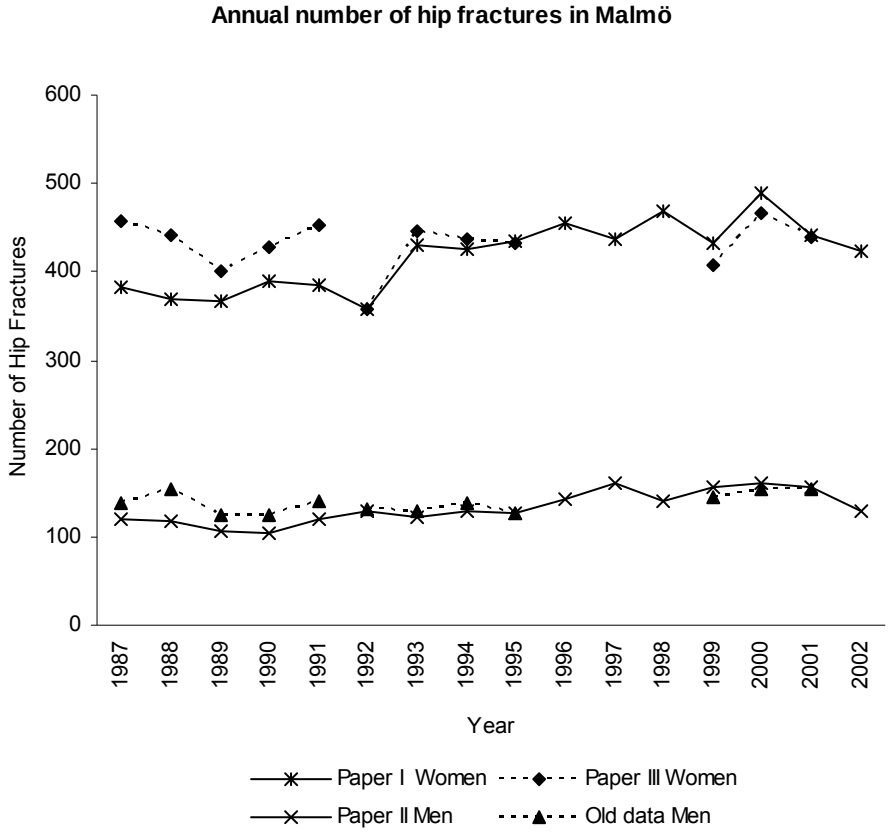

Figure 4

Errors in data input in the discharge register are bound to be either random or systematic, and in the data extraction process only systematic. This is important especially when calculating absolute numbers or values based on absolute numbers (such as incidence) and not so much when examining secular trends. We end up with a lower number of hip fractures than the common view in Sweden of about 18 000 annual hip fractures. Although it is often mentioned (Rikshöft, Thorngren 1998, Socialstyrelsen 2003), the origin of this number is unclear. When taking into account the 15% underestimation rate present in Malmö (Paper I and II) as compared to the golden standard of reviewing medical records (Paper III), the numbers are still lower but fairly similar (Table 6).

ANNUAL NUMBER OF HIP FRACTURES IN SWEDEN

Year	Women	Men	Total	Total Corrected*
1987	10 404	3 699	14 103	16 218
1988	10 917	3 919	14 836	1 7 061
1989	10 871	3 790	14 661	16 860
1990	11 113	4 001	15 114	17 381
1991	11 239	4 099	15 338	17 639
1992	11 336	4 199	15 535	17 865
1993	11 843	4 351	16 194	18 623
1994	11 951	4 395	16 346	18 798
1995	12 014	4 640	16 654	19 152
1996	12 231	4 786	17 017	19 570
1997	12 118	4 709	16 827	19 351
1998	11 794	4 559	16 353	18 806
1999	11 744	4 692	16 436	18 901
2000	11 821	4 520	16 341	18 792
2001	11 716	4 552	16 268	18 708
2002	11 344	4 583	15 927	18 316

*Corrected by a factor of 1.15 as derived from comparison with validated data.

Table 6

Changes in population at risk

There were major changes in demographics in Sweden during the examined years, with not only an increasing number of individuals but also shifts in the age distribution as presented in Figure 5 and Table 7.

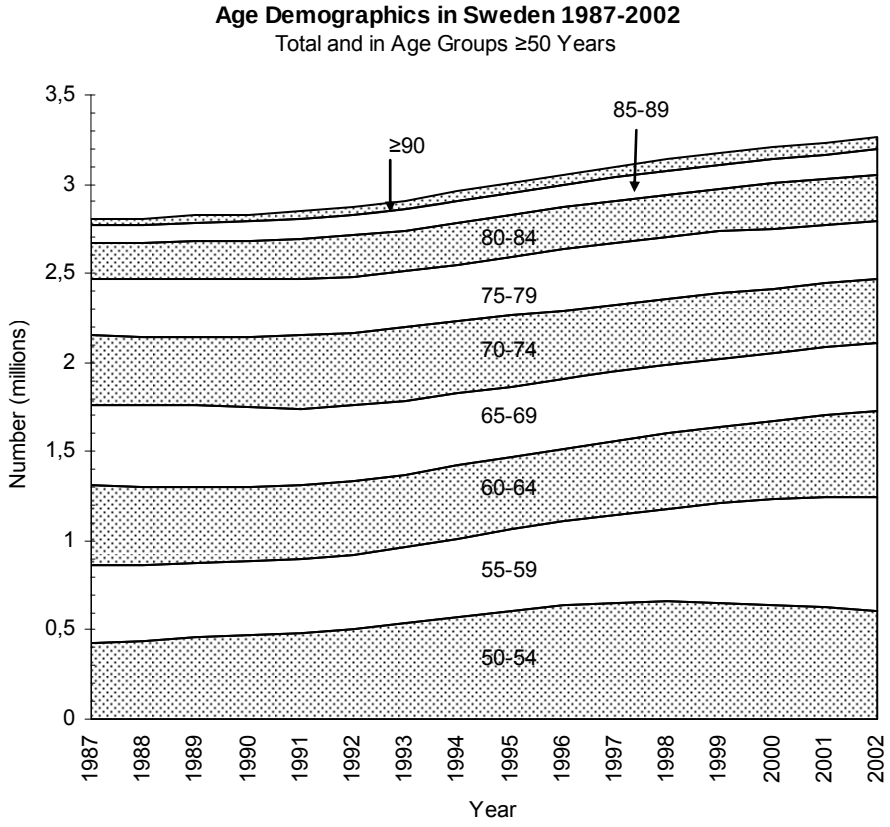
Age Demographics in Sweden 1987-2002
Total and in Age Groups ≥50 Years
Number (millions)
Year
≥90
85-89
80-84
75-79
70-74
65-69
60-64
55-59
50-54
0
0,5
1
1,5
2
2,5
3
3,5
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002

Figure 5

Demographics in Sweden 1987 and 2002

Gender	*Variable*	*Age Group*	*1987*	*2002*
Women				
	Number	≥50 years	1 521 248	1736 190
	Life expectancy at age 50	≥50 years	32.0 years	33.4 years
	Number	≥80 years	218 843	302 042
	Percentage	≥80 years	14.4%	17.4%
Men				
	Number	≥50 years	1 281 548	1525 342
	Life expectancy at age 50	≥50 years	27.0 years	29.6 years
	Number	≥80 years	116 488	167 484
	Percentage	≥80 years	9.1%	11.0%

Table 7

Worldwide the past, recent and future expected changes in demographics (2010) are even more striking (Figure 6).

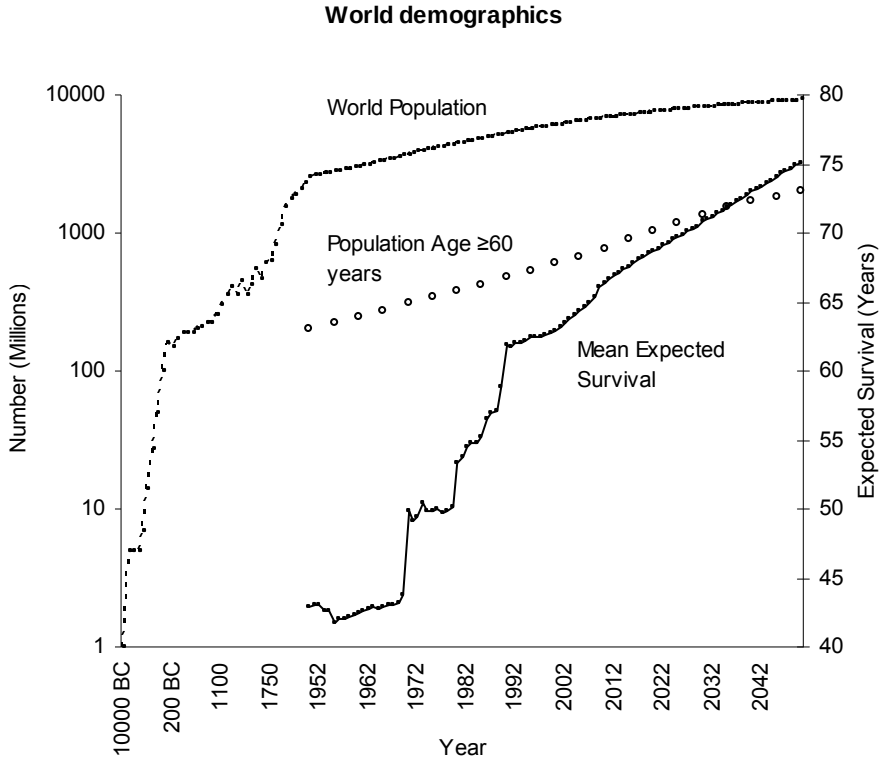

Figure 6

Differences between crude and age-adjusted incidence

In an environment with changes in demographical age structure, not only changes in the number of individuals but also changes within the population at risk must be taken into account when comparing data from different years. In direct age standardization, actual age-specific (as narrow as possible) incidence figures are applied to a standard population (Table 8). Comparable incidence figures are thereby attained even though changes within the population are present. We have used 1-year age-specific calculations throughout our work (Papers I–IV). In order to show differences when using different standardization, data for hip fracture incidence in Sweden 1987–2002 are presented as (i) unadjusted (crude) incidence, (ii) age standardized in 10-year age classes, (iii) age standardized in 5-year age classes and (iv) age

standardized in 1-year age classes in Figure 7. There are however also disadvantages with the method as comparisons between studies using different reference populations are hard to interpret. For hip fracture epidemiological research it would be equally important to have a standardized protocol for data extraction from discharge registers regarding hip fractures and to use standard populations (such as the world standard population or the European standard population) for reference in standardization in order to obtain internationally comparable results.

Directly Age Standardized Incidence Rate (DASIR)

$$\text{DASIR} = \sum_i (ras_i\ pas_i)/P$$

ras = age-specific incidence rate in the examined population.

pas = number of individuals in the age group in the standard population.

P = number of individuals in the total standard population.

Table 8

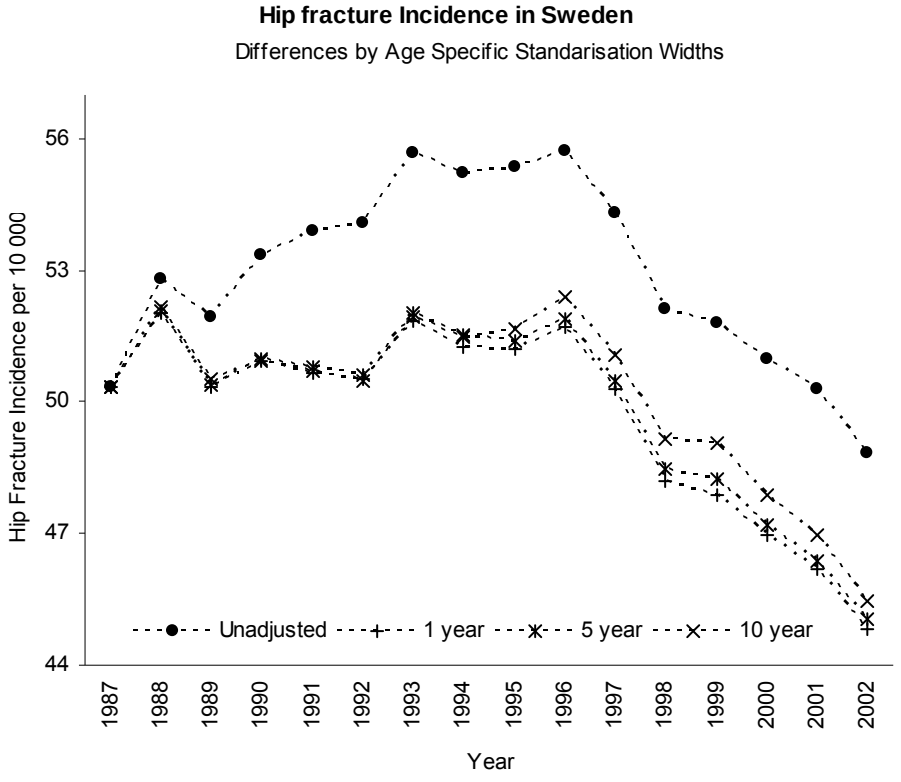

Figure 7

A common way, at least in the past, was to try to get around the problem by stratifying the population into 5- or 10-year age classes. The method has its advantages, but as there will also be shifts within these classes there will be differences when comparing with standardized rates (Figure 8).

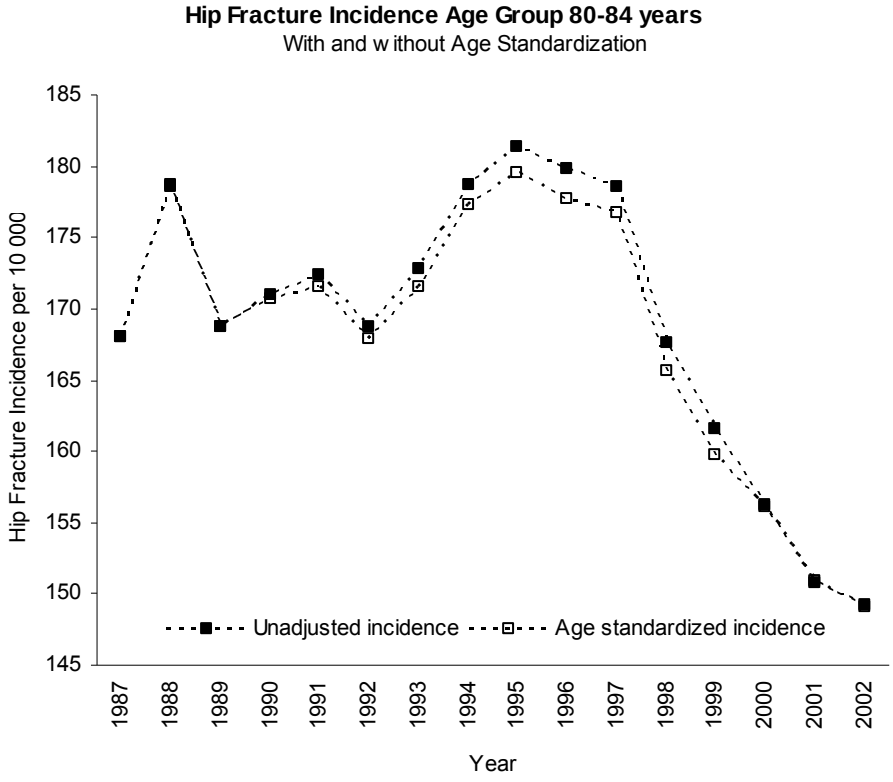

Figure 8

Secular changes in hip fracture incidence and risk factors

In the cohorts of urban and rural men and women (Papers I, II, III) there was a stable hip fracture incidence during the examined years. Even though the cohorts were fairly large, especially regarding the city of Malmö, there were substantial variation between years also when pooling the results for urban and rural women (Paper I) and urban and rural men (Paper II) separately (Figures 9a and 9b) or together (Figure 9c).

To overcome the risk of a type II error we decided to analyze also nationwide hip fracture data (Paper IV).The recently reported change in hip fracture incidence presented in many settings (Rogmark et al. 1999, Melton et al. 1996, Melton et al. 2009, Kannus et al. 2006, Jaglal et al. 2005, Nymark et al. 2006, Lofman et al. 2002, Chevalley et al. 2007, Icks et al. 2008, Leslie et al.

2009, Abrahamsen et al. 2010) was verified also in nationwide Swedish hip fracture data 1987–2002 (Paper IV), where a stable hip fracture incidence was present until 1996, after which a decrease was apparent. The finding is concordant with the findings from a recent Canadian study (Leslie et al. 2009), with the same apparent break-point year, and a recent study from Denmark (Abrahamsen et al. 2010) showing a decrease after 1997. For some unknown reason there seems to be a temporal shift of the decrease in hip fracture incidence between different countries. In the US Melton presented data from Olmstead County of a secular decrease in women already in 1950 and in men in 1980(Melton et al. 1996), now also present in Sweden (Paper IV) from the mid 1990s.

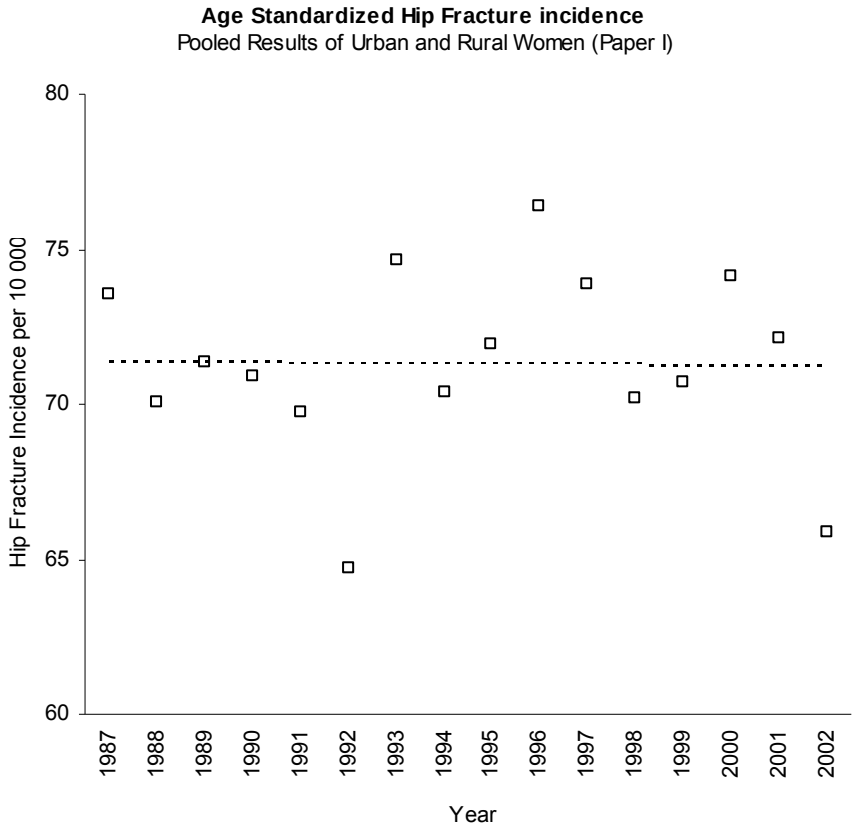

Figure 9a

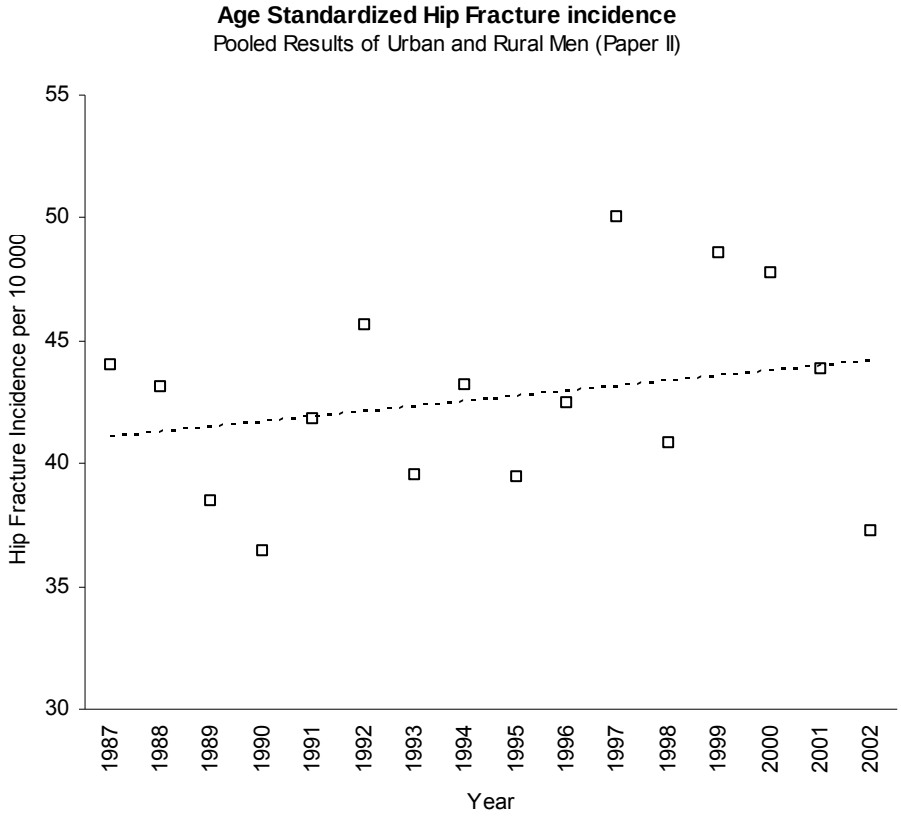
Age Standardized Hip Fracture incidence
Pooled Results of Urban and Rural Men (Paper II)
Hip Fracture Incidence per 10 000
55
50
45
40
35
30
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
Year

Figure 9b

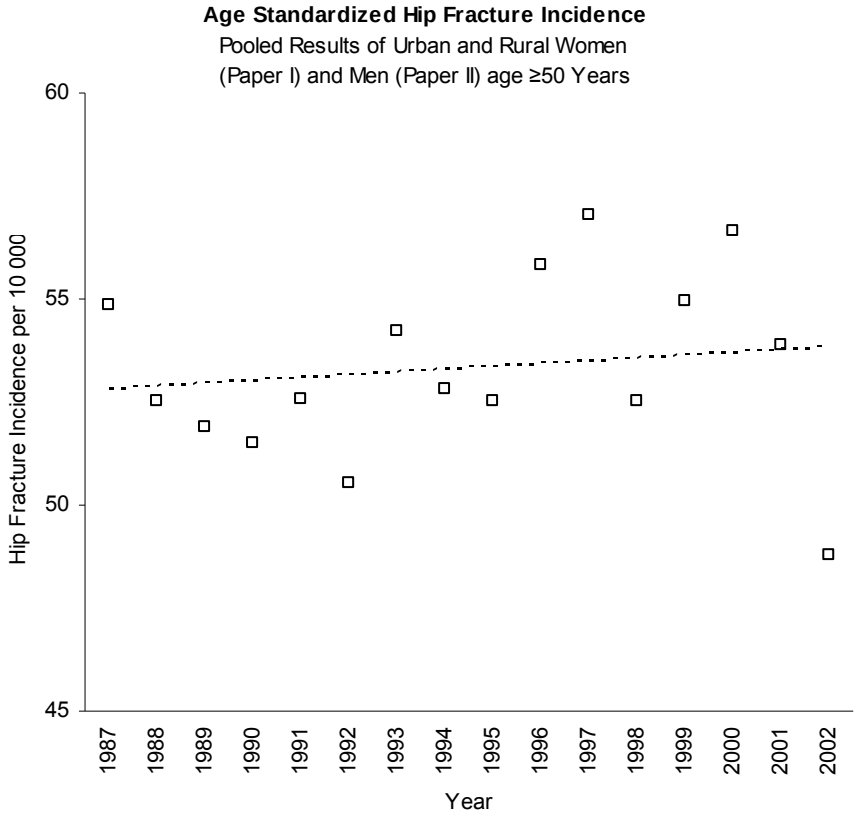

Figure 9c

Differences in hip fracture incidence have been described not only between countries but also within countries, including between urban and rural settings in several studies with higher incidence in the urban areas(Sanders et al. 2002, Mannius et al. 1987, Sernbo et al. 1988, Jonsson et al. 1992; Melton et al. 1999; Chevalley et al. 2002). Others have not been able to fully reproduce these results however (Larsson et al. 1989, Luthje et al. 1995, Jarnlo et al. 1989, Dilsen et al. 1993). In our examination (Papers I and II) there were statistical differences between urban and rural women (Figure 10a) as well as men (Figure 10b) regarding the mean age adjusted hip fracture incidence (difference 4.4 per 10 000 (95% confidence interval 0.8, 8.0) in women and 3.7 (0.3, 7.0) in men) but not in hip fracture incidence progression in women (-0.3 per year (-0.7, 0.1)) or men (-0.2 per year (-0.6, 0.2)) (Figure 10a and 10b).

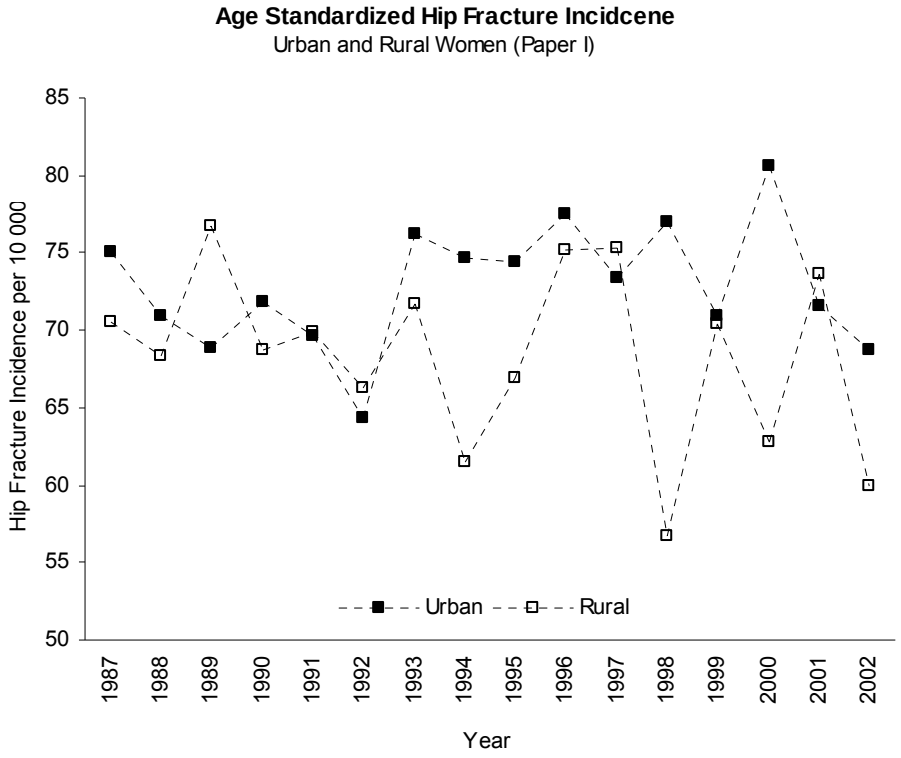
Age Standardized Hip Fracture Incidcene
Urban and Rural Women (Paper I)
Hip Fracture Incidence per 10 000
85
80
75
70
65
60
55
50
Urban
Rural
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
Year

Figure 10a

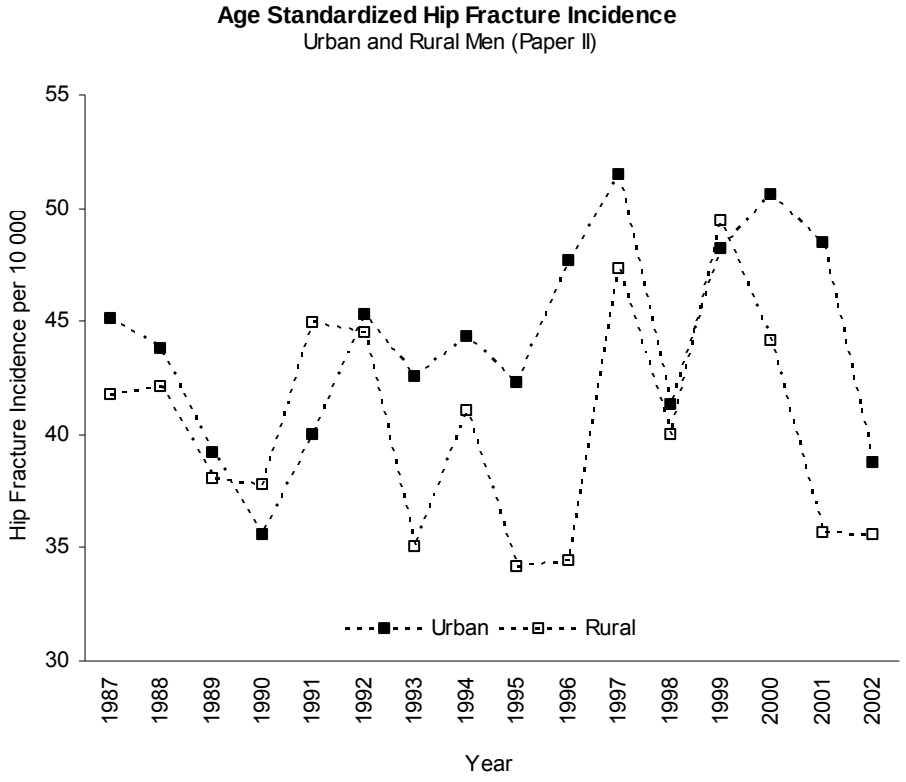

Figure 10b

With further analysis of hip fracture epidemiology in nationwide hip fracture data from 1987 to 2002 by an APC model, a decrease in hip fracture incidence rate ratio (IRR) by subsequent cohorts (Paper IV) was evident in women, with a factor of as much of 2.2 between women born 1889–96 and those born 1945–52. Hence at least a part of the secular decrease in incidence seems attributable to the relative higher hip fracture incidence in the earlier cohorts (born in the late 19th or early 20th century) from which the individuals do not contribute to overall incidence any more. APC modeling is widely used in cancer research for analysis of the temporality of changes in risk factors or burden of disease. However, the model has been used for evaluation of hip fracture epidemiology in only one previous study (Evans et al. 1997) including only a small sample size and only cohorts born from 1860 to 1919. The changes in hip fracture incidence reported to occur during the recent two decades in a variety of settings (Rogmark et al. 1999, Melton et al. 1996,

Melton et al. 2009, Kannus et al. 2006, Jaglal et al. 2005, Nymark et al. 2006, Lofman et al. 2002, Chevalley et al. 2007, Icks et al. 2008, Leslie et al. 2009, Abrahamsen et al. 2010) could therefore have been missed in this evaluation. In contrast, this period was covered in Paper IV, which included individuals born 1889 to 1952. Direct comparison of Evans's results with the outcome presented in Paper IV is not possible, since Evans uses an unequal group distribution which causes particular difficulties (Holford 2006) not addressed in the study. Samelson (Samelson et al. 2002) has also described increasing hip fracture risk among subsequent cohorts but without addressing any concomitant period effects, which makes the results difficult to interpret. The age effect on hip fracture incidence rate ratio derived from Paper IV is concordant with findings from other studies (Kanis et al. 2000) and is presented in Figure 11.

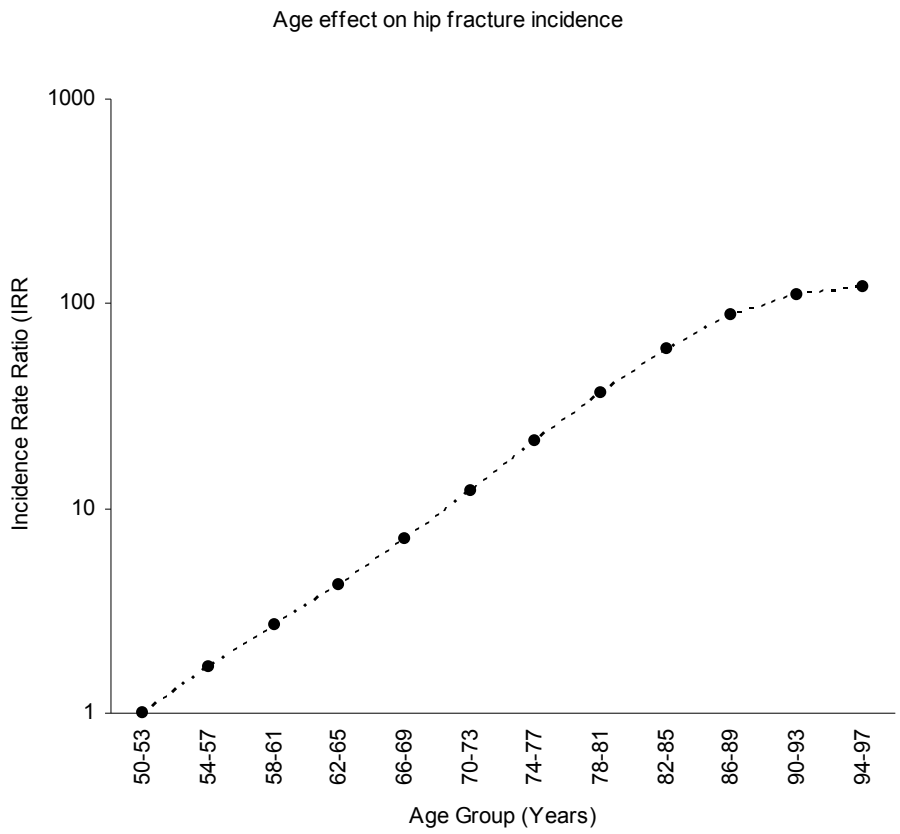

Figure11

OVERVIEW OF AGE, PERIOD AND COHORT EFFECTS

Age effects	Effect of age in terms of risk.
Period effects	Effects applicable to all individuals living at a specific time.
Cohort effects	Effects exerting an influence only on some individuals (usually birth cohorts). For example factors influencing only newborns or only individuals before reaching peak bone mass. (The effect hence is not related to the birth itself.)

Table 9

For the purpose of illuminating the nature of age, period and especially cohort effects (Table 9) let us hypothetically assume the introduction of a new drug in 2010. If taken every day the drug will bestow a 50% decrease in hip fractures risk for the individual taking it, but only if the treatment is initiated before the age of 30. Hence individuals born before 1980 will have no effect of the drug, and because the majority of hip fractures occur at ages around 75–85 years the impact of the drug will only gradually be apparent. Not until all individuals not under the effect of the drug are dead will the incidence of hip fractures reach 50% of the original incidence.

The decrease in hip fracture incidence by cohort and period found in Sweden (Paper IV) may reflect changes on a population level in a variety of factors affecting either bone strength or fall risk or both. Such factors (Table 4) include frailty, nutrition and activity level, medication, fall risk, obesity and bone mineral density. Although a secular decrease in hip fracture incidence has been evident in many countries, further analysis to describe the origin of the changes has been scarce and has mostly focused on the possible impact of the increase in BMD testing and the prevalence of anti-resorptive treatment (Jaglal et al. 2005, Abrahamsen et al. 2010).

In our three studies (Papers I, II and III) examining not only hip fracture epidemiology but also risk factors for hip fracture, none could verify any secular differences in the prevalence of osteoporosis or in BMD, a most interesting result not previously shown. Our results for women regarding the prevalence of osteoporosis (Papers I and III) ranging from 10 to 17% are even though not fully comparable to other studies using DXA, still interesting (Table10).

PREVALENCE OF OSTEOPOROSIS IN WOMEN DIAGNOSED WITH DXA IN POPULATION BASED SAMPLES

Country	*Year*	*Number*	*Age group*	*Prevalence of osteoporosis*	
				Femoral neck	*Lumbar spine*
Australia (1)	2004	1256	60+	28.6%	25.6%
US (2)	1997	1880	50+	20%	
Canada (3)	2000	578	50+	7.9%	12.1%
China (4)	2003	1040	50-79	10.1%	36.4%
Japan (5)	2001	1522	50-79	11.6%	38%

1 (Nguyen et al. 2004)
2 (Looker et al. 1997)
3 (Tenenhouse et al. 2000)
4 (Wu et al. 2003)
5 (Iki et al. 2001)

Table 10

BMD is said to describe 60–80% of bone strength (Bouxsein 2005), but the proportion of hip fractures attributable to osteoporosis has been inferred by some to be only 20–30% (Stone et al. 2003), and a recent study even proposes that the burden of low-trauma fractures is not related to the prevalence of osteoporosis but to a more comprehensive assessment of fracture risk (Langsetmo et al. 2008) including fall risk, also strongly advocated by others (Jarvinen et al. 2008). In our analysis of secondary risk factors for hip fracture risk we found no differences in reported fall incidence (Papers I and II), even though surrogate markers for fall risk such as balance and gait velocity were better at the second measurement in 1998/99 in both urban and rural women (Paper I) and urban men (Paper II). Other examined and well-established risk factors for hip fracture are low weight and low BMI (Cummings et al. 1995, De Laet et al. 2005). In our studies (Papers I and II) we found no differences in BMD between the two measurements.

Differences in estrogen use were apparent between the first and second evaluation in Paper I following prescription trends described by others (Barrett-Connor et al. 2005). The until recently widespread "menopause treatment" with estrogen has probably influenced hip fracture numbers, as a

risk reduction for hip fracture of about 35% has been described for users (Rossouw et al. 2002, Banks et al. 2004). The effect of present and future lower prescription rates due to the apparent risk of cardiovascular and neoplastic disorders is difficult to estimate, but the effect on hip fracture risk seems to disappear shortly after treatment ceases (Banks et al. 2004). It could also be advocated that prolonged exposure to estrogen caused by the earlier menarche (de Muinich Keizer et al. 2001) and possible later menopause during recent years (Dratva et al. 2009) could influence BMD and hip fracture, as would changes in the prevalence of oophorectomy. The decreasing fertility rate in the western world (mainly due to a postponed first childbirth) and the possible decreased rate and duration of breastfeeding may also have an impact.

The introduction of bone resorption agents in the mid 1990s could have had some impact on hip fracture risk on a population level. Even though effects on fracture risk are rapid, these were probably of minor importance since the initial prescription rates were very low. Recent results show that the magnitude of the decrease in hip fracture incidence also present in Denmark could not be attributed to changes in anti-osteoporosis treatment (Abrahamsen et al. 2010). Other drugs have also been inferred to influence hip fracture risk, and changes in prescription patterns, especially of anti-hypertensive pharmaceutical agents such as beta blockers, ACE-inhibitors, calcium channel blockers and thiazide diuretics which have been inferred to give a risk reduction of 7–19% (Wiens et al. 2006, Rejnmark et al. 2006) for fragility fracture, are bound to influence the epidemiology of hip fractures.

There is no conclusive evidence on the effect of protein intake on hip fracture risk, but changes in food composition during the 20th century could have contributed to the changes in hip fracture epidemiology, as a correlation between hip fracture incidence and both total protein content and animal protein content has been shown, as well as an inverse correlation to vegetable protein intake (Frassetto et al. 2000). Also, changes in lifestyle risk factors such as activity level, caffeine intake, cigarette smoking and alcohol use during the lifespan could have played a role in the development of hip fracture risk.

There are reports indicating that 4% of the population >80 years old in Malmö, Sweden, have undergone joint replacement surgery for osteoarthritis of the hip (Rogmark et al. 1999), thereby decreasing the population at risk of hip fracture. However, since osteoarthritis is associated with a much lower hip fracture incidence than in the general population (Vestergaard et al. 2009),

small changes in the prevalence of hip arthroplasty would only lead to minor effects on hip fracture incidence. At least theoretically it could be argued that the earlier higher hip fracture incidence rendered a population with more individuals reinforced by osteosynthesis material in the hip due to a previous hip fracture and at lower risk of a new hip fracture.

Sweden did not participate in the First or the Second World War and was not struck by famine during the great depression or in any other period during the latter part of the 19th century, and experienced a series of nationwide social reforms during the first part of the 19th century. From the late 19th century the country was progressively transformed from a poorly developed, mainly agricultural society into an industrialized modern nation. Examples of reforms that may be of major importance would be the unconditional child allowance which decreased social misery and early undernourishment caused by poverty, as did the nationwide expansion of free school lunches. A government authority supplying statutory prophylactic as well as regular healthcare for newborns and toddlers (Barnavårdcentraler; BVC) was launched and became compulsory for every child, a reform that could also influence general health. In these health centers, led by doctors and nurses, the growth and health of children were followed from birth to age 7 in order to identify and treat children with specific health or nourishment needs. This could be important, as higher birth weight and increased childhood growth are reported to predict not only adult bone size and bone strength (Javaid et al. 2006, Oliver et al. 2007) but also hip fracture risk in later life (Cooper et al. 2001). The reforms described above all led to changes in the social and health structure that could be responsible for some of the cohort difference in hip fracture incidence when comparing those born before and after the reforms. Immigration to Sweden, apparent mainly from the 1960s onwards, could also have influenced the secular development of hip fracture epidemiology, as pointed out by others (Furugren et al. 2007).

Intake of calcium and vitamin D also exerts an influence on hip fracture risk, and during the last century major changes were apparent. At the beginning of the 20th century the Milk Drop institution (Mjölkdroppen) was introduced in Sweden to give advice to breastfeeding mothers as well as free milk to the children of the needy. Later the institutions were taken over by the government and transformed into the BVC described above. Fish liver oil (with high vitamin D content) was recommended to all infants from 1940 onwards, later replaced by drops of vitamin A and D. After World War II vitamin D was added to dairy products such as milk and margarine in Sweden

(Becker 2000). The major increase in mean expected survival during the relatively short study period (Paper IV) together with the improved surrogate markers for well-being in Sweden during 20th century reported in the literature (such as increased height (Eiben et al. 2005) reflecting well-being during early life and increased weight and Body Mass Index (BMI) (Eiben et al. 2005) reflecting well-being at large) point toward a more well-nourished and gradually healthier population. When discussing BMI it must be pointed out that low BMI is a risk factor for osteoporotic fractures, especially for hip fracture, and the higher risk with lower BMI remains even after adjustment for Bone Mineral Density (BMD) (De Laet et al. 2005). The relationship of BMI and hip fracture risk is non-linear, however, as the risk increases substantially more with a low BMI than it decreases with a high BMI (De Laet et al. 2005, Gnudi et al. 2009). For example, a BMI of 20 kg/m^2 is inferred to give a relative risk (RR) of 2.0 for hip fracture compared to a BMI of 25 kg/m^2, whereas a BMI of 30 kg/m^2 gives a RR of 0.83 compared to a BMI of 25 kg/m^2 (De Laet et al. 2005). In perspective the above-mentioned study of BMI by birth cohort in 70-year-old Swedes (Eiben et al. 2005) (born between 1901 and 1930) showed only minor absolute differences in hip fracture risk context, though significant in mean BMI (BMI ranging from 25.4–26.9 kg/m^2 in men and 25.5–27.1 kg/m^2 in women during the study period). However, even if the secular differences in mean BMI were small there was an evident redistribution between BMI classes, with increasing prevalence of overweight and obesity in consistency with recent results concerning middle-aged Swedes (Lissner et al. 2008) and a prior nationwide survey (Lissner et al. 2000). The secular trends in BMI were quite different in the genders, with a more rapid increase in men than in women before 1992, after which the increase continued in women while it was stable in men. It should be pointed out that the mean BMD in the population does not undoubtedly reflect any BMI changes in the especially frail hip fracture population. In Sweden a majority of hip fracture patients (71%) have been shown to be at nutritional risk (Beck et al. 1998), with a BMI below 24 kg/m^2 (Bachrach-Lindstrom et al. 2000).

Projections for the future burden of hip fractures

Projections on the future number of hip fractures are scarce and have mainly been based on incidence figures derived from older studies with trends of an increasing incidence rate. Some have used advanced models, or at least models with multiple outcomes, depending on different assumptions, while others have used simple models based on one incidence rate or a linear trend of

increasing incidence and future population estimates worldwide or in parts of the world. Most have presented an increasing annual number of hip fractures over time, partly ascribed to a changing population at risk and partly to an expected increase in hip fracture incidence (Gullberg et al. 1997, Cooper et al. 1992, Kannus et al. 1999, Maggi et al. 1991, Johnell et al. 1992, Dodds et al. 2009, Schwenkglenks et al. 2005, Chipchase et al. 2000, Burge et al. 2007, Papadimitropoulos et al. 1997) while only one expected stable or decreasing annual numbers (Lofman et al. 2002).

To exemplify the difficulties with projections, we used data from Paper I (one-year age-specific hip fracture incidence figures from 1987 and the actual population figures from 1987 to 2002) and made a hypothetical projection from 1987–2002. The projection would result in 11% overestimation in 2002, as seen in Figure 12.

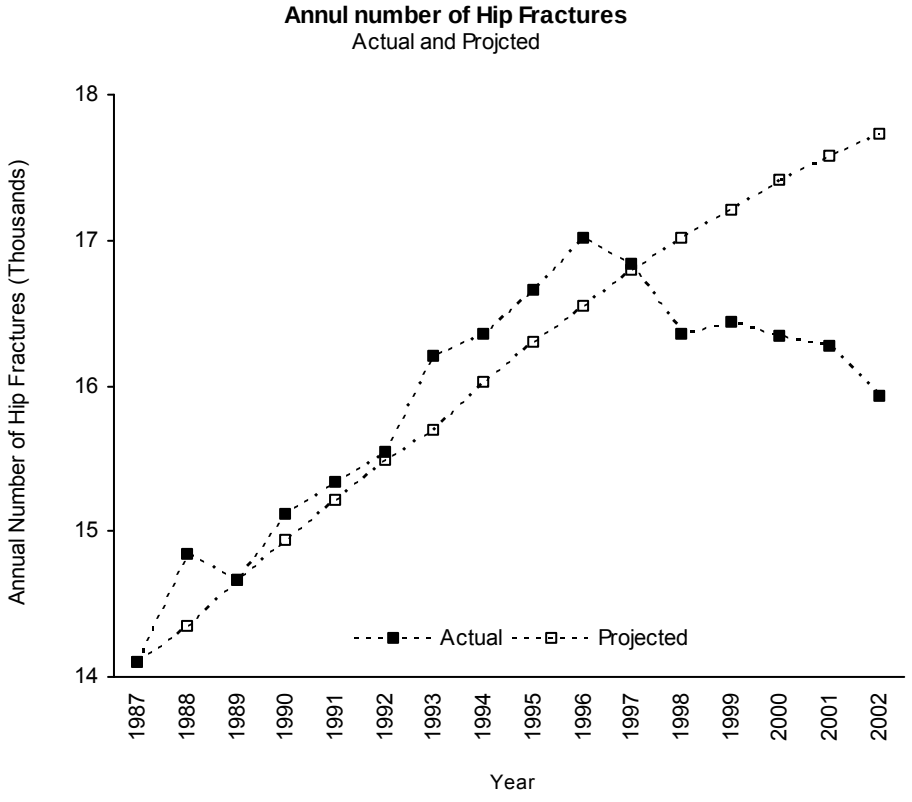

Figure 12

This indicates that when we make projections for future hip fracture resource allocation, apart from changes in the population at risk (which can readily be anticipated from national birth records), we must also take estimated secular changes in hip fracture incidence into account, the latter is of course much more difficult to assess. The decrease in hip fracture incidence present in Sweden after 1996 (Paper IV) will not continue until the incidence is zero but will eventually level out, but we do not know at what rate and when. Hence, even though statistical estimates of future demographics are available, any projections for the future will be dependent on the future progression of incidence chosen. The large birth cohorts of women and men born after 1940, as apparent in Figure 5 and in the demographic examination in Paper IV will although the incidence is decreasing, contribute to increasing annual numbers of hip fractures as they grow older. New analysis including eight more years (2003–2010) are under way, and if the decreasing progression of hip fracture incidence is still apparent, new projections must be made.

General conclusions

- The examined Swedish population age ≥50 years increased, and substantial changes in the age distribution were apparent during the study period from 1987 to 2002.
- The annual number of hip fractures in Sweden increased in both women and men from 1987 to 1996, after which the annual numbers deceased. In the examined cohorts of rural women and men the annual number of hip fractures was stable from 1987 to 2002 while an increase was apparent in urban women and men during the same period and in Malmö regarding women from 1967 and 2001.
- The annual hip fracture incidence in Sweden was stable from 1987 to 1996, after which a decrease was apparent, especially in age-standardized incidence, which emphasizes the importance of taking demographic changes within the population at risk into account. In the examined cohorts of urban and rural women and men, age-standardized hip fracture incidence was stable from 1987 to 2002 as was it in Malmö regarding women from 1967 to 2001.
- Examination of national hip fracture data for Sweden from 1987 to 2002 found period+cohort effects in women, with a major reduction in hip fracture incidence by subsequent birth cohorts (estimated incidence rate ratio 2.2 comparing women born 1889–1896 to women born 1945–52).
- BMD and prevalence of osteoporosis were stable both in women in Malmö from 1970 to 1999 and between 1988/1989 and 1998/1999 in the examined cohorts of Swedish urban and rural women and men, as was BMI.
- As regards falls, no difference was evident between 1988/1989 and 1998/1999, but surrogate markers for falls, such as balance and gait velocity, were better in 1998/1999 in both urban and rural women and in urban but not rural men.
- During the lifespan of the examined individuals aged ≥50 from 1987 to 2002, major changes in Swedish society and the healthcare system took place, with probable influences on hip fracture risk.

Populärvetenskaplig sammanfattning på svenska

Nedsatt benmassa, eller benskörhet alternativt osteoporos som det också kallas, är vanligt förekommande bland äldre individer. Det försvagade benet ger då en ökad risk för att även vid lättare fall drabbas av frakturer. Dessa frakturer drabbar främst handleder, axlar, kotor, bäcken och höfter. Det allvarligaste benbrottet, höftfrakturen, är en omskakande händelse för den drabbade, då skadan ofta medför nedsatt livskvalitet, autonomi, självkänsla och t o m förtida död. Omhändertagandet av personer med höftfraktur leder dessutom till enorma kostnader för samhället. I Sverige beräknas omkring 3% av de totala sjukvårdskostnaderna gå till omhändertagandet av höftfrakturpatienter.

Den vetenskapliga litteraturen har sedan 1950-talet redovisat ett ökat antal höftfrakturen per år, som en del av att vi har en allt mer åldrad befolkning. Men även antalet höftfrakturer per 10 000 invånare och år i respektive åldergrupp, eller incidensen som begreppet också kallas, har ökat. Det senaste decenniet har det dock i andra länder framkommit data som talar för att incidensen inte längre ökar. I stället har incidensen planat ut eller kanske t o m minskat. Orsakerna till förändringarna är inte klarlagda men en bidragande faktor skulle kunna vara att förekomsten av benskörhet i samhället har minskat.

Riskfaktorer för höftfraktur hos kvinnor (arbete I) och män (arbete II) i Malmö och Sjöbo undersöktes därför 1988/1989 och 1998/1999. Det framkom inte några skillnader mellan de två mättillfällena vad beträffar benmassa eller osteoporos. En genomgång av bentäthetsmätningar av kvinnor som gjorts i Malmö under perioden 1970 till 1999 visade också liknande resultat, dvs. att andelen kvinnor med benskörhet inte förändrats över den undersökta tidsperioden (arbete III). Dessa studier talar därför att vi måste leta efter andra orsaker än osteoporos till att incidensen av höftfrakturer har förändrats över tiden.

Förekomsten av höftfrakturer, dvs. hur man på olika sätt registrerar att en individ har drabbats av en höftfraktur, undersöktes också. Bland individerna boende i Malmö användes sjukhusets unika röntgenarkiv, där alla röntgenbilder sparas, för att få fram höftfrakturdata för kvinnor från 1967 till 2001 (arbete III). Genom att använda patientregistret, som registrerar individer med höftfrakturer i hela landet, kunde höftfrakturdata för män och kvinnor i Malmö och i Sjöbo med närliggande kommuner analyseras (arbete I och II). Dessa data användes också när antalet frakturer i hela Sverige under åren från 1987 till 2002 (arbete IV) värderades.

I Malmö samt i Sjöbo med närliggande kommuner var höftfrakturincidensen, när man med statistiska matematiska beräkningar hade justerat för att ålderspyramiden ändrade sig under undersökningsperioden, stabil (arbete I, II och III) medan den i hela Sverige var stabil fram till 1996 varefter den minskade (arbete IV). Antalet årliga höftfrakturer i hela Sverige ökade fram till 1996 och minskade därefter. Genom att applicera ytterligare en statistisk modell som kallas APC och som vanligen används inom cancerforskning, på de data för höftfrakturer i hela Sverige under tidsperioden 1987-2002 som vi har fått fram, kunde vi visa att risken för höftfraktur var mer än dubbelt så stor för kvinnor födda i slutet av 1800-talet jämfört med dem som föddes omkring 1950 (arbete IV).

Denna avhandling visar att höftfrakturincidensen inte längre ökar i Sverige. Tvärtom verkar incidensen från år 1996 minska. Detta trendbrott verkar inte bero på förändringar i förekomsten av låg benmassa eller andelen av individer som har drabbats av osteoporos. Man kan spekulera att det snarare beror på de omvälvande förändringar i samhället som införandet av allmän barnhälsovård och sjukvård i skolan samt fri skolmat som införts under 1900-talet. Andra möjliga orsaker är bättre boende och bättre kost men i dag vet vi ej orsakerna och detta måste undersökas i framtida forskning. Att utföra dessa beräkningar är av stor vikt för samhället då beslutsfattarna skall avsätta resurser för den framtida höftfrakturvården. Vi kan i dag bara spekulera kring den framtida incidensen av höftfrakturer då vi i dag inte vet om incidensen av höftfrakturer kommer att fortsätta att minska och i så fall hur länge. Däremot kan vi beräkna att andelen äldre kommer att öka då de stora kullarna som föddes på 1940-talet blir äldre. Slutsatserna i avhandlingen är särskilt viktiga för att på rätt sätt kunna beräkna framtida behov både vad gäller sjukvårdsresurser och kostnader för samhället. Alla förändringar beskrivna ovan måste beaktas när vi planerar för omhändertagandet av höftfrakturpatienter de kommande 30 åren.

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