Health-Related Quality of Life in Postmenopausal Women with Osteoporotic Fractures

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To all women with osteoporotic fractures
The whole of science is nothing more than a refinement of everyday thinking.

Albert Einstein (1879-1955)
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ABSTRACT

Background: The global burden of osteoporosis includes considerable numbers of fractures, morbidity, mortality and expenses, due mainly to vertebral, hip and forearm fractures. Underdiagnosis and undertreatment are common. Several studies have shown decreased health-related quality of life (HRQOL) after osteoporotic fracture, but there is a lack of data from long-term follow-up studies, particularly regarding vertebral fractures, which are often overlooked despite patients reporting symptoms.

Aim: The overall aim of this thesis was to evaluate the usefulness of a recent low-energy fracture as index event in a case-finding strategy for osteoporosis and to describe and analyse long-term HRQOL in postmenopausal women with osteoporotic fracture. The specific aims were to describe bone mineral density and risk factors in women 55-75 years of age with a recent low-energy fracture (I), estimate the impact of osteoporotic fractures on HRQOL in women three months and two years after a forearm, proximal humerus, vertebral or hip fracture (II), investigate the changes and long-term impact of vertebral or hip fracture on HRQOL in women prospectively between two and seven years after the inclusion fracture (III), and describe how HRQOL and daily life had been affected in women with vertebral fracture several years after diagnosis (IV).

Design and methods: Data were collected from southern Sweden between 1998 and 2008. A total of 303 women were included in Study I, and this group served as the basis for Studies II (n=303), III (n=67), and IV (n=10). A cross-sectional observational, case-control design (I), and a prospective longitudinal observational design (II-III) were used. In Study IV a qualitative inductive approach with interviews was used and data were analysed using a qualitative conventional content analysis.

Results: The type of recent fracture and number of previous fractures are important information for finding the most osteoporotic women in terms of severity (I). Hip and vertebral fractures in particular have a significantly larger impact on HRQOL evaluated using the SF-36 than do humerus and forearm fractures, both during the three months after fracture and two years later, compared between the different fracture groups and the reference population (II). Women who had a vertebral fracture as inclusion fracture had remaining pronounced reduction of HRQOL at seven years. At the mean age of 75.5 years (±4.6 SD), the prevalence of vertebral fracture suggests more negative
long-term impact on HRQOL, more severe osteoporosis and a poorer prognosis than a hip fracture does, and this effect may have been underestimated in the past (III). Study IV demonstrates that the women’s HRQOL and daily life have been strongly affected by the long-term impact of the vertebral fracture several years after diagnosis. The women strive to maintain their independence by trying to manage different types of symptoms and consequences in different ways.

Conclusions and implications: Type and number of fractures should be taken into account in the case-finding strategy for osteoporosis in postmenopausal women between 55 and 75 years of age. The long-term reduction of HRQOL in postmenopausal women (age span 55-75 yr) with vertebral fracture emerged clearly, compared to women with other types of osteoporotic fractures and references in this thesis. The results ought to be taken into consideration when developing guidelines for more effective fracture prevention and treatment, including non-pharmacological intervention for women with osteoporotic fractures, with highest priority placed on vertebral fractures and multiple fractures, to increase or maintain HRQOL.

Keywords: Bone Mineral Density, Hip Fracture, Osteoporosis, Spinal Deformity Index, Vertebral Fracture
LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by their roman numerals.


III. Hallberg I, Bachrach-Lindström M, Hammerby S, Toss G, Ek A-C. Health-related quality of life after vertebral or hip fracture: a seven-year follow-up study. (Accepted for publication in *BMC Musculoskeletal Disorders* 2009-10-12)


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## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>BMC</td>
<td>Bone Mineral Content (g/cm)</td>
</tr>
<tr>
<td>BMD</td>
<td>Bone Mineral Density (g/cm²)</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index, calculated as weight/(height squared)</td>
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<tr>
<td>DXA</td>
<td>Dual-energy X-ray Absorptiometry</td>
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<tr>
<td>FRAX®</td>
<td>Fracture Risk Assessment Tool</td>
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<tr>
<td>HRQOL</td>
<td>Health-Related Quality Of Life</td>
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<tr>
<td>QALY</td>
<td>Quality-Adjusted Life-Years</td>
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<td>QCA</td>
<td>Qualitative Content Analysis</td>
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<td>QOL</td>
<td>Quality Of Life</td>
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<tr>
<td>SDI</td>
<td>Spinal Deformity Index</td>
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<tr>
<td>T-score</td>
<td>Value by SD units compared to mean of young adults of the same sex</td>
</tr>
<tr>
<td>Z-score</td>
<td>Value by SD units compared to mean of same age and sex group</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>WHOQoL</td>
<td>World Health Organization Quality of Life</td>
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INTRODUCTION

Osteoporosis is a common and serious public health problem. Diagnosis and osteoporosis-specific treatment have not been available for more than 20 and 15 years, respectively. Much about osteoporosis, its aetiology and its consequences, remains to be explored. Osteoporosis is a silent disease until it results in fractures after minimal trauma or spontaneously. Worldwide, by the year 2000 there were an estimated nine million new osteoporotic fractures annually, of which 1.7 million were in the forearm, 1.6 million were in the hip, and 1.4 million were clinical vertebral fractures (Johnell & Kanis 2006). In Sweden, more than approximately 70,000 clinical osteoporotic fractures occur annually. More than every second Swedish woman suffers at least one osteoporotic fracture during her lifetime (Sääf et al. 2003). Osteoporosis occurs in a wide range of severity, from mild cases with no fracture or only a single forearm fracture during a lifetime to severe disease with accumulating sequelae.

Today, there are effective diagnostic and treatment methods, but still the majority of individuals with osteoporosis and osteoporotic fractures are left without examination and treatment due to lack of knowledge and financial incitement. There is growing evidence that pharmacological treatment prevents new fractures, but much less is known about its potential to improve or maintain health-related quality of life (HRQOL) after osteoporotic fracture. It is noteworthy that only a few clinical trials have shown treatment benefits regarding HRQOL (Xenodemetropoulos et al. 2004). The goal of osteoporosis care must be to prevent new fractures and to improve HRQOL in individuals with an osteoporotic fracture. The ultimate goal of preventing and treating disease is for each individual to achieve optimal health and well-being according to the WHO definition (WHO 1948).

A 64-year-old woman from the clinical setting described that life changed a great deal after her vertebral and forearm fractures:

“I used to stay active but that’s impossible now…I always experience some level of pain…I get really sad and tired…my husband does all the housework…I am 9 cm shorter and my clothes are either too tight or don’t fit”
Introduction

Much in life may change for a woman after a fracture. Some have pain and trouble for a long time, which encroaches on their everyday life. Unfortunately, this patient group is overlooked in health care routines. A common belief is that symptoms after a fracture will fade spontaneously. The suffering woman is sent home with the message that things will improve soon. This results in many women not seeking further help.

The severity of osteoporosis has largely been, and still is, assessed mainly in terms of bone mineral density and incident fracture rates. A great deal fewer studies are done on its impact on HRQOL. Many studies are based on cross-sectional data with different times since fracture. Research on HRQOL after osteoporotic fracture in women has seldom focused on prospective longitudinal data in a clinical routine setting. As osteoporotic fractures are very common and pose an increasing health problem, especially among postmenopausal women, more knowledge about the long-term impact of the fracture on HRQOL and daily life is needed. Therefore, this thesis aims at describing and analysing HRQOL in postmenopausal women with osteoporotic fractures while focusing on long-term perceived outcomes and evaluating the usefulness of a recent low-energy fracture as index event in a case-finding strategy.
BACKGROUND

Osteoporosis

Definition

The World Health Organization (WHO) defines osteoporosis as a “systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture” (1993a).

Osteoporosis has been operationally defined on the basis of bone mineral density (BMD) assessment. The WHO has proposed diagnostic thresholds based on both low BMD and fracture anamnesis (1994, Kanis 1994), and has defined the following criteria based on the BMD, for diagnosing and assessing osteoporosis:

There are four categories:
- Normal: A BMD not more than 1 standard deviation (SD) below the young adult normal mean (T-score ≥-1).
- Osteopenia (or low bone mass): A BMD between 1 and 2.5 SD below the young adult normal mean (T-score < -1 and > -2.5).
- Osteoporosis: A BMD 2.5 or more SD below young adult normal mean (T-score ≤ -2.5).
- Established (or severe osteoporosis): A BMD 2.5 or more SD below young adult normal mean (T-score ≤ -2.5) in the presence of one or more fragility fractures.
Osteoporosis as a public health problem

Osteoporosis is a serious public health problem, and is of clinical concern because of the fractures associated with it. Morbidity and disability due to osteoporosis are caused mainly by fractures of the hip, vertebrae, humerus and distal radius (2003). Osteoporotic fractures are one of the most common causes of morbidity and mortality, particularly in developing countries (Johnell & Kanis 2004, 2006, O’Neill et al. 2004), and are a major contributor to medical care costs in many regions of the world (Cummings & Melton 2002). Worldwide, osteoporotic fractures account for 0.83% of the global burden of non-communicable disease and 1.75% of the global burden in Europe (Johnell & Kanis 2006).

The incidence of osteoporotic fractures has been rising rapidly. Worldwide, the number of hip fractures is expected to rise from 1.7 million in 1990 to 6.3 million by 2050 (Cooper et al. 2008). In Sweden, the incidence of hip fractures in women seems to be stabilized (Löfman et al. 2002). According to the International Osteoporosis Foundation in 2008, more than 40% of middle-aged women in Europe will suffer one or more osteoporotic fractures during their remaining lifetime (Kanis et al. 2008a, Kanis et al. 2000b). Sweden and Norway have the highest rates in the world in terms of fracture of the hip and vertebrae (2002, Johnell et al. 1992, O’Neill et al. 1996). Vertebral fracture is the most frequent osteoporotic fracture (Cauley et al. 2007), but underdiagnosis is a worldwide problem (Delmas et al. 2005).

Osteoporosis affects a large part of the elderly population and results in fractures with costly consequences in both human and economic terms. A recent study in Sweden concluded that the mean direct and indirect fracture-related costs the year after a vertebral, hip or forearm fracture were estimated at €12,544, €14,221 and €2,147, respectively (exchange rate of 9.13 SEK/€). Based on these findings, the annual burden of these types of fractures in Sweden could be estimated at €0.5 billion. Adding to this the estimated loss of quality adjusted life years (QALYs), the first year was 0.26, 0.17, and 0.06 for vertebral, hip and forearm fracture, respectively, according to EuroQoL (Borgström et al. 2006). After 13-18 months there were higher long-term costs and greater loss in QOL among vertebral fracture patients (86% women) than previously believed, but this group included a number of patients who were hospitalized that is higher than is common in the total group of patients with vertebral fracture. The mean costs 13-18 months after a vertebral, hip or
forearm fracture were estimated at €3,628, €2,422, and €316. Between 12 and 18 months after vertebral, hip and forearm fractures the utility increased by 0.05, 0.03, and 0.02, respectively (Ström et al. 2008). The total annual societal burden of osteoporosis in Sweden, including the first year after the incident fractures, long-term costs of prevalent cost and annual value of QALY lost are estimated at €1.66 billion (exchange rate of 9.13 SEK/€), based on vertebral, hip and forearm fractures, which account for about 60-80% of the total fracture costs (Borgström et al. 2007). Costs after the first 18 months are mainly unknown and have to be studied further.

All fractures may lead to a reduced HRQOL and disability (Ettinger et al. 1992, Gold 2001, Lips & van Schoor 2005, Nevitt et al. 1998). Hip and vertebral fractures are also linked to increased mortality (Caliri et al. 2007, Hasserius et al. 2005, Ismail et al. 1998, Kado et al. 1999).

**Osteoporotic fracture**

The skeleton normally has enough strength to carry our body and protect vital parts such as the brain, spinal medulla and other organs. Normal bone is a living, strong and flexible tissue that adapts to mechanical load. However, in some people and situations, bone is more brittle and fractures may occur secondary to little or no trauma. This may occur in both sexes at any age, but is more common in women over 50. Women with osteoporosis may sustain several fractures with accumulative sequelae. This process could shorten their vital and good period in life and add to other limitations caused by aging. Fifty percent of Swedish women and about 80% of Swedish men will never sustain a fracture in their lifetime, whereas some are sooner or later severely stricken by osteoporosis and sustain several fractures.

Osteoporotic fracture (II,III) is also termed low-energy fracture (I), osteoporosis-related fracture, low-trauma fracture or osteoporotic fragility fracture in other studies. Osteoporotic fracture is defined as a fracture associated with minimal trauma, i.e. a fall from standing height or less, or occurring spontaneously (Compston et al. 1995).

Typical osteoporotic fractures are fractures of the vertebrae (spine), hip, proximal humerus and distal forearm (wrist). It has been shown that almost all types of fractures are related to low bone mineral density (BMD) and,
therefore, the majority of all types of age-related fractures could be osteoporotic in nature (Cummings & Melton 2002). Irrespective of the type of the fracture, women with prior fractures had twice the risk of subsequent fracture compared with women without prior fracture (Klotzbuecher et al. 2000). The adverse outcome of osteoporotic fractures fall into three main areas: morbidity, mortality and cost (Cummings & Melton 2002).

Distal forearm fractures (Colles’ or Smith’s fractures) account for approximately 25,000 annual fractures in Sweden (Sääf et al. 2003). The lifetime risk of forearm fracture for 50-year-old women in Sweden has been estimated to 21% (Johnell & Kanis 2005).

Proximal humerus fractures account for approximately 10,000 fractures in Sweden annually (Sääf et al. 2003). Pelvis and ribs fractures often occur in women with osteoporosis. However, all fractures except facial and skull fractures are related to low BMD or osteoporosis, and are more common in this population (Stone et al. 2003).

Hip fractures are either cervical or trochanteric, and account for approximately 26% (18,000) of the 70,000 fractures recorded annually in Sweden health care (Sääf et al. 2003). The lifetime risk of hip fracture is about 23% for Swedish women. The fracture occurs at the mean age of 81, and risk increases with higher age (Kanis et al. 2000a). Many women suffer decreased mobility and pain after their hip fracture. About 10% of all patients sustaining a hip fracture are long-term institutionalized, and 20-30% of hip fracture patients die within one year after fracture (Johnell & Kanis 2005).

The vertebral fracture can be classified into two major categories, subclinical and clinical. Overall, only about one third of all patients with vertebral fractures identified on radiographs came to clinical attention. About 50% of patients reported back pain and 8% were hospitalized (Ross 1997). Even when there is a vertebral fracture on the radiograph, it is often not mentioned by the radiologist, is rarely noted in the medical records, and infrequently prompts preventive medical treatment (Gehlbach et al. 2000). The prevalence of radiographic vertebral deformity increases with age. For example, in Europe the prevalence rises from 11.5% in women 50-54 years of age to 35% in women 75-79 years of age (O’Neill et al. 1996). Vertebral fractures most commonly occur at the thoracolumbar junction and in the mid-thoracic area (Papaioannou et al. 2002). The lifetime risk of a clinically defined vertebral
fracture at the age of 50 for a Swedish woman has been estimated at 15.1% (Johnell & Kanis 2005). It is generally believed that pain and disability after a vertebral fracture persist only for a few weeks or months (Silverman 1992). Some studies, however, have described women who suffer from long-lasting pain and disability (Cook et al. 1993, Hasserius et al. 2005, Ross et al. 1991), as well as psychosocial consequences (Gold 1996), for several years after this type of fracture. Further studies of HRQOL after vertebral fracture are needed, as are methods for early identification of women at high fracture risk.

**Assessment of fracture risk**

As menopausal women are at most risk for osteoporotic fractures, this group was selected for these studies. Natural menopause occurs between 45 and 55 years of age everywhere in the world. Early menopause, occurring either naturally or due to surgery, increases the risk of developing osteoporosis. Oestrogen deficiency is suggested to play a major role in postmenopausal bone loss, a suggestion strongly supported by the higher prevalence of osteoporosis in women than in men (Nilas & Christiansen 1987). Osteoporosis remains under-recognized and under-treated. Much of the disease burden could be avoided if women at risk were identified and appropriate interventions against new fractures were started in a timely manner.

Methods for early detection, i.e. case-finding strategies for high fracture risk, are under development. Old age and being female are important clinical risk factors in the assessment of fracture probability (Kanis et al. 2008a), as are having sustained a previous low-energy fracture, mainly of the hip, forearm or vertebrae, including morphometric vertebral fracture (Klotzbuecher et al. 2000); heredity usually expressed as a hip or vertebral fracture in any parent (Kanis et al. 2004a); oral glucocorticoid treatment; low body mass index (BMI); smoking and diseases causing osteoporosis (called secondary osteoporosis), for example prolonged rheumatoid arthritis, celiac disease and primary hyperparathyrodism (Kanis et al. 2008a, Kanis et al. 2005).

BMD is a measurable and strong risk factor for osteoporotic fractures. The measurement of bone mineral density is a central component of risk assessment. A major problem is that about 50% of all osteoporotic fractures occur in individuals who have osteopenia and not yet osteoporosis as defined
by bone mineral density (Wainwright et al. 2005). If treatment is restricted to only those individuals with a T-score in the osteoporosis range, many opportunities to prevent fractures will be missed. If, however, other risk factors such as those mentioned above are included with BMD in a compound risk score, a more valid estimation of the absolute fracture risk for the individual patient will be obtained. An algorithm based on data from several large prospective studies utilizes several well evaluated risk factors to calculate the individual five- or ten-year risk for hip fracture or any of the four typical osteoporotic fractures (Kanis et al. 2008a, Kanis et al. 2005). The best clinically useful instrument for estimating individual absolute fracture risk was released in February 2008 under the name of FRAX® and is available to anyone online (http://www.shef.ac.uk/FRAX/). This algorithm is rapidly developing and is being gradually implemented in health care planning and routine health care. The current version of FRAX® makes no distinction between types of osteoporotic fracture, and the number of past fractures is not included in the algorithm (Kanis et al. 2008b).

At present there is no universally accepted recommendation for population screening of bone mineral density in Europe, but a case-finding strategy is recommended for the targeting of individuals at high risk for osteoporotic fracture. One strategy recommended by several expert committees is to use the occurrence of a new osteoporotic fracture in a postmenopausal woman as a major indication for investigation for osteoporosis. Therefore, Study I focuses on different risk factors in women with a recent osteoporotic fracture.

**Health**

There are many definitions of health. The definition that is chosen at a particular point in time depends on the purpose and context. The definitions of health can be described simply from one of two perspectives, biostatic or holistic. The biostatic, disease-oriented perspective represented by the philosopher Boorse states that health is the absence of disease. Health is normal functioning, where the normality is statistical and the functions biological (Boorse 1977). The humanistic, holistic perspective characterized by Nordenfelt states that having health is related to the extent to which the individual can realize his/her goals under standard conditions (Nordenfelt 1996, Nordenfelt 2000). These two perspectives are combined in the WHO definition of health, which states that “health is a state of complete physical,
mental and social well-being and not merely absence of disease or infirmity” (WHO 1948). Over the years, the definition of health have changed from that of a goal to that of a resource in daily life (WHO 1986).

A woman with osteoporotic fractures suffers a deviation in health both from a biostatic perspective, in the shape of abnormal bone mineral density, and from a holistic perspective as she cannot do whatever she wants due to her fracture.

**Health-related quality of life**

The concept of quality of life (QOL) has its roots in Aristotle (384-322 BC), who defined good QOL as “the good life”, or “doing well” as the same as being happy (Fayers & Machin 2007). Today, there is no universally accepted definition or understanding of what the concept of QOL stands for. This is perhaps not surprising, since QOL is not only a concept but is also a term about which there is an intuitive understanding: “...a term that everyone understands but which few can define”. It is a “vague and ethereal entity, something that many people talk about but which nobody clearly knows what to do about” (Campbell 1976). The concept is therefore particularly difficult to frame and analyse. But, regardless of how QOL is defined, there are some common features in the definitions presented. QOL covers all aspects of life including health status, environment, financial aspects and human rights (Lips & van Schoor 2005). It is also clear that QOL means different things to different individuals, and takes on different meanings according to the area of application.

The WHO definition of QOL is based on “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person’s physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment” (1993b). They regard QOL not as confined to domains of health, but as broad-ranging and affected by an individual’s physical health, mental state, personal beliefs, and social and environment relationships (Bowling 2005).

The development of health care demands methods for measuring the effects of disease and treatments on QOL, and a great number of questionnaire
instruments have therefore been developed to measure health-related quality of life (HRQOL). HRQOL still has a loose definition; it is generally agreed that the relevant aspects can vary but can include general health, physical symptoms, physical and emotional functioning, social well-being and functioning (Fayers & Machin 2007). It is more common to use the term HRQOL instead of QOL within the area of clinical medicine and clinical trials to avoid ambiguity.

According to Wilson and Cleary, most conceptualizations of HRQOL include the dimensions of physical functioning, social functioning, role functioning, mental health and general health perceptions, with important concepts such as vitality (Wilson & Cleary 1995). In their HRQOL model, Wilson and Cleary divide relationship and interaction into five levels: biological and physiological factors, symptoms, functioning, general health perceptions, and overall quality of life. All interactions and relationships in the concept model are also affected by the characteristics of the individual and his/her environment (Wilson & Cleary 1995).

The Medical Outcomes Trust short form questionnaire, most often referred to as the SF-36, has been prepared and developed as a general measure with widespread use. What is measured and clearly indicated is HRQOL, which represents a pragmatic definition mainly related to a person’s functioning and well-being during illness and treatment and includes the main areas in which health can affect one’s life (Ware & Sherbourne 1992). Method development takes its starting point in the broad concept of health as defined by the WHO in 1948 (WHO 1948). As a starting point, the model includes definitions of the five health concepts: physical health, mental health, social function, role function and general health. As health is more than merely the absence of disease and disability, well-being is also included in the model (Ware 1987).

In this thesis HRQOL was conceptualized by the WHO definition of health (WHO 1948), which the SF-36 questionnaire is also based on (Ware 1987, Ware & Sherbourne 1992) and which was used as the framework in these studies. The HRQOL model begins with health-related factors and includes biological and physical factors, symptoms and functioning. Health-related factors are affected by characteristics of the individual and from the environment, and vice versa. General health perceptions are influenced by all the earlier components in the model and are subjective in nature. The final component,
HRQOL, is subjective well-being, related to how satisfied or happy someone is, as related specifically to women’s health (Figure 1).

![HRQOL Diagram]

**Figure 1. Model for HRQOL used in this thesis. Modified version inspired by Ware, 1992, and Wilson & Cleary, 1995.**

The model was also inspired by Wilson and Cleary, but differs in certain areas (Wilson & Cleary 1995). Biological and physiological factors, symptoms and functioning were grouped into Health-related Factors, and overall quality of life into HRQOL. The box Non-medical Factors was deleted because all non-medical factors can be categorized as characteristics of either individual or environment, which are already included in the model.

**Measurement of health-related quality of life**

Formal HRQOL measures are rarely used in clinical practice routines. In clinical trials, however, HRQOL or health status surveys are increasingly being used as primary outcome. The reasons for this gap between clinical routines and research activities are complex, but likely include a lack of understanding of the definition of HRQOL, a lack of familiarity with the surveys and a perception that these measures are “soft” and unimportant (Rumsfeld 2002).

HRQOL questionnaires can be classified into generic (or general) and disease-specific (or disease targeted) instruments (Bowling 2005, Fayers & Machin 2007, Lips & van Schoor 2005). Generic instruments focus on general questions regarding health status and can be used in various diseases, and enable comparisons between different groups and diseases. Examples of the most
widely used generic instruments for individuals with osteoporosis are the SF-36 (Ware & Sherbourne 1992) and the EQ-5D (EuroQoL) (Brooks 1996). The SF-36 was used in the studies (II, III) and is further described in the methods.

Disease-specific questionnaires are designed for individuals with a specific diagnosis, and are suitable for one diagnosis only. A disadvantage is that different disease groups and background populations cannot be compared. Advantages are that these instruments can provide a more valid and precise evaluation of HRQOL related to the specific disease. Most of these osteoporosis-specific instruments were developed for women with vertebral fracture. Examples of the most common osteoporosis-specific questionnaires are the QUALEFFO-41 (Lips et al. 1999) and the Osteoporosis Assessment Questionnaire (OPAQ) (Silverman et al. 2001).

Qualitative research methodology is characterized as an attempt to understand the life world of an individual and a group of people. Moreover, the methods are characterized by the investigation of phenomena or experiences, typically in an in-depth and holistic fashion, through the collection of rich narrative materials using a flexible design (Patton 2002, Polit & Beck 2004). A qualitative approach makes it possible to find new aspects that have not been asked about in structured questionnaires and gain a deeper understanding. This methodology was chosen for Study IV.

Health-related quality of life in women with osteoporotic fractures

Several studies have shown more or less impairment of HRQOL in women who have sustained a vertebral, hip or forearm fracture (Lips & van Schoor 2005). However, the long-term impact of osteoporotic fracture on HRQOL has not been prospectively or sufficiently examined.

Forearm and humerus fractures
Forearm fractures lead to acute pain and loss of function, but recovery is usually good. Six months after the fracture, a good or excellent result was achieved in 77% (Kaukonen et al. 1988). The total loss of QALYs was 0.02 for one year (Dolan et al. 1999). In one population-based cohort, women with a history of wrist fracture were nine times more likely to have difficulty cooking than women who had never fractured their forearm (Greendale et al. 1995).
**Hip fracture**

Six to twelve months after fracture, patients with hip fracture scored significantly lower in all domains of the SF-36 compared with controls (Hall et al. 2000). In one study, 32 patients with hip fracture and 29 controls completed the SF-36 and the OPAQ questionnaires at one week and 12-15 weeks after fracture. The patients had lower baseline scores and a significant decrease in HRQOL in most domains compared with controls (Randell et al. 2000). Also, the EQ-5D index decreased after hip fracture, with scores decreasing from 0.78 before the fracture to 0.51 at 17 months, after a femoral neck fracture treated with internal fixation (Tidermark et al. 2002).

**Vertebral fracture**

During recent decades, cross-sectional studies (Begerow et al. 1999, Hall et al. 1999, Oleksik et al. 2000, Papaioannou et al. 2006, Salaffi et al. 2007, Tosteson et al. 2001) and some follow-up studies (Borgström et al. 2006, Oleksik et al. 2005, Papaioannou et al. 2009, Silverman et al. 2001, Ström et al. 2008) after vertebral fracture have reported that HRQOL is severely impaired. Studies of women with subclinical as well as clinical vertebral fractures reported association with decrements in function and HRQOL. The decrements in function were greater when the number of fractures was higher and the severity greater (Fink et al. 2003, Ross et al. 1991). A study by Hall et al. showed similar results in women with vertebral fractures, but no domains of the SF-36 or functional measure correlated with either the number of vertebral fractures or the time since the last vertebral fracture (Hall et al. 1999). New vertebral fractures, even those not diagnosed clinically, are associated with substantial increases in back pain and functional limitations due to back pain (Cook et al. 1993, Ettinger et al. 1992, Nevitt et al. 1998). The clinical impact of vertebral fractures in the form of psychosocial consequences is also described (Gold 1996).

Few studies use qualitative methods to examine what it means to live with a vertebral fracture. One describes the experience of five women with vertebral fractures, with each participant describing significant challenges in maintaining daily functioning (Paier 1996). Two studies focus on how self-concept provides an understanding of the range of strategies that women with osteoporosis use in order to manage their chronic illness in daily life (Wilkins 2001a, b).
Physical performance

The extent to which the impairment of HRQOL is due to fracture or other co-morbidity or biological ageing is not known. In elderly women with osteoporosis, impairment of balance has been reported (Sinaki et al. 2005). A recent study has also reported that balance impairment was related more to the presence of vertebral fractures than to thoracic kyphosis in women with osteoporosis (Greig et al. 2007).

Pain and fractures are independently related to decreased handgrip strength and walking speed (Ekström & Elmstähl 2006). Handgrip strength is necessary for performing activities of daily living and is essential for maintaining functional autonomy, and may also mirror ageing and fragility. Therefore, further studies are needed on the role of these factors in HRQOL after fracture.
AIMS

The overall aim of this thesis was to evaluate the usefulness of a recent low-energy fracture as index event in a case-finding strategy for osteoporosis and to describe and analyse long-term health-related quality of life in postmenopausal women with osteoporotic fracture.

Specific aims

- To describe bone mineral density and risk factors in women 55-75 years of age with a recent low-energy fracture. Should any type of fracture have higher priority for the investigation of osteoporosis than any other? Is the number of previous fractures useful information? (Study I)

- To estimate the impact of osteoporotic fractures on health-related quality of life in women three months and two years after a forearm, proximal humerus, vertebral or hip fracture and compare different fracture groups and the reference population regarding health-related quality of life. (Study II)

- To investigate the changes and long-term impact of vertebral or hip fracture on health-related quality of life in postmenopausal women prospectively between two and seven years after the inclusion fracture, compare health-related quality of life results between fracture and reference groups and study the relationship between health-related quality of life and physical performance, spinal deformity index and bone mineral density at seven-year follow-up. (Study III)

- To describe how health-related quality of life and daily life had been affected in women with vertebral fracture several years after diagnosis. (Study IV)
METHODS

Design

Two approaches based on paradigms from different scientific traditions, i.e. a positivistic paradigm with deductive quantitative research methodology and a naturalistic paradigm with inductive qualitative research methodology, were used in this thesis. The first paradigm, inspired by the nomothetic science tradition, focuses interest on what is general, objectively, and the ontology or view of reality is atomistic. The second paradigm, inspired by the idiographic science tradition, focuses interest and understanding on what is individual, unique and concrete, and on the underlying meaning (Nilstun 1995, Polit & Beck 2008).

For the quantitative studies in the thesis a cross-sectional, observational, case-control design (Study I) and a prospective longitudinal observational design compared with reference groups (Studies II-III) were used.
In Study IV, a qualitative approach content analysis was chosen, as the aim of the study was to describe the women’s experiences of living with vertebral fracture from an insider view to obtain a deeper understanding of the women’s everyday life.

Data were collected for the period 1998-2008. For an overview of the design, participants, fracture types, methods and analyses in the thesis, see Table 1.
Participants

The participants in this thesis were originally recruited through a written invitation sent to 600 consecutive women 55-75 years old in southern Sweden, with a recent (within 6 months) osteoporotic fracture of the distal forearm, proximal humerus, vertebrae or hip. The newly diagnosed low-energy fracture referred to as “index fracture” (I) was also termed “inclusion fracture” (II, III). The study was confined to women 55 to 75 years old in order to minimize confounding due to other diseases and to ensure good adherence. The women were identified using the radiographic register or the records at the emergency unit. Four hundred and forty-five women replied by phone, while 155 did not (passive refusers). Forty-five women refused participation (active refusers).
External dropout was 33% (n=200), and 67% responded (n=400). A short standardized interview was carried out by phone to assess inclusion and exclusion criteria. Internal exclusion due to the inclusion and exclusion criteria was 97 (24%); for details, see Figure 2.

**Figure 2. Flow chart of inclusion, exclusion and dropouts in Studies I-II.**

A total of 303 participants were included in Studies I and II (baseline data) and were examined 6-170 days after fracture diagnosis. This group will serve as the basis for Studies II-IV in this thesis (Figure 3). All women were Swedish-speaking. Mean age was the same for the non-participant group and the study group (68 years). There was a higher rate of hip fractures and vertebral fractures in the non-participant group, 19% vs. 13% and 22% vs. 18%, respectively. Regarding the forearm fractures there was a lower rate (46% vs. 56%), and there were similar figures for humerus fractures.

In Study II, 292 of the 303 women participated in the two-year follow-up. Of these women, eight (3%) declined further examination and three (1%) had died. A random sample (n=36) of the passive refusers at baseline examination was performed two years after the fracture, and four of them were found to have died (11%).

In Study III, 91 women examined two years after an osteoporotic vertebral or hip fracture were invited to a new examination after seven years. Of these women, eight refused the follow-up visit, three were excluded due to stroke or dementia, and 13 (three from the hip fracture group and 10 from the vertebral fracture group) had died. The remaining 67 women were included in the study. Using data from the two-year follow-up, a dropout analysis between
the missing group (n=24) and the women participating in the seven-year follow-up (n=67) showed that the missing group had significantly lower values regarding the SF-36 in the general health and social function domains. They also had lower weight, body mass index and bone mineral density in the hip, but age did not differ.

Study IV included women with vertebral fractures who participated in Study III, two years earlier. A purposeful sampling of ten information-rich women with experiences of living with vertebral fracture and a strategic sampling to achieve maximal variation on dimensions of interest was chosen (Patton 2002). Variations were chosen with regard to age, living conditions and number of vertebral fractures (X-ray data from Study III) and other previous fractures.

![Flow chart of the participants in Studies I-IV.](image)

**Figure 3. Flow chart of the participants in Studies I-IV.**

**Reference groups**

In Study I, the reference population was recruited from three previous population-based studies (Löfman et al. 2002, Löfman et al. 1997). They were originally selected through a random sampling procedure from the population register. Women with a history of previous clinical fracture were excluded.
from the reference group. To avoid confounding by age, the population was age-matched at group level through a random, interactive process. Sub-samples of the reference population were used to match the respective fracture type groups, which differ somewhat in age. In all, 209 women 55 to 75 years of age were included in the reference group.

As a reference for BMD (I-III) in the hip, the National Health and Nutrition Examination Survey’s reference database NHANES III (Looker et al. 1998) was used, and for BMD in the spine the reference data published by Favus (Favus 1993) were used. Although minor differences were found, with somewhat lower values in the hip and spine with the exception of premenopausal women in spine BMD in our reference population and in NHANES III and Favus’s reference populations, it was decided, for reasons of comparability, that the machine-specific database for calculation of T- and Z-score would be used in this study.

In Study II, a non-pharmacologically treated fracture control group (n=93) was used and examined only two years after fracture. This group was recruited from the same area six months before and six months after inclusion of the primary study group, from a nearby hospital in the same county. Of the women in this group, 59 had a forearm fracture, 11 had a humerus fracture, 9 had a vertebral fracture and 14 had a hip fracture.

In Study II, reference values for HRQOL using the SF-36 questionnaire were obtained from a large local population in Southeast Sweden in 1999, from which age- and sex-matched references were randomly selected, 647 for baseline values and 412 for two-year follow-up (Eriksson & Nordlund 2002).

In Study III, an age- and sex-matched reference group was chosen from a large local population study in Östergötland County, Sweden, during 2006, to obtain normative values for the SF-36. The population study was comprised of 804 women aged 64 to 82 years, who formed the reference group (mean age 75.7, SD 4.7) (Walter & Noorlind Brage 2006).
Methods

Assessments

Background data

Before each visit a self-administered questionnaire was sent to the women, focusing on previous and new fractures, falls, concomitant diseases, back pain, pharmacological treatments and lifestyle factors of importance for osteoporosis and fracture risk (i.e. physical activity, falls, smoking and calcium intake) (I-III). For the assessment of leisure-time physical activity level a seven-grade scale was used, modified from the original four-grade scale (Saltin & Grimby 1968). The physical activity levels included household and leisure-time activities. The lowest grade of physical activity was 1, while 7 was denoted as the “highest level”. A verbal graphic rating scale (GRS) was used to measure current and recurrent back pain, in the previous two weeks. The scale used descriptors along a continuum (none-insignificant-mild-moderate-severe-unbearable). The absence of pain was rated as 0 mm, and the worst possible pain as 100 mm (Turk & Melzack 2001).

Physical examination, function and clinical tests

Body height (m) was registered using a stadiometer and body weight (kg) using calibrated scales. Body mass index (BMI) was calculated using the formula kg/m². Body height and weight were measured in indoor clothes without shoes (I-III). A physical examination was done by a physician or orthopaedic surgeon from the research group. Laboratory tests were performed according to current routine (I-II).

In Study III, physical function was assessed by measuring handgrip strength and one-leg static balance testing. Handgrip strength (kg) was measured in the dominant hand using the standard JAMAR, an electronic dynamometer. For standardization, the adjustable handle was set at the second position for all women. Participants sat comfortably with their elbow flexed at 90 degrees and their shoulder adducted and neutrally rotated. Each test was performed three times and the mean value was used. Reference values were obtained from
Mathiowetz et al. (Mathiowetz et al. 1985) and were adapted to the metric system. The instrument’s calibration was tested periodically during the study. Mathiowetz has recommended the use of the mean of three tests, to achieve the highest test-retest reliability. Static balance was assessed by asking the patients to stand on only their dominant leg with their eyes open. The one-leg-stance tests were performed without shoes with the opposite foot lifted halfway up on the calf of the supported leg and the arms in vertical position. The time was recorded until the supporting foot was moved from its initial position. The static balance tests were timed with a digital stopwatch and were limited to a maximum of 30 s. Static balance tests were performed three times, and the best value on the dominant leg was used in the final score (Bohannon et al. 1984, Johansson & Jarnlo 1991).

**Bone mineral density**

In these studies (I-III), bone mineral density (BMD) was measured using dual-energy X-ray absorptiometry (DXA), and was performed with Hologic QDR 4500 Acclaim™ (Hologic Inc., Bedford, MA) of the lumbar spine, hip (femoral neck and total hip) and forearm, non-dominant or non-fractured side. These method and measurement sites are currently used as the “gold standard” for the clinical diagnosis of osteoporosis. The women were examined in a horizontal position for lumbar spine and hip, and in a sitting position for forearm measurement (Figure 4). Each DXA measurement took about 1-5 minutes to obtain. The DXA technique involves a very low radiation dose, similar to that of natural background radiation (~7µSv/day) (Blake et al. 2006).

Figure 4. Device for measuring bone mineral density.
Measurements of bone mineral content (gram) and area (cm²) are provided for each measurement site. Results are generally expressed as a mean “areal” density (BMD g/cm²). Precision measures the reproducibility of the bone densitometry technique and is expressed as a coefficient of variation (CV), and for DXA total hip and lumbar spine is approximately 1-2%. The accuracy of DXA lies between 8 and 10%, which is considered acceptable, and refers to the closeness of the BMD measured by densitometry to the actual calcium content of the bone (Adams 2008).

The women were classified as osteoporotic if their T-score was 2.5 or more standard deviations (SD) below the mean value of young normal (T-score ≤-2.5) at lumbar spine or hip total, and osteopenic if the lowest of these values was between <-1 and >-2.5 SD (1993a). For interpretation, BMD was compared with an appropriate ethnic- and gender-matched reference database, and was expressed as a standard deviation score (SD) from the mean of either young adult (T-score) or age-matched (Z-score) (Adams 2008). Internal variation was checked regularly with an everyday calibration using a phantom. Good precision depends on scanners being operated by skilled and appropriately trained staff; therefore, specially trained nurses (DXA operators) performed all the measurements in the studies.

**Pharmacological and non-pharmacological treatment in the studies**

The studies in this thesis are based on a routine health care setting. At baseline basic non-pharmacological intervention was given to all women, verbally and written, irrespective of fracture diagnosis and BMD. The advice focused mainly on the importance of physical activity, nutrition, fall prophylaxis and non-smoking. Fracture treatment was performed in Jönköping or Linköping according to standard routines. The women were prescribed pharmacological treatment according to the current local consensus guidelines at study start (1997). Most women were advised to take a supplement of calcium in combination with vitamin D. Women with a T-score of the hip or spine below –2.5 SD were also advised to follow a pharmacological anti-osteoporosis treatment with bisphosphonate, oestrogen or raloxifen.
At three, six, 12 and 18 months after baseline visit, each woman was phoned by a research nurse and asked about medications, adherence and symptoms or distress due to the fracture. The women also had the opportunity to phone the appropriate osteoporosis unit themselves if they had any queries or if problems arose.

At two-year follow-up the women were prescribed continued osteoporosis medication, usually bisphosphonate, calcium and vitamin D, for the following year. The women were also referred to their general practitioner for further treatment and follow-up.

Health-related quality of life

In these studies (II, III), the generic SF-36 questionnaire was chosen for use due to its extensive validation and capacity for comparisons between different groups. The SF-36 was the most widely used and evaluated measurement in a bibliographic review of patient-assessed health outcome measures (Garratt et al. 2002), and was also favoured as a core instrument in the study group regarding clinical trials within the osteoporosis area (Greendale et al. 1993). At the start of the baseline study there was no osteoporosis-specific questionnaire available that had been translated into Swedish and validated.

The SF-36 questionnaire is comprised of 36 items, with two to six response options according to an ordinal scale, assessing eight health concepts or domains: physical function (PF) (10 items), role limitations due to physical health problems (RP) (4 items), bodily pain (BP) (2 items), general health (GH) (5 items), vitality (VT) (4 items), social function (SF) (2 items), role limitations due to emotional problems (RE) (3 items) and mental health (MH) (5 items). All but one of the 36 items about health changes during the past year are used to score the eight SF-36 scales. Each domain allows a score of 0-100, with a high score indicating better HRQOL. The Swedish standard version 1.0 was used in Studies II-III (Sullivan et al. 1994).

For the SF-36 (II, III), items within each domain were coded, scored and summarized to derive the eight domains. The scores were then translated into a 0-100 scale where 0 indicated the worst possible HRQOL and 100 the best, according to the manual and interpretation guide for the SF-36 (Sullivan et al.
Methods

SF-36 scores were computed if the respondent answered half or more of the items on the scale; i.e., a person-specific mean score was calculated based on the non-missing items (Sullivan et al. 1994).

In Study II only, physical (PCS) and mental (MCS) component summary indexes were used, but it was later concluded that the current PCS and MCS scoring procedure inaccurately summarizes subscale profile scores and should therefore be revised. Until then, component scores should be interpreted with caution and only in combination with profile scores (Taft et al. 2001). It was therefore decided that these measurements would not be used in Study III, as the principal behind the calculation algorithm has been exposed to a great deal of criticism.

The SF-36 has been well evaluated through psychometric and clinical tests of validity and reliability (McHorney et al. 1993). The instrument has been translated into Swedish, and adjusted and tested in a Swedish population (Persson et al. 1998, Sullivan & Karlsson 1998, Sullivan et al. 1995).

Vertebral fracture assessment

At baseline, vertebral radiological examinations were performed only in the group with vertebral fracture (II). In Study III, a lateral digital radiograph of the thoracic and lumbar spine was performed in all women within four months after their visit, except in one woman who was examined nine months before her visit date.

The number and grade of vertebral deformities were assigned according to the Genant visual semiquantitative criteria (Ferrar et al. 2005, Genant et al. 1993). Each of the T4 to L4 vertebrae was assigned a grade of 0, 1, 2 or 3. A score of 0 was assigned to normal, non-fractured vertebrae; 1 to a mild deformity; 2 to a moderate deformity; and 3 to a severe deformity. A mild fracture was defined as a 20%-25% reduction in anterior, middle or posterior vertebral height, and a reduction of area of 10-20%. Moderate and severe vertebral fractures were defined as a 25%-40% reduction in any height and a reduction in area of 20-40% and a > 40% reduction in any vertebral height and area, respectively. A Spinal Deformity Index (SDI) score was defined as the sum of the individual vertebral scores (range 0-39). By combining the number and severity of vertebral fractures, the SDI score provided a valuable descriptor of the fracture
Methods

burden (Figure 5). Any previous X-rays were also examined to evaluate the occurrence of any new vertebral fractures. All the radiological examinations were evaluated by the same experienced skeletal radiologist.

![Figure 5. The visual semiquantitative grading system for evaluation of vertebral deformities, adopted from Genant et al., 1993. (Illustration by Per Lagman)](image)

Qualitative interviews

A qualitative research interview is a conversation with a purpose. The interview gives participants an opportunity to describe in their own words their experiences in detail and give their perspectives and interpretations. This method accesses the participants’ understanding of their real life and experiences (Silverman 2006). A semi-structured interview guide was used (IV), which gave the interviewer the freedom to converse with the women in each specific predetermined topic area (Patton 2002).

The central question was: Could you tell me how your quality of life and daily life have been affected by the vertebral fracture? Further topics were: How do you cope with your symptoms after the vertebral fracture? What is most important to you, what matters most in life? What kinds of support would make your daily life easier? The interviewer posed probing questions in order
to deepen, clarify and develop the women’s responses. Examples of probing questions in the study were “How did you feel?” and “What did you think?”.

Interviews were conducted by the author and lasted 29 to 69 minutes, excluding the informal conservation that took place before and after the interview to build contact and allow the women to ask questions. The data collection was performed in the women’s homes (n=7) or at the author’s office (n=3), according to the women’s preference. The data were collected from April to November 2008. Interviews were digitally recorded (MP3, Philips digital voice tracer 7890) and transcribed verbatim, by the author and a professional secretary, including any nonverbal or background sounds. A transcription guide was used to increase the quality of data preparation and transcription, and included information about text formatting, content, pauses, sensitive information and storage of the information (Mclellan et al. 2003b).

Data analyses

Statistical analyses

Descriptive statistics are presented as arithmetic mean value (M), standard deviation (SD), confidence interval (CI) and percent. Analytic statistical methods used in the different studies are described in Table 2.

For correlation between data, Pearson’s product moment correlation, Spearman’s rho analysis and univariate regression were used.

For comparisons between groups, the unpaired two-tailed t-test and one-way analysis of variance (ANOVA) were used. In comparisons between multiple groups (three or more), Bonferroni’s test correction was applied before significance was considered (Altman 1991).
Chi-square was used to analyse categorical data. For comparisons within groups, the paired two-tailed t-test was used.

Odds ratios (ORs) and confidence intervals for risk of osteoporosis were calculated from a 2-by-2 table for the different fracture groups in accordance with a case-control design (I).
Stepwise multiple linear regression analyses (II) were used to investigate the relationship between dependent variables, the eight SF-36 dimensions and summaries scores, and the effects of different factors that might influence HRQOL. Independent variables were age, body mass index (BMI), BMD (lumbar and hip total), different types of osteoporotic fractures, and number of fractures.

ANCOVA were used in Study III for controlling the effect of covariates, age, new fracture since two-year follow-up and new co-morbidity since two-year follow-up.

Partial correlation was used in Study III, in which the relationship was measured, controlling for the effect of covariates on both variables. Variables in the partial correlation were the eight SF-36 dimensions and static balance on dominant leg with eyes open, handgrip strength on dominant hand, spinal deformity index (SDI), physical activity, bone mineral density in hip total, and fall frequency in the past year. The covariates were age, new co-morbidity since two-year follow-up, new low-energy fracture since two-year follow-up (dichotomous variables, yes=1 or no=2) and fracture group (vertebral=1 hip=2).

In Study III, missing group bias was analysed by testing the difference between the respondents and non-respondents regarding two-year HRQOL data using independent t-tests.

Additional analysis based on data from Study III, responsiveness using Cohen’s $d$ to detect effect size (ES) measures for two independent groups, was used at seven-year follow-up and was estimated as the mean difference between the groups divided by the pooled standard deviations (also called standardized mean difference). As a general convention, effect sizes of 0.2 to 0.49 were considered “small”; 0.5 to 0.79 were “moderate”, and those of 0.8 or above were “large” (Fayers & Machin 2007).

Sample size calculation regarding the main outcome of the SF-36 in most domains showed that a sample size of 27-45 women per group was needed to detect a difference of approximately ten points (approx 0.5 SD units for most scales) between groups and a sample size of 21-36 women per group to detect differences over time within one group with an alfa level of 0.05 and 80% power (Ware et al. 1993). A half SD is a conservative estimate of clinical

A significance level (or alpha level) of p< 0.05 was considered significant. All statistical analyses in Studies I-III were performed using SPSS® for Windows, version 10.0-15.0 (Statistical Package of Social Sciences, SPSS Inc., Chicago, IL).

Table 2. Statistical methods in Studies I-III.

<table>
<thead>
<tr>
<th>Study</th>
<th>Analytic statistical methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Pearson’s correlation</td>
</tr>
<tr>
<td></td>
<td>Student’s unpaired t-test</td>
</tr>
<tr>
<td></td>
<td>Odds ratio with 95% confidence interval (2-by-2 table)</td>
</tr>
<tr>
<td></td>
<td>ANOVA (Analysis of variance) and Bonferroni’s test correction</td>
</tr>
<tr>
<td>II</td>
<td>Chi-square test</td>
</tr>
<tr>
<td></td>
<td>Spearman’s and Pearson’s correlations</td>
</tr>
<tr>
<td></td>
<td>Student’s unpaired and paired t-test</td>
</tr>
<tr>
<td></td>
<td>Mann-Whitney U-test</td>
</tr>
<tr>
<td></td>
<td>ANOVA (analysis of variance) and Bonferroni’s test correction</td>
</tr>
<tr>
<td></td>
<td>Stepwise multiple linear regression analyses</td>
</tr>
<tr>
<td>III</td>
<td>Chi-square test</td>
</tr>
<tr>
<td></td>
<td>Pearson’s correlation and univariate regression analyses</td>
</tr>
<tr>
<td></td>
<td>Student’s unpaired and paired t-test</td>
</tr>
<tr>
<td></td>
<td>ANCOVA (Analysis of covariance)</td>
</tr>
<tr>
<td></td>
<td>Partial correlation</td>
</tr>
</tbody>
</table>

Qualitative content analysis

Qualitative content analysis (QCA) is a flexible research technique. This method shows several distinct approaches adaptable for different research purposes. In conventional QCA, coding categories are derived directly from the text (an inductive approach), which means that new information may appear.

An inductive conventional approach of content analysis was chosen according to the aim and was used in this study (Elo & Kyngas 2008, Hsieh & Shannon 2005). Qualitative content analysis has no clear scientific theoretical roots, but to some degree its roots are found in hermeneutics, sociology and psychology as well as symbolic interaction (Patton 2002). The goal of content analysis is “to provide knowledge and understanding of the phenomenon under study”
Methods

(Downe-Wamboldt 1992). Qualitative content analysis focuses on human communication and is suited to research involving meaning, interpretations, context and consequences (Downe-Wamboldt 1992). The coding process of a content analysis is to express the content in a large quantity of text in a few categories (Weber 1990). Categories are themes that are directly expressed in the text or derived through analysis (Hsieh & Shannon 2005).

The analysis in this study (IV) were inspired by Hsieh and Shannon (Hsieh & Shannon 2005). The conventional content analysis consisted of the following steps:
1. Transcripts were checked for accuracy.
2. The analysis started with a reading from beginning to end of all the transcripts by the authors independently.
3. Each transcript was read carefully, word by word, and the text that appeared to be relevant to the aim was highlighted by the first author.
4. The texts were broken down into phrases, using the participants’ words (keywords or statements that are related to each other based on their content and context), which were then condensed. The label of the condensed phrase was referred to a preliminary code and was related to the comprehensive content of the phrase. Nonverbal sounds, pauses and filler words such as “hm” supported the interpretation. This analysis was performed by the first author, and then all the authors took part in the interpretations and labelled the phrases as codes.
5. After open coding of four transcripts, preliminary codes and a coding scheme was decided. The remaining transcripts were coded and the original ones recoded, using these codes and adding new ones when the data did not fit into an existing code.
6. When all transcripts had been coded the first author grouped the codes, according to how they were related, which were then agreed on by the other authors. Some codes were combined during this process.
7. The final step was to implement the coding process in all transcripts and organize them into a hierarchical structure in the form of subcategories and categories. The various subcategories were compared in terms of similarities and differences. Subcategories with similar content were grouped together and preliminary categories were formulated. The analysis process involved continuous movement between the whole and the parts of the text. Finally, themes were formulated from the underlying meaning of the categories.
Validity and reliability

The concepts of validity and reliability can be used in both qualitative and quantitative methods. The way they are used and the content of the concept are different (Polit & Beck 2004, Silverman 2006).

In Studies I-III, validity refers to the degree to which an instrument or questionnaire measures what it is supposed to measure. Reliability refers to the accuracy and consistency of data obtained in the study. In order to achieve high reliability and validity regarding bone mineral measurements, the same DXA techniques scanners were used. Internal variation was checked regularly with an everyday calibration using a phantom. Specially trained nurses performed the measurements. All the radiological vertebral assessments were evaluated by the same experienced skeletal radiologist according to a standardized method. In Studies II-III, Cronbach’s alpha ranged from 0.78 to 0.93 in the domains of the SF-36; see Table 4. Internal consistency reliability reveals that a Cronbach’s alpha coefficient of 0.7 to 0.9 is good (Streiner & Norman 2003).

Table X. Cronbach’s alpha scores of the 8 domains of the SF-36 in Studies II and III and Swedish reference for comparison.

<table>
<thead>
<tr>
<th>Domains SF-36</th>
<th>Swedish reference*</th>
<th>Baseline (II)</th>
<th>2-year (II)</th>
<th>7-year (III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>0.91</td>
<td>0.91</td>
<td>0.92</td>
<td>0.90</td>
</tr>
<tr>
<td>Role-physical</td>
<td>0.88</td>
<td>0.92</td>
<td>0.92</td>
<td>0.84</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>0.93</td>
<td>0.91</td>
<td>0.93</td>
<td>0.93</td>
</tr>
<tr>
<td>General health</td>
<td>0.84</td>
<td>0.82</td>
<td>0.83</td>
<td>0.78</td>
</tr>
<tr>
<td>Vitality</td>
<td>0.85</td>
<td>0.81</td>
<td>0.85</td>
<td>0.84</td>
</tr>
<tr>
<td>Social functioning</td>
<td>0.83</td>
<td>0.82</td>
<td>0.86</td>
<td>0.80</td>
</tr>
<tr>
<td>Role-emotional</td>
<td>0.79</td>
<td>0.91</td>
<td>0.91</td>
<td>0.87</td>
</tr>
<tr>
<td>Mental health</td>
<td>0.87</td>
<td>0.82</td>
<td>0.86</td>
<td>0.86</td>
</tr>
</tbody>
</table>

*Swedish reference (Sullivan et al. 1995)

In order not to confuse the significance of what the terms validity and reliability involve in qualitative research, it is an advantage to also use other concepts. In Study IV, within a naturalistic paradigm the criteria for validity and reliability use the term trustworthiness. The criteria used for trustworthiness in qualitative studies are credibility, transferability, confirmability and dependability (Lincoln & Guba 1985).
Credibility was addressed in the study through critical judgement, with all authors taking an active part in the data analysis. The analyses were discussed at several meetings, leading to a refinement of the coding process. The authors compared and contrasted the codes, subcategories and categories and themes with the original text until agreement was reached.

Transferability concerns the researcher’s ability to clearly define the population and findings but leaves it to the reader to decide whether or not the findings can be transferred to other settings (Patton 2002). Transferability was addressed through describing the context of setting, selection and characteristics of the women. Using quotations from the women to illustrate the findings may help the reader judge the situations, thereby enhancing the transferability of the findings.

Confirmability is the criterion for evaluating data quality, referring to the objectivity or neutrality of data and not colouring the findings with the pre-understanding of the phenomenon. There was agreement about the content of categories and themes in the study between the researchers, despite different experiences in the research area and methodologies, which also is a form of investigator triangulation (Patton 2002).

Dependability concerns the quality of the technical instrument(s), which in this study was the digital recorder (MP3). A transcription guide was used and all transcriptions were proofread. The researcher’s ability to carry out interviews of good quality also affects the dependability of the study. The interviewer in the study was a nurse with specific expertise regarding osteoporosis, which could be not only a strength but also a limitation due to preconceptions within the area (Lincoln & Guba 1985, Patton 2002).

**Ethical considerations**

Studies I and II (Dnr F97-328) and III and IV (Dnr M173-05) were approved by the Regional Ethical Review Board at the faculty of Health Sciences, University of Linköping. All participants were given both verbal and written information before considering participation in the studies. Written informed consent was obtained from all participants in Studies III and IV. The aims of the studies were clearly described, as were the possible benefits and negative effects of participating in the studies. The participants were given information
about how to contact the study nurse, researcher or investigators if they wanted more information about the studies. They were also informed that their participation was voluntary and that they could cease it at any time without giving a reason, and that confidentiality was guaranteed. In Study IV, the women were also informed that the digitally recorded interview would be transcribed and that their names would be given specific code numbers to ensure confidentiality. If the women declined to participate, they received information stating that this decision would not affect their other health care.

All women who were included in the study were recommended treatment according to current guidelines. Ethical considerations regarding the risk of causing emotional or psychological problems through measurement, interviews and questionnaires were made in all studies involving participants. All studies have been planned and conducted in accordance with the Declaration of Helsinki (WMA 2008).
RESULTS

Bone mineral density, risk factors and a case-finding strategy

Of the 303 fractured women in the study group, 171 (56%) had a forearm fracture, 55 (18%) had a vertebral fracture(s), 40 (13%) had a hip fracture (24 cervical and 16 trochanteric) and 37 (12%) had a fracture of the proximal humerus (Study I). As only a few women had been examined using radiography of the spine, little was known about the true prevalence of vertebral fractures or deformities in women with fractures other than vertebral. The mean age of women with fracture of the forearm or humerus was 67 years and the mean age of women with vertebral or hip fractures was 69 years.

The fractured women were slightly taller than the non-fractured reference group (difference +1.5 cm, p<0.01), but there were no differences in weight, BMI or hip axis length (HAL). The total fracture group had a significantly lower mean BMD in all sites measured, compared to the references. Almost half (148/303) of the fractured women had sustained at least one previous fracture and 57 (18%) had sustained at least two previous fractures (Tables 4 and 5). In the total fracture group, 26% had suffered from co-morbidity.

According to the WHO criteria cut-off (T-score<2.5), 46% of the total fracture group had osteoporosis, 46% osteopenia (T-score <-1 to 2.5) and 8% normal BMD (T>1 SD), which was a significantly different proportion from that of the reference group. When using a higher cut-off level (T-score <-2.0) as suggested by the Medical Products Agency of Sweden (1997), the prevalence of osteoporosis increased, particularly in hip and forearm groups.
### Table 4. Forearm and humerus fracture groups compared to references.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Forearm Fracture</th>
<th>Reference</th>
<th>p</th>
<th>Humerus Fracture</th>
<th>Reference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>171</td>
<td>209</td>
<td>-</td>
<td>37</td>
<td>209</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
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<td>66</td>
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<td>67</td>
<td>67</td>
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<tr>
<td>Height</td>
<td>162</td>
<td>161</td>
<td>&lt;0.01</td>
<td>162</td>
<td>161</td>
<td>0.4</td>
</tr>
<tr>
<td>Weight</td>
<td>69</td>
<td>69</td>
<td>0.6</td>
<td>70</td>
<td>69</td>
<td>0.6</td>
</tr>
<tr>
<td>BMI</td>
<td>26</td>
<td>26</td>
<td>0.5</td>
<td>27</td>
<td>26</td>
<td>0.4</td>
</tr>
<tr>
<td>HAL (hip axis length)</td>
<td>11.5</td>
<td>11.4</td>
<td>&lt;0.05</td>
<td>11.4</td>
<td>11.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Z-Lumb. spine</td>
<td>-0.12</td>
<td>0.32</td>
<td>&lt;0.01</td>
<td>-0.36</td>
<td>0.39</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Z-Hip total</td>
<td>-0.10</td>
<td>0.28</td>
<td>&lt;0.01</td>
<td>-0.19</td>
<td>0.29</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Z-Arm (1/3)</td>
<td>0.02</td>
<td>0.21</td>
<td>0.1</td>
<td>-0.06</td>
<td>0.23</td>
<td>0.2</td>
</tr>
<tr>
<td>Current smokers %</td>
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<td>13</td>
<td>1</td>
<td>8</td>
<td>11</td>
<td>0.6</td>
</tr>
<tr>
<td>Number of previous fractures</td>
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<td>54</td>
<td>100b</td>
<td>54</td>
<td>100b</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>31</td>
<td>0</td>
<td>27</td>
<td>0</td>
<td></td>
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<tr>
<td></td>
<td>2</td>
<td>10</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Percent in respective group with specified number of previous fractures.

*In the reference group by definition there were no previous fractures.

Women having one or more vertebral fractures are only counted as having one previous fracture.

### Table 5. Hip and vertebral fracture groups compared to the references.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hip Fracture</th>
<th>Reference</th>
<th>p</th>
<th>Vertebral Fracture</th>
<th>Reference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>40</td>
<td>161</td>
<td>-</td>
<td>55</td>
<td>173</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td>69</td>
<td>69</td>
<td>1</td>
<td>69</td>
<td>69</td>
<td>0.8</td>
</tr>
<tr>
<td>Height</td>
<td>163</td>
<td>161</td>
<td>&lt;0.05</td>
<td>161</td>
<td>161</td>
<td>1</td>
</tr>
<tr>
<td>Weight</td>
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<td>69</td>
<td>0.1</td>
<td>68</td>
<td>69</td>
<td>0.5</td>
</tr>
<tr>
<td>BMI</td>
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<td>26</td>
<td>0.2</td>
<td>26</td>
<td>26</td>
<td>0.9</td>
</tr>
<tr>
<td>HAL (hip axis length)</td>
<td>11.7</td>
<td>11.4</td>
<td>&lt;0.05</td>
<td>11.3</td>
<td>11.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Z-Lumb. spine</td>
<td>-0.22</td>
<td>0.70</td>
<td>&lt;0.01</td>
<td>-0.55</td>
<td>0.54</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Z-Hip total</td>
<td>-0.69</td>
<td>0.32</td>
<td>&lt;0.01</td>
<td>-0.67</td>
<td>0.33</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Z-Arm (1/3)</td>
<td>-0.05</td>
<td>0.26</td>
<td>0.2</td>
<td>-0.45</td>
<td>0.26</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Current smokers %</td>
<td>15</td>
<td>13</td>
<td>0.8</td>
<td>14</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Number of previous fractures</td>
<td>0</td>
<td>52</td>
<td>100b</td>
<td>40</td>
<td>100b</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>20</td>
<td>0</td>
<td>36</td>
<td>0</td>
<td></td>
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<td>2</td>
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<td>0</td>
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<td>10</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Percent in respective group with specified number of previous fractures.

*In the reference group by definition there were no previous fractures.

Women having one or more vertebral fractures are only counted as having one previous fracture.
The odds ratio (OR) for women aged 55-75 years with vertebral fracture resulting from osteoporosis (<-2.5 SD) was at least 17, and for those who had sustained a hip, forearm or humerus fracture the OR (lower 95% limit) was at least 8, 6 or 5, respectively, compared to the age-matched non-fractured reference group (Table 6).

<table>
<thead>
<tr>
<th>Group</th>
<th>Normal % (T&lt;1)</th>
<th>Osteopenia % (T&lt;-1 to -2.5)</th>
<th>Osteoporosis % (&lt;-2.5) a</th>
<th>OR/95% CI</th>
<th>All fractures n=303</th>
<th>Forearm n=171</th>
<th>Humerus n=37</th>
<th>Hip n=40</th>
<th>Vertebral n=55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fracture n=209</td>
<td>58</td>
<td>26</td>
<td>-</td>
<td>16</td>
<td>-</td>
<td>18</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>All fractures n=303</td>
<td>8</td>
<td>46</td>
<td>13</td>
<td>46</td>
<td>20</td>
<td>57</td>
<td>22</td>
<td>13-39</td>
<td>16</td>
</tr>
<tr>
<td>Forearm n=171</td>
<td>11</td>
<td>58</td>
<td>11</td>
<td>37</td>
<td>13</td>
<td>53</td>
<td>16</td>
<td>6.1-20</td>
<td>8.6-30</td>
</tr>
<tr>
<td>Humerus n=37</td>
<td>11</td>
<td>38</td>
<td>7.9</td>
<td>51</td>
<td>18</td>
<td>54</td>
<td>16</td>
<td>2.5-25</td>
<td>5.6-55</td>
</tr>
<tr>
<td>Hip n=40</td>
<td>5</td>
<td>45</td>
<td>20</td>
<td>50</td>
<td>37</td>
<td>65</td>
<td>42</td>
<td>4.6-91</td>
<td>9.5-184</td>
</tr>
<tr>
<td>Vertebral n=55</td>
<td>2</td>
<td>35</td>
<td>43</td>
<td>64</td>
<td>129</td>
<td>67</td>
<td>119</td>
<td>5.6-329</td>
<td>17-980</td>
</tr>
</tbody>
</table>

a According to WHO guidelines (WHO Technical report, 1994).
b According to suggestion from the Medical Products Agency of Sweden.

There was a strong association between bone mineral density and number of previous fractures. Women with three or more previous fractures had the lowest BMD Z-score for the hip and forearm. On the other hand, the BMD Z-score of the lumbar spine decreased for the first two fractures but was higher for women who had sustained three or more fractures.
The lowest BMD was seen in the subgroups that had previous fracture(s), low BMI (<22) and were current smokers.
Health-related quality of life: a two-year follow-up

Two hundred and ninety-two of the 303 women participated in the two-year follow-up (Study II). A new fracture had occurred in 28 (9.6%) women and 41% reported additional concomitant disease of minor or greater importance during the two-year follow-up. At baseline, 80% were prescribed pharmacological treatment (including calcium and vitamin D) for osteoporosis according to current guidelines (1997). The most common prescribed active drug was etidronate, followed by oestrogen, alendronate and raloxifene. After two years, most women took calcium and vitamin D. In the vertebral group 78% had started anti-osteoporosis treatment and 56% had completed the treatment. For the hip group these figures were 67% vs. 56%, for the humerus group 54% vs. 43%, and for the forearm group 44% vs. 36%.

Study II demonstrated that HRQOL, assessed using the SF-36, was significantly reduced at baseline regarding all SF-36 domains after vertebral, (p<0.002) and mostly after hip, fractures (p<0.02), except for general health and mental health. The forearm group had lower values for role-physical, bodily pain, general health and role-emotional (p<0.01), whereas humerus fractures only showed reduced values in the role-physical and bodily pain domains (p<0.001). HRQOL differed between age groups (55-64 vs. 65-75 years) only with regard to physical function (p<0.001), which decreased with older age. In the total fracture group, women examined less than 83 days after fracture had lower HRQOL in all domains (p<0.012) except general health, vitality and mental health, compared with women examined 84 days to six months after fracture.

Two years after hip fracture, HRQOL had improved but was below reference data in the domains of physical functioning, role-physical and social function (p<0.022), while after vertebral fracture, although role-physical, bodily pain and social function had improved, all domains were still significantly below reference values (p<0.003). Women with forearm or humerus fractures had normalized HRQOL, compared with the reference group, in all domains at the two-year follow-up (Table 7).
Table 7. HRQOL values (SF-36) in reference groups and different fracture groups at baseline and after two years.

<table>
<thead>
<tr>
<th>SF-36</th>
<th>Reference group n=412</th>
<th>Forearm n=166</th>
<th>Humerus n=35</th>
<th>Vertebral n=53</th>
<th>Hip n=38</th>
</tr>
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<tr>
<td></td>
<td>Baseline</td>
<td>Two-year</td>
<td>Baseline</td>
<td>Two-year</td>
<td>Baseline</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical function</td>
<td>69.91</td>
<td>72.61</td>
<td>68.11</td>
<td>63.24</td>
<td>69.02</td>
</tr>
<tr>
<td></td>
<td>73.24</td>
<td>66.81</td>
<td>67.90</td>
<td>49.01</td>
<td>49.92</td>
</tr>
<tr>
<td></td>
<td>p1=0.680</td>
<td>p2=0.016</td>
<td>p1=0.669</td>
<td>p2=0.667</td>
<td>p1=0.759</td>
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<td></td>
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<td>p2=0.001</td>
<td>p2=0.001</td>
<td>p1=0.002</td>
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<tr>
<td>Role-physical</td>
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<td>38.10</td>
<td>66.81</td>
<td>66.81</td>
<td>49.12</td>
</tr>
<tr>
<td></td>
<td>68.19</td>
<td>33.33</td>
<td>67.15</td>
<td>18.36</td>
<td>37.50</td>
</tr>
<tr>
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<tr>
<td>Bodily pain</td>
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<td>70.67</td>
<td>60.54</td>
<td>49.17</td>
</tr>
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<td>32.32</td>
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<tr>
<td>General health</td>
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<td>70.94</td>
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<td>65.81</td>
<td>54.28</td>
</tr>
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<td>p2=0.001</td>
<td>p1=0.001</td>
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<tr>
<td>Vitality</td>
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<td>63.67</td>
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</tr>
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<td>p2=0.001</td>
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<td>82.01</td>
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<td>87.86</td>
<td>71.15</td>
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<td>62.48</td>
<td>71.01</td>
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<td>Role-emotional</td>
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<td>79.65</td>
<td>83.83</td>
<td>57.44</td>
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<td>81.01</td>
<td>57.71</td>
<td>55.55</td>
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<td>Mental health</td>
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<td>77.67</td>
<td>80.18</td>
<td>78.35</td>
<td>57.44</td>
</tr>
<tr>
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<td>69.96</td>
<td>71.59</td>
<td>66.88</td>
<td>75.51</td>
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<td>p1=0.462</td>
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<td>40.01</td>
<td>44.37</td>
<td>37.31</td>
<td>42.31</td>
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<td>37.31</td>
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<td>p1=0.006</td>
<td>p2=0.424</td>
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<td>Mental Component Summary Index</td>
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<td>51.01</td>
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<td>44.27</td>
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<tr>
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<td>p2=0.171</td>
<td>p2=0.171</td>
<td>p1=0.242</td>
</tr>
</tbody>
</table>

p1: indicates longitudinal change since baseline in different fracture groups (paired t-test).

p2: indicates comparison between two-year follow-up values and reference group (unpaired t-test).

The strongest determinant for low HRQOL two years after fracture was physical function explained by fracture type, BMI and BMD hip total (adjusted R² was 23.8%), according to multiple linear regression analyses. HRQOL in relation to number of fractures shows that women with one or more previous fractures before the inclusion fracture had lower HRQOL in most domains at baseline, and in all domains except general health after two years (p<0.05), compared with women without previous fracture. In addition, women with osteoporosis (T<-2.5) had lower values regarding HRQOL in physical function, role-physical, and vitality (p<0.03) than did those with normal BMD at those follow-ups.

Compared with a non-pharmacologically treated fracture group (n=93), women with forearm and humerus fracture in Study II did not differ in HRQOL two years after fracture. On the other hand, women with hip and...
vertebral fracture in the non-pharmacologically treated fracture group had lower values in physical function, bodily pain and general health (p<0.04) than did women with these types of fractures in Study II.

Health-related quality of life: a seven-year follow-up

At seven-year follow up, 67 of 91 women participated, with 42 having suffered a vertebral fracture and 25 a hip fracture as inclusion fracture (Study III). The mean age (±SD) was 75.8 (4.7) in the vertebral group and 75.0 (4.7) in the hip group. More women in the vertebral group (22/42), than in the hip fracture group (7/25) had sustained a new clinical fracture (p=0.05). The vertebral group reported more back pain (p=0.02) during the past 14 days, assessed by GRS>30, than did the hip group (36/42 vs. 15/25). In the vertebral group 48% took painkillers regularly, 24% sometimes and 28% never. In the hip fracture group 32% took painkillers regularly, 20% sometimes and 48% never (p=0.263). The most frequently used painkillers were paracetamol (93%), opioids (44%) and NSAID (41%), alone or in combination, regularly or as required. Anti-osteoporosis treatment (mostly bisphosphonate) was currently being used by 34%, 14/42 and 8/25 respectively, and calcium supplements with vitamin D by 86% in the vertebral group and 70% in the hip group.

One or more new co-morbidities of greater importance since two-year follow-up were reported by 67% in the vertebral group and by 72% in the hip group. Body height was significantly higher in the hip group (162 cm vs. 158 cm, p=0.03); however the mean height loss did not differ from baseline between the groups (19 mm vs. 21 mm). Self-reported mean body height loss since young adulthood was significant, with a mean loss of 7.4 cm in the vertebral group and 4.5 cm in the hip group; the height loss was also significant between the groups (p<0.01).

Handgrip strength was better in the hip fracture group than in the vertebral group (19.8 vs. 16.7, p=0.04). BMD, fall frequency in the past year and static balance did not differ significantly between the groups. According to the spine radiographs and the assessment of SDI, 51 women had one or more vertebral fractures, nine of whom originally had a hip fracture as inclusion fracture. In the vertebral group SDI was 7.8 (±6.1 SD) and in the hip group 2.3 (±4.2 SD).
Longitudinal change regarding HRQOL between the two- and seven-year follow-ups showed that the vertebral fracture group had no significant changes in any SF-36 domains except bodily pain, which had decreased significantly at seven-year follow-up, indicating increased pain. The hip fracture group had no significant changes in any domain. There were no significant mean value differences between the groups between two and seven years, or after controlling for the covariates, age, new co-morbidity and new fracture. In the total group, women with new fracture (n=29), of whom 22 belonged to the vertebral group, had significantly lower values at seven-year follow-up regarding role-physical, bodily pain, general health and social function (all p<0.01). The group with no new fracture (n=38), of whom 20 belonged to the vertebral group, had no significant changes. The group with new co-morbidity (n=46) had no significant changes, and neither did the group without new co-morbidity (n=21).

At seven-year follow-up the vertebral group had significantly lower values than the reference group in all domains, except for general health and mental health. The hip fracture group did not differ from the reference group, but better values were found for their mental health (Table 8). In the vertebral and hip groups the effect size of mean differences shows moderate effect in bodily pain, vitality, social functioning, role-emotional and mental health, indicating clinical significance. Even after controlling for covariates, age, new co-morbidity and new fracture the vertebral fracture group had significantly lower values for bodily pain, vitality, role-emotional function and mental health compared to the hip fracture group (Table 9). Regarding differences between the vertebral and hip groups, the covariate age was significantly related to physical functioning, role-physical, bodily pain and vitality. The covariate new co-morbidity was significantly related to role-physical, bodily pain, vitality and role-emotional. The covariate new fracture was significantly related to role-physical, bodily pain and social functioning.

A partial correlation showed that in the total fracture group, physical activity correlated positively with all domains except the role-emotional one, and static balance showed a significantly positive correlation to most of the SF-36 domains except social function and role-emotional function. In addition, handgrip strength showed a significantly positive correlation to role-physical, vitality and mental health. Fall frequency showed a negative correlation with bodily pain and vitality. BMD in the hip and SDI were not significantly correlated with the SF-36.
Table 8. HRQOL mean values (SF-36) in reference and different fracture groups at seven-year follow-up.

<table>
<thead>
<tr>
<th>SF-36</th>
<th>Reference group n=804</th>
<th>Vertebral group n=42</th>
<th>Hip group n=25</th>
<th>p-value*</th>
<th>ES** Reference - Vertebral</th>
<th>ES** Reference - Hip</th>
<th>ES** Vertebral - Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function (SD)</td>
<td>62.7 (26.7)</td>
<td>50.4 (25.9)</td>
<td>58.2 (21.1)</td>
<td>( p&lt;0.01 ) (^a)</td>
<td>0.47</td>
<td>0.19</td>
<td>-0.33</td>
</tr>
<tr>
<td>Role-physical (SD)</td>
<td>55.9 (44.9)</td>
<td>27.4 (37.8)</td>
<td>41.0 (39.4)</td>
<td>( p&lt;0.01 ) (^a)</td>
<td>0.69</td>
<td>0.35</td>
<td>-0.35</td>
</tr>
<tr>
<td>Bodily pain (SD)</td>
<td>59.0 (27.5)</td>
<td>41.6 (23.5)</td>
<td>60.6 (26.7)</td>
<td>( p&lt;0.01 ) (^{a,b})</td>
<td>0.68</td>
<td>-0.06</td>
<td>-0.76</td>
</tr>
<tr>
<td>General health (SD)</td>
<td>58.2 (22.8)</td>
<td>55.8 (24.4)</td>
<td>65.4 (17.6)</td>
<td>( p=0.23 )</td>
<td>0.10</td>
<td>-0.35</td>
<td>-0.45</td>
</tr>
<tr>
<td>Vitality (SD)</td>
<td>58.0 (25.4)</td>
<td>48.0 (25.1)</td>
<td>63.2 (18.1)</td>
<td>( p&lt;0.03 ) (^a)</td>
<td>0.40</td>
<td>-0.24</td>
<td>-0.69</td>
</tr>
<tr>
<td>Social function (SD)</td>
<td>77.3 (26.3)</td>
<td>67.0 (28.3)</td>
<td>83.0 (18.4)</td>
<td>( p&lt;0.03 ) (^{a,b})</td>
<td>0.38</td>
<td>-0.25</td>
<td>-0.67</td>
</tr>
<tr>
<td>Role-emotional (SD)</td>
<td>71.3 (40.6)</td>
<td>54.0 (45.4)</td>
<td>80.0 (33.3)</td>
<td>( p&lt;0.02 ) (^{a,b})</td>
<td>0.40</td>
<td>-0.23</td>
<td>-0.65</td>
</tr>
<tr>
<td>Mental health (SD)</td>
<td>74.7 (21.0)</td>
<td>71.2 (22.3)</td>
<td>82.7 (12.7)</td>
<td>( p=0.09 )</td>
<td>0.16</td>
<td>-0.46</td>
<td>-0.63</td>
</tr>
</tbody>
</table>

Significant tests: One-way ANOVA.

\(^a\) p-value of the model, significance level \( p < 0.05 \) is given in bold.

Significant difference between:

\(^a\) Reference and vertebral groups, after Bonferroni correction.

\(^b\) Vertebral and hip groups, after Bonferroni correction.

When reference and hip groups were compared, the differences were not significant.

**Effect size (ES) is estimated as the mean difference between the groups divided by the pooled standard deviations; moderate effect (>0.5) in bold.

Table 9: HRQOL (SF-36) adjusted mean values in vertebral and hip fracture groups at seven-year follow-up.

<table>
<thead>
<tr>
<th>SF-36</th>
<th>Vertebral group n=42</th>
<th>Hip group n=25</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function</td>
<td>51.6 (44.5-58.8)(^a)</td>
<td>56.0 (46.7-65.4)</td>
<td>( p=0.464 )</td>
</tr>
<tr>
<td>Role-physical</td>
<td>30.5 (20.0-41.1)</td>
<td>35.7 (21.8-49.5)</td>
<td>( p=0.563 )</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>42.9 (36.1-49.6)</td>
<td>58.5 (49.7-67.3)</td>
<td>( p=0.007 )</td>
</tr>
<tr>
<td>General health</td>
<td>56.2 (49.3-63.1)</td>
<td>64.9 (55.9-73.9)</td>
<td>( p=0.136 )</td>
</tr>
<tr>
<td>Vitality</td>
<td>48.5 (42.3-54.7)</td>
<td>62.3 (54.2-70.4)</td>
<td>( p=0.010 )</td>
</tr>
<tr>
<td>Social function</td>
<td>68.5 (61.1-75.9)</td>
<td>80.4 (70.7-90.0)</td>
<td>( p=0.060 )</td>
</tr>
<tr>
<td>Role-emotional</td>
<td>54.7 (42.0-67.3)</td>
<td>78.9 (62.3-95.4)</td>
<td>( p&lt;0.026 )</td>
</tr>
<tr>
<td>Mental health</td>
<td>71.2 (65.4-77.1)</td>
<td>82.7 (75.0-90.4)</td>
<td>( p&lt;0.023 )</td>
</tr>
</tbody>
</table>

\(^a\) Values in parentheses correspond to 95% confidence intervals.

**Significant tests: ANCOVA, means controlling for the effect of covariates, age, new co-morbidity, and new fracture since two-year follow-up. Significance level \( p < 0.05 \) is given in bold.
Independence as health-related quality of life

This qualitative study aimed to describe how HRQOL and daily life had been affected in women with vertebral fracture several years after diagnosis, mean 8-9 years since the inclusion fracture (Study IV). The findings revealed three themes relating to how vertebral fractures affect HRQOL and daily life, how the women cope with their symptoms, what is most important in life and what kinds of support could make daily life easier. The subcategories and categories within each theme are displayed in Table 10.

<table>
<thead>
<tr>
<th>Subcategories</th>
<th>Categories</th>
<th>Themes</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Constant back pain</td>
<td>- Back pain</td>
<td>A threatened independence</td>
</tr>
<tr>
<td>- Activity-related back pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- The body as a hindrance in everyday life</td>
<td>- Consequences in daily life</td>
<td></td>
</tr>
<tr>
<td>- Dependent on others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Feelings of loneliness</td>
<td>- Anxiety</td>
<td></td>
</tr>
<tr>
<td>- Fear and threat</td>
<td>- Self-image</td>
<td></td>
</tr>
<tr>
<td>- Self-esteem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Loss of roles</td>
<td>- Emotional</td>
<td>Strategies for maintaining independence</td>
</tr>
<tr>
<td>- Bodily change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Optimistic coping</td>
<td>- Support</td>
<td>The importance of maintaining independence</td>
</tr>
<tr>
<td>- Pessimistic coping</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Self-care</td>
<td>- Activity</td>
<td></td>
</tr>
<tr>
<td>- Social support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Professional health care support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ability to perform everyday activities</td>
<td>- “Managing”</td>
<td></td>
</tr>
<tr>
<td>- Experience health</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Next of kin and friends</td>
<td>- “Loving”</td>
<td></td>
</tr>
<tr>
<td>- Social activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Living conditions</td>
<td>- “Having”</td>
<td></td>
</tr>
<tr>
<td>- Something meaningful to do</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The first theme, “A threatened independence” describes how HRQOL had been affected by the vertebral fracture through constant and activity-related back pain. One woman said, “It was a long-lasting and serious pain that really affected my whole life”. The other type of pain is described as a pain that comes on suddenly during specific physical activities and makes continued activity impossible. Anxiety in the form of feelings of loneliness or worry about being alone, even the feeling of being a burden to others, was common. The fear and threat of sudden back pain gave a sense of uncertainty. In addition, the threat of falling and fracture was common and was experienced as a handicap affecting daily life. The category regarding consequences describes the body as a hindrance in everyday life, i.e. adjusting their daily life to a more careful, slower or reduced rate, or the fact that the handicap was not visible making the situation even worse. Dependence on others and the sense of feeling like a burden emerged in the interviews. The category regarding self-image is described in terms of self-esteem, i.e. feeling left out and not feeling sociable or nice enough in interaction with others, or loss of roles, i.e. not being able to manage one’s home and bodily change, for example not being able to keep one’s body erect and a sense of becoming old prematurely and being a shrunken old woman.

The second theme, “Strategies for maintaining independence”, describes how the women were trying to manage their situation through various emotional, activity and support strategies. Optimistic coping entailed that the women tried to think positively and make the best of the situation while pessimistic coping referred to their having a negative attitude about the situation and feelings of hopelessness, and sometimes expecting the worst to happen. Self-care, for example in the form of painkillers, rest, exercise and aids to provide relief from back pain, were common activity strategies. Support in the form of social support from next of kin and from health care professionals played an important role, but most women expressed both positive and negative experiences of support they had received. Most women felt that the help they received consisted largely of medicine and radiological examinations. Some received back pain relief from pain killers, but most believed that they had not received adequate treatment.

The third theme, “The importance of maintaining independence”, means managing in the form of the ability to perform everyday activities, and experiencing health. The women described health as the ability to manage on their own and take care of themselves. “Managing” everyday life can be
understood as having the opportunity to influence one’s life and being able to realize one’s vital goals in life. Good relationships, social interactions and the ability to participate in social activities can be understood as “Loving”. “Having” can be described as material needs like housing and something meaningful to do, like knitting, as well as the factors associated with these things.

This study demonstrates, especially with regard to the long-term aspects, that the women’s HRQOL and daily life had been strongly affected by the impact of the vertebral fracture. The women were striving for independence, or maintaining their independence, by trying to manage different types of symptoms and consequences in different ways. The most important factors in life were managing on their own, having good relationships and having something meaningful to do.
DISCUSSION

Results

The overall aim of this thesis was to evaluate the usefulness of a recent low-energy fracture as index event in a case-finding strategy for osteoporosis and to describe and analyse long-term health-related quality of life in postmenopausal women with osteoporotic fracture.

Main findings
The main findings in the present studies were that vertebral and hip fractures were stronger markers for osteoporosis than forearm or humerus fractures, and that multiple fractures were stronger markers than a single fracture; that vertebral fracture(s) had a greater negative impact on HRQOL compared to forearm, humerus, and hip fractures; and that vertebral fracture had a long-term negative impact on HRQOL, even seven years after diagnosis. Furthermore, a qualitative study produced a more detailed view than the SF-36 instrument did of how HRQOL is impaired after vertebral fracture.

Case-finding strategy in osteoporosis
Osteoporosis is a silent disease until fractures occur. It may be tempting to screen using bone mineral measurements in age cohorts who are approaching the ages of high fracture risk in order to prevent a first fracture. Most expert groups, on the other hand, recommend a case-finding strategy by which people presenting risk markers are invited to osteoporosis examinations. The most commonly presented strategy is that postmenopausal women who have recently sustained a low-energy fracture in forearm, humerus, hip or vertebra are examined using bone mineral measurement. Our findings support such a strategy, as we found that half of the total fracture group had osteoporosis (T-score < -2.5 SD) while only 16% of the women in the non-fracture group had osteoporosis at this age. Only 8% of the women in the fracture group had normal BMD, compared to 58% in the non-fracture group. These results are in accordance with a recent Swedish study (Åstrand et al. 2006). In another study, approximately 20% of Swedish women in this age group (65-69 yrs) had
Discussion

osteoporosis (measured with DXA in the femoral neck) (Kanis et al. 2008a). In our total fracture group, the odds ratio of having osteoporosis according to the WHO criteria was 20 (CI 12-36) compared to the non-fractured reference group. Furthermore, BMD differed between groups with different fracture types. Vertebrae and hip fracture were stronger predictors of osteoporosis than were fractures of the forearm and humerus.

There is plenty of evidence that the risk for future fracture is inversely related to bone mineral density. A meta-analysis of prospective studies showed that at the age of 65 years, the risk ratio for subsequent hip fracture increased by a factor of three for each decrease of 1 SD in hip BMD, exponentially (Johnell et al. 2005).

Half of the total fracture group had prior osteoporotic fracture(s) before the inclusion fracture, although few of them had been referred for BMD measurement and only 14% of 400 women with fracture who had responded to the invitation had in fact been treated for osteoporosis. This finding is in accordance with other studies (Andrade et al. 2003, Feldstein et al. 2003, Freedman et al. 2000), and calls to attention the fact that a strategy for investigating women with a recent osteoporosis fracture and treating those with osteoporosis has to be implemented in routine health care without further delay. A study from Sweden showed that screening of fracture patients for osteoporosis effectively increases the pharmacological treatments according to current guidelines (Åstrand et al. 2008). Another report from Glasgow, presenting a system for identifying, evaluating and treating patients with fractures, shows similar results (McLellan et al. 2003a).

Risk factors for fractures have hitherto mainly been used to determine the relative risk of sustaining a fracture. Recently, the need to know an individual’s absolute fracture risk has resulted in the presentation of algorithms in which several risk factors are combined and a five- or ten-year risk for hip fracture or any osteoporosis fracture is given. The most advanced of these was published in February 2008 under the name of FRAX® and is available to anyone on the Internet (Kanis et al. 2008b). Although it may be useful in its present form, further development is desired.

Several studies have reported that one osteoporotic fracture is associated with a doubled overall risk of future fractures independent of BMD, compared with non-fractured references (Kanis et al. 2004b, Klotzbuecher et al. 2000).
However, different types of fractures seem to have different predictive values. A vertebral fracture has been reported to predict a fourfold higher risk of new vertebral fracture and a twofold higher risk for hip fracture (Klotzbuecher et al. 2000). In another study, the presence of one or two vertebral fractures was associated with a 7.4-fold increase of the rate of new vertebral fractures (Ross et al. 1993). After a forearm fracture, the risk of future hip fracture was found to be increased by 40% (Cuddihy et al. 1999). The FRAX® algorithm does not yet distinguish between different fractures.

Study I demonstrated that women with a recent vertebral fracture had a greater number of previous fractures than did women with hip, humerus or forearm fractures (60% vs. 46-48%). The number of previous fracture is rather easy to access and is of value in clinical routine when selecting individuals for further investigation. In some cases the fracture history has to be validated against the radiographic report or register.

The predictive value of multiple fractures has seldom been studied or considered in other reports, and is not yet included in the FRAX® model (Kanis et al. 2008b). The fracture probability is thus likely underestimated in people with multiple fractures. The individual absolute risk for vertebral fracture is not given by the current FRAX® version. In one validation study of various risk factors for radiographic vertebral fracture, the combination of age, femoral neck BMD and the presence/absence of vertebral fracture had the best predictive ability, while none of the other eight risk factors used in the FRAX® algorithm increased the predictivity further (Donaldson et al. 2009).

The strategy of waiting until a first fracture has occurred may appear cynical, but as the present and previous studies have shown, a single fracture in the forearm or humerus usually does not result in a long-term reduction in HRQOL, assessed with different questionnaires.

Health-related quality of life
At the start of Study II, previous studies had shown more or less severe impairment of HRQOL after fractures in vertebrae, hip, or forearm, but most of these studies were cross-sectional. The level of impairment to HRQOL after osteoporotic fractures varies markedly between different studies and different types of fractures. No prospective study comparing HRQOL after different types of fractures, measured with the same instrument and at the same interval after fracture, was found. Furthermore, the long-term consequences of
vertebral fractures and other fractures are less well studied. To our knowledge, Study III has the longest prospective longitudinal follow-up published regarding HRQOL, after vertebral or hip osteoporotic fracture in a routine health care setting.

**Forearm and humerus fractures**

Women with forearm and humerus fractures reported some impact on role functioning and bodily pain domains at baseline, assessed with the SF-36, but two years later all domains were at the same level as in the reference group. Similar findings were obtained with the EQ-5D in a Swedish study after a forearm fracture up to one year (Borgström et al. 2006) and 18 months (Ström et al. 2008). Similar results were also found in a five-year population-based study from Canada, in which the impact of incident fractures was measured (Papaioannou et al. 2009). On the contrary, outcomes two years after an isolated humeral shaft fracture treated with a fracture brace showed lower SF-36 scores than did those of the reference population, especially in the physical functioning domain but not in bodily pain (Ekholm et al. 2006).

**Hip fracture**

Hip fracture had a profound impact on HRQOL at baseline. Significant improvements had occurred two years later, but the group had significantly lower scores than the reference group regarding physical, role-physical and social functions. The hip fracture group had stable values in all domains between two and seven years. A follow-up study of older individuals describes a substantially decreased HRQOL up to 17 months after femoral neck fracture, assessed with the EQ-5D (Tidermark et al. 2002). This result is in contrast to findings in the present thesis of improvement during the two years after hip fracture. Furthermore, a one-year prospective study after hip fracture showed no restoration regarding total QOL during the year following the fracture (Theander et al. 2004). Regarding the hip fracture group in the present studies, it should be noted that the mean age of the women was 69 years at time of fracture, and most were able to return to an active life. Hip fracture at this relatively early age may thus be mainly a transient problem for the women, in contrast to vertebral fracture. The hip fracture group, despite incident or prevalent vertebral fracture(s) (mainly subclinical fractures) in nine women, did not differ from the reference group regarding HRQOL after seven years, and even had better values for mental health. The discrepancy between the present studies and other ones may be due to the lower age of the women in these studies.
Vertebral fracture

Vertebral fracture caused the most severe impairment of HRQOL at baseline and at two-year and seven-year follow-ups. Role-physical, bodily pain and social functions had improved at two-year follow-up, but values were still significantly below reference values in all domains. At seven-year follow-up the vertebral group had scored lower than the reference group in most domains, except general health and mental health. Bodily pain had also become worse between two and seven years, which might be explained by new fracture.

It is generally believed that pain and disability after vertebral fracture persist for only a few weeks or months (Silverman 1992). Our results demonstrate the opposite: despite the passing of several years between diagnosis and interview, the women still complained about pain and various limitations and consequences. Vertebral fracture seems to receives less attention from health care professionals, next of kin, friends and society than do fractures in the forearm or hip, possibly because its symptoms are invisible. Individuals with vertebral fractures have been dismissed as less important and less ill or traumatized, although research on the impact of vertebral fracture on psychosocial status and physical function has shown that these fractures can create serious decrements in HRQOL (Gold 1996, 2001, Ross 1997). Recent research regarding the natural course up to 12 months after acute vertebral fracture showed that this type of fracture has a more severe impact on pain, disability, activities of daily living and HRQOL than generally believed (Suzuki et al. 2008, 2009). It was found that more than 75% of individuals with vertebral fracture had severe pain lasting at least one year (Suzuki et al. 2008). Up to 18 months after vertebral fracture, there were greater losses in HRQOL and higher long-term costs than previously believed (Borgström et al. 2006, Ström et al. 2008). A cross-sectional study found severely reduced SF-36 values in all domains in 74-year-old women with vertebral fracture compared with age-matched controls when examined an average of 5.1 years after the clinical vertebral fracture (Hall et al. 1999). A recent population-based study from the Canadian Multicenter Osteoporosis Study (CaMos) with five-year prospective data on the long-term impact of incident osteoporotic fractures on HRQOL showed that vertebral fractures exerted the greatest negative impact on HRQOL, which supports the conclusions in the present thesis (Papaioannou et al. 2009). These findings are also corroborated in a Swedish retrospective study showing that women, 12 years after vertebral fracture, had more back pain.
than did age-matched controls (72% vs.33%) (Hasserius et al. 2005). A prospective three-year study showed that for each new vertebral deformity, HRQOL deteriorated further (Oleksik et al. 2005). Similar results have been reported by others (Hasserius et al. 2005, Nevitt et al. 1998, Silverman et al. 2001).

**Comparison between vertebral and hip fracture groups**

At baseline the vertebral fracture group had worse HRQOL than the hip fracture group in bodily pain and general health, and at two-year follow-up in the domains regarding vitality. This finding was in accordance with a 12-month follow-up after hospital-treated patients, mean age 81, in which the vertebral fracture group had worse total HRQOL compared with the hip fracture group, but a similar decrease in activity of daily living (Theander et al. 2004). At seven-year follow-up the vertebral fracture group had significantly worse value than the hip fracture group regarding bodily pain, vitality, role-emotional function and mental health after controlling for age, new fracture and new co-morbidity. In the age span of 64-82 years (mean age 75.5), the prevalence of vertebral fracture suggests more negative impact on HRQOL, more severe osteoporosis and a poorer prognosis than a hip fracture does. The differences in HRQOL between vertebral and hip fracture groups at seven-year follow-up was not explained by age, new disease or new fracture since two-year follow-up in this study. Why do women with vertebral fracture have lower HRQOL compared to those with hip fracture? Is it due to different biological age? Or different comorbidity? Could it be because women suffering from hip fracture benefit from care and treatment including orthopaedic surgery while women with vertebral fracture have to “wait and see”?

**Mortality**

Although the present study was not designed to evaluate mortality, we noted significantly higher five-year mortality in the vertebral fracture group (10/53) compared to the hip fracture group (3/38) (III). Approximate expected mortality during the five-year period (since the two-year follow-up) for the two fracture groups was assessed based on age-specific death risks in Sweden 2006. The age-adjusted numbers of expected deaths in the group with vertebral fracture (n=53) and hip fracture (n=38) were five (CI 2-9) and four (CI 1-7), respectively (2006). Several previous studies have shown increased mortality after vertebral and hip fracture (Cauley et al. 2000, Ismail et al. 1998, Kado et al. 1999). A recent study has shown that all low-trauma fractures were
Discussion

associated with increased mortality for five to ten years (Bliuc et al. 2009). The mechanisms behind the increased mortality are still unknown. Recent results from a three-year controlled study with an annual intravenous injection of zoledronate showed not only reduced fracture incidence but also increased survival (Lyles et al. 2007). These studies support the hypothesis that osteoporosis and fracture may be causative factors of increased mortality. The findings of reduced handgrip strength and static balance in the vertebral fracture group may support a relationship with general frailty (III). But which is the chicken and which is the egg?

**Physical performance**

In the total group at seven-year follow up there were relationships between HRQOL and physical activity, static balance and handgrip strength, and in some domains fall frequency, even after controlling for covariates such as age, fracture group, new fracture and new co-morbidity. Static balance, expressed as the ability to stand on one leg with one’s eyes open, is often used as a clinical test of balance, and is considered to be sensitive to age-related changes in balance (Bohannon et al. 1984) and an important predictor of injurious falls in older people (Vellas et al. 1997). Healthy Swedish women aged 70 years held this position for a mean of 18 s (Johansson & Jarnlo 1991). The women in the present study maintained their balance while standing on their dominant leg with their eyes open for an average of 8 s, which suggests an impairment of static balance. Handgrip strength was significantly lower in the vertebral fracture group than in the hip fracture group. A recent population study from Sweden assessed handgrip strength in 75- and 80-year-old women and grouped them into risk or no risk for malnutrition (19.7 vs. 23.5 kg) (Johansson et al. 2009). The vertebral group in the present study had lower handgrip strength (16.7 kg) than both groups studied by Johansson et al. However, the handgrip strength in the hip fracture group (19.8 kg) in the present study was at the level of women at risk for malnutrition (Johansson et al. 2009).

**New osteoporotic fracture**

In the total group (III) at seven-year follow-up, as many as 43% had sustained one or more new fractures during the five-year period since two-year follow-up. More women in the vertebral fracture group (52%) than in the hip fracture group (28%) had sustained a new clinical fracture (p=0.05). This high fracture incidence may be ascribed to the degree of osteoporosis as well as to the less ambitious treatment.
Spinal Deformity Index
The results support the value of the SDI (Genant et al. 1993) as a measure to be used in clinical routine. The SDI has been demonstrated as a good predictor of incident vertebral fractures and it has been suggested that individuals with the highest SDI should receive the highest priority for treatment (Kerkeni et al. 2009). This approach is more objective and reproducible than a visual qualitative assessment of vertebral fracture (Ferrar et al. 2005). Accurate radiographic diagnosis is very important, as the underdiagnosis of vertebral fracture may lead to decreased rates of diagnosis and treatment of osteoporosis in women (Delmas et al. 2005), which increases the risk of further incident fractures and decreased HRQOL.

Findings from qualitative and quantitative approaches
From the qualitative approach, new perspectives emerged that had not appeared in the quantitative studies. The findings from different paradigms complement each other. A qualitative approach seeks patterns through an inductive process, unlike the quantitative approach, which seeks generalizations through a deductive process. Study IV shows how HRQOL and daily life had been affected in women with vertebral fracture several years after diagnosis, as had the meaning of HRQOL and daily life for these women.

Important findings from the interviews not reached through the SF-36 questionnaire show that the women described that their independence was threatened by back pain, anxiety and other consequences in daily life, and that they experienced a negative impact on their self-image. Regarding back pain, different types of back pain and threat of back pain appeared. Several women claimed that their pain affected their whole life. Consequences in daily life were described as a sudden disruption of and change in everyday life, i.e. the body as a hindrance in everyday life and the vertebral fracture keeping the women from “living”. They also expressed difficulties with the change in their life situation because they were dependent on others in coping with everyday life. Anxiety related to feelings of loneliness and the threat and fear of further back pain, falling and fracture were common. Self-image was affected through self-esteem, which in turn was influenced by the woman’s view of herself and by her interaction with others, loss of roles and bodily changes. However, aspects of the theme “A threatened independence” were also partly illuminated by physical function, role functioning due to physical or emotional causes, bodily pain and vitality, but SF-36 mainly measures frequencies and focuses on physical function mostly concerning the ability to walk. The bodily pain
domain measures the pain magnitude and interference with work during the past four weeks. Aspects of the themes “Strategies for maintaining independence” and “The importance of maintaining independence” were not illuminated in the SF-36.

Women who used strategies to maintain their independence in the form of optimistic coping, the ability to perform active self-care, and social support from the environment expressed a sense of balance in life. On the other hand, those with more pessimistic coping and a lower ability to perform self-care and who experienced decreased social support from next of kin and/or friends perceived a threatened independence in the form of more back pain, anxiety, consequences in daily life and a negative impact on their self-image. The findings that the women were striving for independence correspond well with the continuity theory (Atchley 1999). According to this theory, older adults try to maintain continuity of lifestyle by adapting strategies that are connected to their past experiences. The core of the continuity theory is the presumption that individuals are motivated to continue using adaptive strategies they have developed during adulthood to diagnose situations and adapt to change. Important elements are idea patterns, lifestyle, personal goals and adaptive capacity, which have a bearing on the outcome (Atchley 1999).

Important aspects of life are described as “managing”, “loving” and “having” in the qualitative study. Being independent, retaining the ability to move about freely and managing to live one’s life as well as possible despite problems offered hope, satisfaction and self-esteem and thus increased quality of life. The women in this study experienced health when they could take care of themselves, which is consistent with Nordenfelt’s holistic theory of health (Nordenfelt 1996), which states that a person is healthy if he/she is in a bodily and mental state that allows him/her to achieve a certain set of goals in life. This set of goals refers to the person’s vital goals, i.e. such goals that are necessary and jointly sufficient for the person’s long-term happiness (Nordenfelt 1996, Nordenfelt 2000).

In the qualitative study (IV), women also told about the feeling of being a burden to others, and that they were not social or friendly enough. It was also found that some women felt that neighbours and health care professionals did not understand their problems even though they had a fracture, because its symptoms are invisible.
It was suggested in a previous study that physical change and functional limitations, including the inability to carry out normal activities and participate in social activities, may influence the loss of self-esteem most directly (Gold 1996). This corresponds with the results in Study IV, but the loss of social roles also had an impact on self-image. A fear and threat of falling were common in this study. A recent study concluded that the greatest negative effect on HRQOL was associated with a self-reported fear of falling (Iglesias et al. 2009).

**Back pain**

At seven-year follow-up, three-fourths of the women in the vertebral group and every second women in the hip fracture group took painkillers regularly or sometimes. Overall, 44% of these women took opioids (50% in the vertebral group, 38% in the hip group), but despite this treatment the women with vertebral fracture had significantly worse scores in bodily pain, indicating increased pain according to the SF-36 compared to both hip and reference groups. Findings from Study IV expressed that the women want more support and information from health care professionals about the treatment for back pain, and help with the exercise programme. Most women felt that the help they received consisted largely of medicine and radiological examinations. Some received back pain relief from painkillers, but most felt they had not received adequate treatment. They also described trying to balance between effect and side effect of the painkillers as well as a fear of addiction. The 2006 report from the Swedish Council on Technology Assessment in Health Care concluded that there is a strong inverse relationship between bodily pain and QOL, and that reduction of pain improves QOL. There is evidence that rehabilitation programmes combining different interventions to increase physical function yield better long-term results for generalized persistent pain than do more limited interventions (SBU 2006). Malmros et al. (1998) found positive effects from a ten-week ambulatory exercise programme with physiotherapy on chronic pain, balance, physical function and quality of life (Malmros et al. 1998). A study based on home-based exercise with minimal supervision found improved HRQOL in elderly women with vertebral fractures (Papaioannou et al. 2003). A recent study suggests that supervised group training is beneficial for women with osteoporotic fracture regarding HRQOL assessed with the SF-36 (Grahn Kronhed et al. 2009).

It is noteworthy that only a few clinical trials of anti-osteoporotic drugs have shown treatment benefits regarding HRQOL (Marquis et al. 2008, Miller et al.
A recent observational study showed that teriparatide was an effective treatment in a real-life setting and caused a significant reduction in the incidence of osteoporotic fractures as well as a reduction in back pain and a clinically significant improvement in HRQOL over an 18-month period (Langdahl et al. 2009). There is a lack of studies on and evidence of non-pharmacological intervention effects assessed through self-reported HRQOL outcomes after osteoporosis fracture. Back pain associated with vertebral fracture provides a great challenge to health care professionals. National guidelines are needed to improve the situation for women with osteoporotic fractures and/or a high risk of sustaining fractures. Improved routines are needed for the early identification of individuals with high fracture risk, as well as for the prevention of fractures and for the treatment, nursing and rehabilitation of those who have suffered osteoporotic fractures. Evaluation of HRQOL in women after osteoporotic fracture can provide more knowledge about the fracture impact on HRQOL. The development of strategies to improve HRQOL after vertebral fracture remains an important goal for future research. A combination of strategies, including not only orthopaedic and pharmacological interventions but also non-pharmacological ones in the form of physiotherapy, psychosocial support and education in the context of a multidisciplinary team may improve HRQOL and should be evaluated (Figure 6).

Figure 6. Theoretical conceptual model of multidisciplinary team management and effects on HRQOL.
Methodological considerations

Design
Studies II-IV explore the same concept: HRQOL in women with osteoporotic fracture. The research design of this thesis consisted of both positivistic quantitative (II-III) and naturalistic qualitative (IV) approaches, which can be considered complementary and to enhance the validity of the findings (Patton 2002).

Quantitative studies
There are, however, some methodological issues that are relevant in the interpretation of the data in this thesis. Strengths of the thesis are its prospective design and the fact that all participants were investigated using well defined methods. A generic HRQOL questionnaire instrument was used in these studies, to allow comparisons with a reference group and between different fracture groups. It is possible that the outcome would have been different if an osteoporosis-specific questionnaire on HRQOL had been used. However, at the start of the baseline study there was no osteoporosis-specific questionnaire available that had been translated into Swedish and validated. Several osteoporosis-specific questionnaires on HRQOL have been developed in recent years for patients with established osteoporosis, and most have been developed and used only for patients with vertebral fracture (Morris & Masud 2001). The studies in the thesis are based on a routine health care setting. The focus in the studies was not on the evaluation of osteoporosis treatment as outcome; if this had been the case, it would have required a randomized controlled study with a control group. However, well-designed observational studies can be an important complement to randomized controlled trials by allowing the generalization of results to broader patient populations (Silverman 2009). Non-experimental observational studies play a well accepted role in medical research, especially in the study of risk factors, prognosis and diagnosis. This design has many strengths, but also important methodological limitations, compared with randomized controlled trials (Sörensen et al. 2006).

The advantages of using the SF-36 are its extensive documented reliability and validity, the fact that it is the most widely used questionnaire, and its capacity for comparisons between different groups (Garratt et al. 2002, Lips & van
Schoor 2005). Another strength lies in the large reference groups for the SF-36, recruited from the same general population during 1999 (II) and 2006 (III). Another promising approach to scoring the SF-36, reported by Braizer et al., is a preference-based health utility index. The SF-6D preferences can be applied to any SF-36 dataset for purposes of economic evaluation, i.e. estimation of QALYs (Brazier et al. 2002). This method development also allows for the economic evaluation from data in this thesis in future studies.

Qualitative study
The sample size of ten women in Study IV was found to achieve variation, generate information-rich data, and maintain depth in the analysis. QCA is usually based on around 20 interviews, but when there is a great deal of material fewer interviews can be sufficient. There are no rules for sample size in qualitative injury; it depends on the purpose of the inquiry (Patton 2002). In QCA with a conventional approach using interpretive data analysis with too much data material, it can be difficult to handle all the data. The findings can probably be transferred to a similar group of patients (Polit & Beck 2004). The conventional approach in content analysis is limited both in the description of participants’ lived experiences and in theory development, because both the sampling and analysis procedures make the theoretical relationship between concepts difficult to assume from the findings. The result of a conventional content analysis is at most a concept development or model-building (Hsieh & Shannon 2005).

Participants and reference groups
One limitation in the studies was that the external dropout rate at baseline was 33%, which may entail a risk of selection bias. A random sample (n=36) of the passive dropout at baseline examination was done two years after the fracture, and four of the women were found to have died. The passive dropout also had more severe fractures and greater co-morbidity, but was in similar age. On the other hand, the dropout was very low at two-year follow-up. The missing group in Study III of 26% since two-year follow-up could also have affected the result. A dropout analysis between the missing group and the women participating in the seven-year follow-up, using data from the two-year follow-up, showed that the missing group had significantly lower values on the SF-36 as well as lower weight, body mass index and bone mineral density in the hip. This can be interpreted as the missing group having poorer health, and the result at seven-year follow-up possibly leading to an overestimation of SF-36 scores for the vertebral and hip groups.
In Studies I and II, the number of previous fractures was probably underestimated regarding vertebral fracture, as only the women with vertebral fracture as inclusion fracture had a baseline radiograph and it was unfortunately not possible to fund this for all women in the study.

The reference groups regarding the SF-36 were handled like a normal background population; we lacked data concerning co-morbidity and fracture status, which would have been advantageous to have in order to adjust for possible covariates.

Response shift
Many patients adapt over time, and their perceptions of HRQOL may change. Learning to cope with problems is a well-recognized characteristic of the chronically ill. Also, individuals may meet others whose condition is worse or better than their own, which can lead to a re-evaluation of their own internal standards and values. Response shift is a psychological phenomenon that results from coping caused by the affecting internal standards or values (Schwartz & Sprangers 1999). A response shift cannot be ruled out in this study; the HRQOL response patterns could have been affected by choice of comparator group. A study conducted by Fayers et al. found that the majority of questionnaire participants reported using different comparison frames of reference when completing an annual HRQOL questionnaire (Fayers et al. 2007). Only one-third of the participants reported using the same comparison reference frame at each yearly interval. There are certainly other factors that are related to other factors in life and the individual characteristics that are known to affect HRQOL, for instance coping strategies and self-esteem, and this may be of importance in the interpretation of the long-term HRQOL in these studies.

Statistics
Overall, parametric methods were chosen as the statistic analytic techniques in the thesis because the SF-36 is based on this methodology, which makes it more easy make comparisons with other studies, which often use this method. The parametric methods were also required in order to adjust for the sampling weight design in the reference group, regarding normative values for the SF-36 (III). In general, parametric tests are considered more powerful than non-parametric tests and are usually preferred, but there are different points of view in this debate. A reasonable assumption is that nonparametric tests are
most useful when the distribution is markedly non-normal or when data cannot in any manner be construed as interval-level, or when the sample size is very small (Polit & Beck 2004, 2008).

Multiple testing increased the risk of obtaining a significant difference purely by chance (Type I error, i.e. rejecting a null hypothesis that is in fact true); therefore, the results in this thesis should be interpreted with caution. In comparisons between multiple groups (ANOVA) in Studies I-II, the Bonferroni correction ($\alpha$/number of comparisons) was applied before significance was considered. No formal adjustments for multiple testing were made in Study III; however if a simple sequentially rejective multiple test procedure (Holm’s method) had been used, most of the results in Study III would still be significant (Blair et al. 1996). On the other hand, general adjustment for multiple testing instead increases the risk for Type II error, i.e. accepting the null hypothesis when it is false (Polit & Beck 2008). A half standard deviation is a conservative estimate of clinical significance, but the minimally important difference may be below $\frac{1}{2}$ SD in specific cases (2007). Due to the small groups in Study III, responsiveness was measured between vertebral and hip groups using Cohen’s $d$ (Fayers & Machin 2007).
Clinical implications

- A recent incident fracture in forearm, humerus, vertebrae, or hip in a woman 55-75 years old is a strong incitement to perform osteoporosis investigation and make decisions about treatment. Women with a fracture in the vertebrae or hip or with multiple osteoporotic fractures should be given higher priority.

- The remaining pronounced reduction of HRQOL and back pain after vertebral fracture at seven-year follow-up and its relationships with physical function warrant more effective treatment including non-pharmacological intervention, and demand collaboration within multidisciplinary teams. Furthermore, women with vertebral fracture need follow-up and a care plan for their persistent pain, with support and advice regarding self-management strategies so they can manage and take responsibility for their own situation.

Research implications

- Further development and evaluation of the usefulness of HRQOL questionnaires suitable for use in routine clinical care are needed.

- The mechanisms behind the long-term reduction of HRQOL and physical performance after vertebral fracture warrant more investigation.

- Health economic evaluations of the long-term consequences of vertebral fractures are needed.

- There seems to be an urgent need for further development, testing and economic evaluation of suitable non-pharmacological interventions in combination with pharmacological treatment to prevent loss of function and improve HRQOL for women with vertebral fracture. This is an important goal for future research.
CONCLUSIONS

• This thesis supports the view that a case-finding strategy for osteoporosis with a recent low-energy fracture as index is useful in postmenopausal women between 55 and 75 years of age.

• Investigation of osteoporosis seems warranted in every woman between the ages of 55 and 75 with a recent low-energy fracture. The number of previous fractures and type of recent fracture are important information for finding the most osteoporotic women in terms of severity. Hip and vertebral fractures are stronger predictors of low BMD compared to humerus and forearm fractures.

• Hip and vertebral fractures in women have a significantly larger impact on HRQOL evaluated using the SF-36 than do humerus and forearm fractures, both after fracture and two years later, compared between the different fracture groups and the reference population. The number of osteoporotic fractures was inversely correlated to HRQOL.

• Women who had a vertebral fracture as inclusion fracture had remaining pronounced reduction of HRQOL at seven years. At the mean age of 75.5 years (±4.6 SD), the prevalence of vertebral fracture suggested more negative impact on HRQOL, more severe osteoporosis and a poorer prognosis than with a hip fracture, and this effect may have been underestimated in the past. HRQOL showed a positive relationship between physical activity, static balance and handgrip strength.

• A qualitative approach of HRQOL after vertebral fracture(s) revealed in more detail, compared to the SF-36 questionnaire, how HRQOL and daily life had changed and been strongly affected. Back pain reduces physical function and well-being to a degree that threatens the women’s independence. The women with vertebral fracture were striving for independence or maintaining their independence by trying to manage different types of symptoms and consequences in different ways.

• The remaining pronounced reduction of HRQOL at seven years after vertebral fracture demands more effective treatment, including non-pharmacological interventions.
Osteoporos (benskörhet) ger inga symtom förrän frakturer inträffar. Risken för att en svensk kvinna någon gång efter 50 års ålder ska drabbas av en osteoporosrelaterad fraktur är 50%, men en mindre grupp drabbas av multipla frakturer. Vanligast sker frakturer i handled, överarm, höft respektive kota. Avhandlingens syfte har varit att utvärdera en metod för att hitta och identifiera kvinnor mellan 55-75 år, med hög risk för osteoporos och nya frakturer (case finding strategy) genom att undersöka kvinnor med en ny osteoporosrelaterad fraktur (I) samt att undersöka hur kvinnornas hälsorelaterade livskvalitet (HRQOL) och det dagliga livet påverkats (II-III) långsiktigt med fokus på kvinnor med höft- eller kotfraktur i delarbetena III och IV.


Delarbete I visade att kvinnor med höft eller kotfraktur hade lägst bentäthet och flest osteoporosrelaterade frakturer före inklusionsfrakturen. Studien resulterade i en rekommendation att särskilt undersöka och behandla kvinnor 55-75 år med en ny osteoporosrelaterad fraktur, med högst prioritet till de med höft eller kotfraktur samt flera frakturer.
Delarbete II visade att kvinnorna med kotfraktur hade signifikant försämrad HRQOL inom alla domäner. Kvinnor med höftfraktur hade nedsatt HRQOL inom de flesta domänerna medan kvinnor med över- och underarmsfraktur hade mer begränsad försämring i HRQOL i genomsnitt 3 månader efter frakturen inträffat. Två år senare hade en signifikant förbättring skett inom vissa domäner för kvinnor med kot- och höftfraktur. Hos kvinnorna med över- och underarmsfraktur var HRQOL normaliserad jämfört med referensgruppen.

Delarbete III som följde upp kvinnor med kot- och höftfraktur 7 år senare visade på en fortsatt nedsatt HRQOL bland kvinnor med kotfraktur medan kvinnorna med höftfraktur inte skiljde sig från referensgruppen.

I delarbete IV, den kvalitativa studien, beskriver kvinnorna vikten av oberoende, hur deras oberoende är hotat av ryggsmärta, oro och konsekvenser i det dagliga livet och strategier de använder för att behålla sitt oberoende för att förbättra sin HRQOL och minska konsekvenserna i det dagliga livet. Viktigt i livet var att kunna klara sig själv, goda relationer och meningsfull sysselsättning.

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