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Risk faktors for fracture in middle-aged men and women

Holmberg, Anna H

2006

Link to publication

Citation for published version (APA):
Holmberg, A. H. (2006). *Risk faktors for fracture in middle-aged men and women*. [Doctoral Thesis (compilation), Orthopedics]. Clinical and Molecular Osteoporosis Research Unit, Clinical Sciences, Malmö.

Total number of authors:
1

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Risk factors for fracture in middle-aged men and women

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Akademisk avhandling
som med vederbörligt tillstånd från Medicinska fakulteten vid Lunds Universitet för avläggande av doktorsexamen i medicinsk vetenskap kommer att offentligen försvaras i Universitetsklinikernas aula, ingång 35, Universitetssjukhuset MAS, Malmö.

Fredagen den 26 maj 2006, klockan 09.00

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Organization
LUND UNIVERSITY

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Document name
DOCTORAL DISSERTATION

Date of issue
May 26, 2006

Sponsoring organization

Author(s)
Anna Holmberg

Title and subtitle

Risk factors for fracture in middle-aged men and women.

Abstract

The number of fractures is increasing worldwide, and fractures frequently cause long-term disability, impaired quality of life and sometimes death. The Malmö Preventive Project, a population-based, prospective study, consisting of 22 444 men, mean age 44 years and 10 902 women, mean age 50 years, provides data for evaluation of common public health conditions, such as fracture and diabetes. The follow-up was 19 and 15 years for men and women, respectively. Multiple risk factors for fracture were identified.
In women, the most important risk factors were advancing age (relative risk RR 1.56, Confidence Interval 95% 1.45-1.68), previous fracture (RR 2.00, CI 95% 1.56-2.58) and diabetes (RR 1.87, CI 95% 1.26-2,79). In men, advancing age (RR 1.19, CI 95% 1.12-1.26), mental health problems (RR 1.92, CI 95% 1.47-2.51), increased levels of γ glutamyl transferase (RR 1.24, CI 95% 1.18-1.31) and diabetes (RR 2.38, CI 95% 1.65-3.42) were major risk contributors.

Impaired glucose tolerance, evaluated through an oral glucose tolerance test, was in both genders associated with a substantially decreased risk of fractures, independent of age, BMI and smoking.

This thesis has identified multiple risk factors for low-energy fracture, in both men and women, highlighting diabetes and mental health problems as major contributors in this age group. Current management strategies and therapeutic guidelines are not addressing a number of the identified risk factors. Subsequently, risk assessment can be substantially improved by adding these risk factors to intervention algorithms for middle-aged individuals.

Key words: Fracture, middle-age, men, women, diabetes, mental health

Classification system and/or index termes (if any):

Supplementary bibliographical information:

Language
English

ISSN and key title:
1652-8220

ISBN
91-628-6851-9

Recipient's notes

Number of pages
102

Price

Security classification

Distribution by (name and address) Dep. of Orthopaedics, Malmö University Hospital SE-205 02 Malmö

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Risk factors for fracture in middle-aged men and women

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2006

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Financial support was obtained from The Swedish Research Council Project K2003-73X-11610-08A, The Kock Fundation, The Herman Järnhardt Foundation, The Malmö University Hospital Funds and regional research grants.

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ISBN: 91-85481-92-0
ISSN: 1652-8220
Language revision by Karin Ryde
Printed in Sweden 2006.
Medicinsk Informationsteknik Björn Henriksson AB,
Universitetssjukhuset MAS
205 02 Malmö

“Äta litet,
Dricka vatten,
Roligt sällskap,
Sömn om natten,
Käckt arbeta,
Lägligt bo,
Stillhet någon stund på dagen,
Det är lagen för min hälsa och min ro.”
Olof von Dahlin

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I **Forearm bone mineral density in 1 294 middle-aged women – a strong predictor of fragility fractures.**
Anna Holmberg, Olof Johnell, Kristina Åkesson, Peter M Nilsson, Jan-Åke Nilsson and Göran Berglund
Journal of Clinical Densitometry 2004 Winter;7(4);419-23

II **Risk factors for hip fractures in a middle-aged population– a study of 33 000 men and women.**
Anna H Holmberg, Olof Johnell, Peter M Nilsson, Jan-Åke Nilsson, Göran Berglund and Kristina Åkesson
Osteoporosis International 2005 Dec;16(12):2185-94

III **Risk factors for fragility fractures in middle age. A prospective population-based study of 33 000 men and women.**
Anna H Holmberg, Olof Johnell, Peter M Nilsson, Jan-Åke Nilsson, Göran Berglund and Kristina Åkesson
Accepted for publication in Osteoporosis International

IV **The Association Between Hyperglycaemia, Diabetes and Early Fracture Risk in Middle-Age. A prospective, population-based study of 22 444 men and 10 902 women.**
Anna H Holmberg, Peter M Nilsson, Olof Johnell, Jan-Åke Nilsson and Kristina Åkesson.
Manuscript

INTRODUCTION

The skeleton is vital for animal life on Earth, and humans have developed bones light enough to allow for rapid movement, and strong enough to avoid disabling fractures at younger ages. However, with advancing age, in both men and women, the bone becomes weaker and more susceptible to fracture. During the later part of the 20th century the incidence of fracture has been increasing worldwide [1-10] although recent studies have indicated a slowing down of the rates of hip fractures in certain regions [11-15]. The generally increasing number of fractures depends on an aging population with longer life expectancy in the western world, but also on an increasing age-specific fracture incidence [3-7, 10, 16]. Fractures are associated with varying degrees of morbidity [17] and sometimes death [18, 19]. In younger age groups the consequences are often limited, but with aging the fractures often lead to permanent disability and impaired quality of life.
The fracture-related costs for society are large. The costs for the first post-fracture year for hip, vertebral and forearm fractures, all osteoporosis-related fractures, have been estimated to 4.6 billion SEK in Sweden 2004 [20]. It equals, for example, the annual amount of money required for treatment of all individuals with multiple sclerosis, or 2/3 of the cost for treatment of diabetes type 2.
Fracture aetiology is complex and multifaceted. At younger ages many fractures are caused by high-energy trauma, but with increasing age bone becomes more brittle and more prone to fracture, also at minor trauma. Factors that contribute to fracture risk include advancing age, low body weight, low bone mass, propensity to fall, smoking, alcohol over-consumption, impaired vision and comorbidities. Many studies have been performed on elderly subjects when fractures are more frequent [21-26], but less is known of those who fracture already in middle age. This is an interesting age group, since previous fracture is one of the strongest risk factors for fracture at higher ages [23, 27-29]. Furthermore, with improved knowledge about individuals that sustain fractures in middle age, preventive measures can be directed towards factors that can be modified within a reasonable time frame.

This thesis is an attempt to provide further knowledge in the area of risk factors for fracture in middle age.

OSTEOPOROSIS

Definition of osteoporosis

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with an enhanced bone fragility and consequently increased risk of fracture [30]. Primary osteoporosis can occur in both sexes at all ages, but becomes more frequent after menopause in women and occurs in higher age groups in men. Secondary osteoporosis is a result of underlying diseases for example intestinal bowel disease and chronic renal failure, medications such as glucocorticoids, life style factors such as alcoholism and smoking, and other underlying conditions for example hypogonadism [31, 32].

Underlying mechanisms

The skeleton contains two kinds of bone structure; the strong, solid cortical bone and the porous, cancellous bone. The amount of cortical and cancellous bone vary in different parts of the skeleton, the amount of cancellous bone is low in the diaphyses such as the femur, but very high in the vertebrae. Cancellous bone contains a larger proportion of osteogenic cells and has a higher rate of bone turnover, commonly 20-25 %, whereas the

turnover in cortical bone is only 3-5 % per year.

Thereby is cancellous bone more sensitive to conditions or diseases affecting bone cells, with rapid changes in response to stimuli. The bone stock of the body is established during childhood and adolescence, and reaches its maximum, peak bone mass, between 20 and 40 years of age [33-36]. Peak bone mass is about 20 % higher in men compared to women, and is influenced by many factors during childhood; calcium intake [37], exercise [38] and perhaps most of all genetic factors [39-41]. The greatest effect of external factors is most likely exerted in the pre-pubertal years, demonstrated in studies performed on pre-pubertal girls [42, 43]. The bone formation is mediated by osteoblasts and osteoclasts, with hormones and signal substances regulating the cellular activity. At the time of peak bone mass the activity of osteoblasts and osteoclasts is balanced, but from menopause in women [44-46] and from the sixth decade in men, bone resorption starts to exceed bone formation. In women, bone loss may reach up to 4 % per year during the first years after menopause [47, 48], but in higher ages the degradation rate is 0.5-2 % per year in both men and women [49]. Since men have larger bones, higher bone mineral density and less bone loss during their life, they have a lower prevalence of osteoporosis and subsequently a lower risk of fracture [50, 51]. Pathogenetic factors favouring the osteoporotic process in both men and women, are those impairing the accumulation of bone during growth, and those accelerating the loss of bone during later life. Bone mineral density, as measured by DXA, is a good surrogate measure of bone strength, and has been estimated to account for 75-90 % of bone strength variation [52, 53].

Diagnosis and diagnostic methods

The diagnostic criterion for osteoporosis most widely used has been established by an expert group of the World Health Organization (WHO)[30]. The diagnosis is determined by measuring bone mineral density (BMD) of the hip or spine, the measurements presented in grams per square centimetre (g/cm²). The measurement is presented in relative terms as a T-score. The T-score describes the individual's BMD in terms of the number of standard deviations (SD) by which it differs from the mean peak value in young adults. Normal bone mineral density is defined as measurements within one SD from the mean peak value of the young adults in the same population.

Osteopenia is defined as BMD measurements between 1 and 2.5 SD lower than the mean of young adults, and osteoporosis is defined as a BMD measurement below 2.5 SD of the mean of young adults. The same absolute BMD value can, after adjustment for body size, be utilised in men [51, 54]. Established osteoporosis is defined as a T-score of –2.5 in combination with at least one fracture – a fragility fracture.
The definite diagnosis of osteoporosis is determined by measurement of BMD. Measurements of BMD can predict fracture risk [55], but not definitely identify individuals who will have a fracture [56], indicating the overlap between bone properties and the propensity to fall for fracture risk.

SPA
The oldest method for measuring BMD is the single photon absorptiometry (SPA) [57]. This method allows for measurement of the peripheral skeleton, usually the distal forearm [58, 59]. The forearm is submerged in water and a gamma-ray source coupled with a scintillation detector is scanned across the area of interest [30]. The beam registers the mineral content of the bone by comparing it with surrounding water and soft tissue.

DXA
SPA is a time consuming method that can only measure peripheral parts of the skeleton. Because of this, and due to improved technique with higher accuracy [30], this method has

been replaced by dual-energy X-ray absorptiometry (DXA) – the current gold standard of methods used to diagnose osteoporosis [60, 61]. This method uses two energy beams from X-ray generators [62, 63], with high intensity and fast scanning, resulting in good spatial resolution and better precision compared to SPA [64]. DXA can be used at central sites such as the proximal femur and the lumbar spine, as well as at peripheral sites, including the distal forearm [62, 65]. The method has a high precision and gives information of areal BMD (g/cm²), but provides no information the microstructure of the bone.

QCT

Quantitative computed tomography (QCT) has been applied both to the appendicular skeleton and to the spine [66, 67]. It provides a measure of true volumetric density of the bone (g /cm³), and information about the microarchitecture of the cancellous bone [32].

Cancellous bone is more responsive than cortical bone to many interventions, and QCT would therefore be suitable for monitoring progress of osteoporosis and treatment effects [59]. This method avoids the effect that degenerative disease can have on measurements, but the downsides are a comparably high exposure to radiation and high cost compared to DXA.

Ultrasound

Ultrasound is one of more recently developed methods for measuring bone density [68, 69]. It can be used only for measurements of the appendicular skeleton, usually the heel bone. The foot is submerged in water, and a sound wave generated by a piezoelectric crystal is sent through the heel bone. The parameters measured are the ultrasound velocity when passing through the bone, speed of sound (SOS), and how much of the ultrasound that is absorbed, broadband ultrasound attenuation (BUA) [70]. From these parameters an additional value can be calculated (stiffness). The advantages of this method are that it is portable, involves no radiation and is cheap, the disadvantage is that the precision is lower.

Fracture – the ultimate outcome

Osteoporosis is a disease that does not cause any pain or other symptoms until the skeleton has weakened enough for fractures to occur. These fractures can be caused by very mild trauma; falling from standing height or less, or be spontaneous, especially fractures of the vertebrae and pelvis. Important determinants of osteoporotic fractures are, in addition to bone strength, the falling mechanism, impact energy created by the fall and energy absorption of the soft tissues around the impact site, and hip fractures commonly occur when falling sideways and landing on the hip [71]. In Sweden, the annual number of fractures associated with osteoporosis is about 70 000, with 18 000 of them occurring in the hip.

The types of fracture usually regarded as osteoporotic are those of the forearm, proximal humerus, vertebrae, pelvis, hip and proximal tibia [72]. These fractures cause varying degrees of pain and disability [17, 72, 73], with hip fractures leading to the most serious consequences. Of those suffering hip fractures in Sweden, 20 % die during the first year post fracture and only 50 % can return to their previous living circumstances [74]. Thus, frailty and comorbidity increase the risk of fracture [27, 32], and are also risk factors for poor outcome.

Definition of high- and low-energy fractures

The amount of energy causing a fracture is often reflected in the severity of the fracture. If the fracture is multi-fragmented and engages large parts of the affected bone, it is commonly the result of high-energy trauma. At younger ages bone is stronger, and a higher amount of energy is required to fracture the bone, whereas in the elderly bone is brittle and fracture easier, with lesser amount of energy required. A fixed definition of what high-energy or low-energy is has yet to be determined.

However, a general agreement seems to be

that falling from standing height or less is considered a low-energy trauma, while traffic accidents and falling from ladders are regarded as high energy-trauma. The accidents and events that do not fit into these categories are more difficult to classify and assumption or extrapolation are commonly used.

Attempts have been made to define osteoporotic fractures [72]. Kanis and co-workers defined osteoporotic fractures as occurring at a site associated with low BMD and with an, at the same time, increased incidence after the age of 50 years [17]. According to this definition, vertebral, hip, forearm, humerus, femoral, rib, pelvic, clavicular, scapular, sternal, tibial and fibular fractures were considered to be osteoporotic in women, while in men, the same fracture types except tibial and fibular fractures were considered osteoporotic fractures. Another dilemma further complication the matter is the following; if an individual with osteoporosis suffer a high-energy accident generating a fracture, is the fracture an osteoporotic fracture or not? Can we be sure that an individual with normal bone mass would fracture? A definite answer is lacking, but the general opinion seems to be that fractures typically associated with osteoporosis are hip, vertebral, forearm, proximal humerus and pelvic fractures, and are thus considered as osteoporotic fractures in most studies.

Epidemiology of osteoporosis

Osteoporosis is a silent disease with significant physical, psychosocial, and financial consequences, affecting men and especially women, in all populations and at all ages [31]. Worldwide, approximately 200 million women have osteoporosis [75], and 20 % of all men over 50 years of age has osteoporosis of the spine, hip or forearm [54]. The prevalence of osteoporosis incrse with icreasing age ([51], and although osteoporosis has its highest prevalence in North America and Europe, it will increase in developing countries, in Asia in particular, as life expectancy continues to increase [76].

Epidemiology of fracture

Fractures related to various types of trauma occur at all ages. Most fractures occur above the age of 65, and a study from Trent has demonstrated that in men, 75% of all fractures occur before the age of 45, whereas the opposite is applicable for women [77]. In both sexes, the age- and sex-specific incidence of fractures is bimodal, with a high rate in childhood and adolescence and a low rate in middle age, but increasing rates for women from age 45, and for men approximately 10 years later [9, 78, 79].

Forearm fracture is the most common fracture type in middle-aged women, with a rapid increase in incidence after menopause, probably due to increased post-menopausal bone loss [80], while in middle-aged men the most common fracture types are, in rank order of frequency, rib, spine and forearm fractures [51].

Fractures of the proximal humerus account for 4-8 % of all fractures [81], and this fracture type is the third most common fracture over age 65 [82]. Both forearm fractures and proximal humerus fractures in middle age seem to occur in relatively fit individuals, especially forearm fractures [73]. The opposite is true about hip fractures, the most devastating type of fracture associated with osteoporosis. Hip fractures are rare at younger ages and are chiefly caused by high-energy trauma [83], but the incidence increase with age. Between 85 and 89 years of age hip fractures comprise 33 % of all osteoporotic fractures in men, and 36 % in women [17].

Prospective studies have shown that the number of almost all types of fracture is higher in individuals with low BMD [25, 84], but the fracture types most commonly associated with osteoporosis are hip, vertebral, forearm, proximal humerus and pelvis fractures. However, it must be noted that low bone mass only partly contribute to fracture risk, several other life-style and environmental factors are of the same importance for generating fractures, the risk of falling in particular.

RISK FACTORS

As with other common multifactorial health conditions, osteoporosis is not linked to a defined specific cause, but is associated with a number of risk factors mainly identified through epidemiological studies. Similarly, fractures – the outcome of osteoporosis, is associated with additional risk factors. Risk factors for osteoporosis, as reflected by low bone density, and the risk factors for fracture overlap, but are not identical. Risk factors for common diseases can be classified as modifiable or non-modifiable, with the aim of intervention to modify risk factors carrying a significant risk. In the following some of the commonly recognised risk factors will be reviewed.

Age and gender

Overall, advancing age is the most important risk factor for fracture in both men and women [85]. The risk factor age indirectly contains other factors affecting fracture that are influenced by age, including co-morbidity, increased risk of falls and impaired vision. Furthermore, age predicts fracture risk independently of BMD, and is probably a surrogate marker of unidentified risk factors [86].

Another factor affecting fracture risk is gender. Postmenopausal women have 3-fold higher risk of fracture compared to men [87], and the lifetime risk of hip fracture at age 50 is 22 % in women, compared to 10 % in men [72]. Similar differences in risk are seen for vertebral and forearm fractures. A study of 5 814 men and women, 55 years and older, demonstrated that women suffered 75 % of all hip fractures, with the incidence rate constantly lower in men [88], and another study found that the risk of hip fracture in women was twice that of men, doubling the risk every 5 years between 70 and 90 years of age in both sexes [89].
Women have in general smaller bodies with smaller bones and a lower peak bone mass. Due to menopause women lose bone more rapidly than men, and the female BMD reaches the limit of osteoporosis at younger ages. This contributes to the higher incidence of fractures in women, as does the lower strength of small bones compared to larger ones.

Anthropometric factors

The skeleton responds to increased load by thickening cortex and increased strength, whereas it becomes thinner and frailer with decreased load. The load on the skeleton is increased with increasing body weight. Body mass index (BMI) is a commonly used anthropometric variable; the body weight divided by the squared body height (kg/m²). Thus, it incorporates both height and body weight, and gives a more accurate description of the body constitution.

Low body weight and low BMI are strongly associated with increased fracture risk [90-98]. This is probably a combination of the fact that individuals with low body weight have lower BMD and have less padding when falling.

High body height has in some studies been associated with increased risk of hip fracture [99-101]. This could depend on that the impact of falling is higher with increasing body height. Furthermore, studies show that individuals with increased hip axis length and wider femoral neck have increased risk of fracture [102-104], and that there are substantial geographical differences in femoral neck geometry as well as in BMD [105]. The geometric variations may contribute to the large variations of hip fracture risk across Europe, and indicate that the increased fracture risk may also be related to structural differences.

Falls and previous fracture

The majority of non-vertebral fractures are caused by a fall. Exercise increases muscle strength and keeps the individual agile, and affects fracture risk in the elderly through decreased risk of falling [24, 106]. The degree of inactivity increases with age, and this may possibly be influenced by increased prevalence of illnesses [107]. Around one third of individuals above 65 years of age fall at least once a year, but only 1 % of falls in women result in hip fracture [108, 109]. Falls account for at least 90% of all hip fractures, and the risk of falling increase with age [110, 111]. Other studies have shown that those suffering hip fracture had a greater number of falls the year preceding the fracture [112, 113].

Apart from increasing age, the experience of a low-energy fracture is in itself one of the strongest risk factors for future fracture, often with a more than doubled risk increase reported[23, 114-121]. This is not surprising, since constitutional risk factors contributing to the first fracture, for example, low bone mass, frequent falls, poor vision and dizziness, in most cases remain. Furthermore, morbidity associated with the primary fracture is added to these risks, enhancing the risk of a second fracture. The increased risk of a new fracture seems to be highest immediately after the first event and decrease with time, reflecting that the morbidity of a fracture also decrease with time [122]. Thus, previous fracture and falling is an important risk factor for fracture.

Life style

Physical activity

Physical activity is of benefit for the well-being and general health of all individuals. Mechanical loading of the skeleton is an important signal for bone remodelling and adapts the bone according to the degree of load. Exercise at young ages is positively associated with bone mass [43, 123, 124], but unless a high level of physical activity is maintained, the bone mass will subsequently decrease and normalise [42, 125, 126]. Physical activity predicts risk of hip fracture after adjustment for self-rated health, and may reflect unidentified factors associated with skeletal fragility [127].

Thus, physical activity on a moderate level retains the bone strength as well as the agility and muscle strength, while inactivity is independently associated with increased hip fracture risk [85].

Smoking

Smoking, both current and former, has in many studies been associated with increased risk of fracture [128]. Smoking has a direct effect on bone, and also alters risk indirectly. The effect of smoking is not only related to nicotine [129] but also to the smoke inhalation. Smoke inhibits both osteoprogenitor cells and osteoblast-like cells [130]. In a prospective cohort study of 1800 men and women between 60 and 80 years of age, Nguyen and co-workers found that current smoking was associated with 5-8 % lower BMD in both hip and spine [131], with other studies showing similar results [132, 133]. Female smokers are thinner, have an earlier menopause and have increased risk of hip fracture compared with non-smokers [107, 134]. Current smoking increases the risk of hip fracture in both men and women [135]. The effect of smoking on bone mass is most pronounced in men, but also in the elderly according to a meta-analysis [136]. Smoking has an independent, dose-dependent effect on bone loss, which increase fracture risk, and may be partially reversed by smoking cessation [131, 136].

Alcohol

Excessive alcohol consumption has been associated with decreased bone mass in both men and women [137, 138], whereas moderate consumption has been demonstrated to decrease risk of fracture [139]. However, a recent study of 17 000 men and women confirmed that a high intake of alcohol confers a significant risk of future fracture, and seems to be largely in-

dependent of BMD [140].
High alcohol consumption is associated with alcohol-related falls and often a more hazardous life style, factors that contribute to fracture risk.

Comorbidities

Individuals suffering illnesses and with high consumption of drugs, are in general thought to have a more frail body constitution, with a higher risk of fracture and increased morbidity and mortality after fracture [114]. This has been demonstrated in elderly with hip fractures [141-145], shoulder fractures [146] and vertebral fractures [18, 147-149], but also in middle-aged men and women suffering low-energy fractures [83]. In the following we are highlighting some of the more frequently occurring conditions in terms of risk factors for fracture.

Diabetes
Diabetes is a chronic, systemic disease affecting nearly 20 % of older adults [150]. It develops from impaired or absent insulin response to glucose stimulation, where type 1 diabetes is caused by deficient pancreatic beta-cell secretion and type 2 is related to a cellular inability to respond to insulin (insulin resistance) or insufficient secretion of insulin at high glucose loads. Diabetes type 1 is a life-long condition, affecting all body organs and it may also affect fracture risk. Diabetes complications increase the risk of falls, with peripheral neuropathy generating decreased sensation in the feet, and with retinopathy causing impaired vision as contributing factors. The deranged glucose balance of the body also seems to have a direct toxic effect on bone.
Diabetes type 1 has been associated with decreased BMD [151] and increased risk of fracture [151-161]. The reason for this increased fracture risk is unknown, but low BMD in combination with increased risk of falls seem to be major contributors.
Diabetes type 2 has in most studies been associated with slightly increased BMD compared to the background population [162-166], and reduced fracture risk, also after adjustment for BMI [165]. Other studies have shown increased fracture risk [152, 155, 167], possibly related to disease duration [158]. Thus, diabetes has several effects on the individual that influence risk of fracture.

Neurological diseases
Neurological diseases frequently cause dysfunction and imbalance in the musculoskeletal system, leading to low physical activity, poor balance and increased risk of falls. In the following two of the major contributors to fracture risk are highlighted; stroke and Parkinson's disease.

A cerebrovascular incident many times leads to varying degree of physical and mental impairment. Stroke has been associated with increased risk of fracture [168-170], and increased risk of falls [171]. The increased fracture risk is attributed to impaired balance and increased risk of falls, as well as decreased BMD on the paretic side [172]. The fractures usually affect the paretic side [168, 173], and the commonest fracture type is hip fracture. Despite this, a study of 63 hip fracture patients with a previous history of stroke had similar functional recovery as those without stroke [173].

Parkinson's disease (PD) is a progressive, neurodegenerative disorder characterized by tremor, muscular rigidity and postural imbalance. Previous studies have indicated an increased rate of fractures in individuals with PD [174, 175], lower BMD at the spine and hip, and increased risk of falls [176]. Both falls and low BMD can contribute to fracture risk, but it is unknown to what extent they each contribute. In a recent study, fractures were registered from the date of diagnosis of PD, and the fracture rate increased significantly in the first 5 years compared to pre-diagnosis [174], a time frame to short to have any large effect on bone mass. The increased fracture rate in PD individuals thus seems to be more connected with their impaired physical capability

and increased rate of falling than a low BMD, although BMD might become more important with increasing disease duration.

Consumption of pharmacological drugs

Pharmacological treatment is an indicator of comorbidities, and used as an indirect measure of this. Pharmacological drugs may, as a side effect, both directly and indirectly increase risk of fracture. The effect can be mediated through a direct effect on bone mass, increasing or decreasing the bone strength, or induce increased risk of falls.

The most recognized group of drugs with effect on bone is glucocorticoids. These drugs can be taken orally or inhaled, and have been shown to decrease bone mass through reduced bone formation and increased resorption, as well as reduced absorption of intestinal calcium, leading to increased risk of fracture [177-179]. Other drugs with direct effect on bone but through different mechanisms are thiazides [180] and lithium [181] both associated with reduced risk of fracture.

Drugs with an indirect effect on fracture risk are those affecting the vision, inducing dizziness or decreasing the level of consciousness, and thus leading to increased risk of falls. Many types of drugs can cause these effects, but anxiolytics, sedatives and antidepressants have been especially examined for these side effects, with studies showing increased risk of most types of fracture including hip fracture [182, 183]. Since prescriptions of antidepressant medication are increasing [184], it is important to recognise this category of drugs as

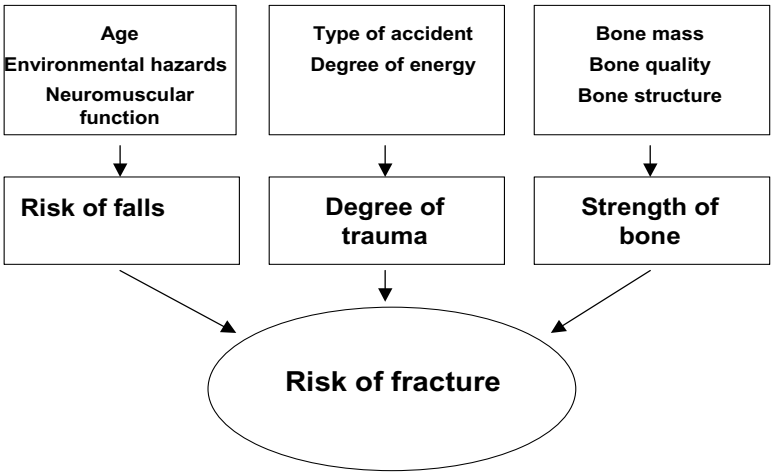


Figure 1
Mechanisms by which factors influence the risk of fracture, related to individual factors, external factors and bone strength.

HOW ARE RISK FACTORS ASSESSED

Methodology

The rationale of epidemiological studies is to analyse prevalence of a condition in the population, and to examine and evaluate background factors or risk factors related to the condition. Studies to identify risk factors are commonly based on either of a few designs, each with advantages and disadvantages.

An analytic cohort study is a study in which subjects are followed prospectively from exposure to outcome [185]. Exposed and unexposed individuals are compared regarding a defined outcome, for instance death or fractures. The study design allows for extended follow-up of many individuals and with different outcomes, also very rare occurrences. A predicament of this study type is that the subjects may differ in characteristics, and these confounding factors may affect the outcome. This can be compared to a randomised intervention study, where the subgroups are more homogenous and confounding factors limited due to inclusion and exclusion criteria in the study, and of course the purpose of such study is different. High response or attendance rate is key in a population-based study, as is random selection [186].

In case-control studies, in contrast to the cohort study, the study subjects are investigated backwards from outcome to exposure. This study design starts with measurement of the outcome, often classifying the subjects into those with or without the outcome or condition, and then tries to identify prior exposure. A case-control study is well suited to investigate rare outcomes, since huge cohorts would be needed to ensure that sufficient number of subjects develop the rare outcome. It is also cheaper due to smaller numbers and no prolonged follow-up. There is however, compared to cohort studies, a higher potential for sample distortion bias and information bias. Using strict inclusion and exclusion criteria and interviewer blinding can minimize this. Confounding factors can be controlled for as in cohort studies.

In cross-sectional studies exposure and outcome are determined simultaneously. Since exposure and outcome are ascertained at a single point in time no follow-up is needed, and this makes these studies fast and comparably inexpensive. Their main contributions are descriptive rather than analytic. Compared to case-control studies, cross-sectional studies are less prone to random error. A major limitation of this study type is that due to the lack of a time variable, it impossible to distinguish cause from effect, what came first the hen or the egg?

Statistical analysis

In epidemiological studies statistical analysis is essential, and are used to compare the groups within a study. In a cohort study the distribution of confounding factors may be uneven between the groups. To examine the impact of the confounding factors the χ^2 test (for dichotomous variables) or Students' T test (for continuous variables) can be used, but a disadvantage is that the significance levels are sensitive to sample size, and not very meaningful when applied to studies with large numbers of subjects [187]. A method to minimize the confounding factors is to stratify the cohort into subgroups, based on characteristics that are believed to confound the analysis, for example sex or age. This may, however, reduce the power of the study to detect effects since the number of participants in each subgroup is smaller than the whole cohort.

Another way to account for confounding factors is by using regression. Regression uses the data to estimate how confounders are related to the outcome, and results in an adjusted estimate of the effect [188]. The choice of method of regression analysis, i.e. linear, logistic,

proportional hazards etc, is dictated by the type of dependent variable analysed. The multiple logistical regression model is a frequently used analysis method, since it provides simultaneous control for any number and combination of continuous and categorical confounders [189]. The model allows for using variables with many outcomes, but does not include the aspect of time related to the observed event. This aspect is provided for in a survival analysis, a statistical technique that allows the investigator to calculate a probability of developing a given outcome, and takes into account the duration of follow-up. This technique makes maximum use of all data on a cohort, including those subjects who withdraw from the study or are lost to follow-up. A weakness is that it can only be used for dichotomous variables.

A further development of the survival analysis technique is the Cox proportional hazard model combining the logistical regression model and the survival model. The Cox analysis models the proportional hazard as a function of exposure and any number of continuous and, categorical confounders [185].

SUMMARY

Risk factors for osteoporosis and fracture have been evaluated in the elderly, the major contributors being high age, previous fracture, low body weight, falls and comorbidities. Less is known about men and women suffering fractures already in middle age. Many factors contribute to fracture risk through mediating the risk of falls, degree of trauma and strength of bone (Figure 1). Fracture risk can be evaluated through risk factor assessment in epidemiological studies. An improved knowledge about individuals that sustain fractures in middle age, allows for preventive measures to be directed towards factors that can be modified within a reasonable time frame, thus preventing fractures later in life.

HYPOTHESIS OF THE STUDY

In this thesis the following specific issues were addressed:

- Is it possible to define risk factors for fragility fractures in middle-aged men and women?
- Is it possible to define risk factors for hip fractures in middle-aged men and women?
- Is hyperglycemia a risk factor for future fracture in middle-aged men and women?
- Can a single bone mineral density measurement of the forearm predict future fracture risk?

SUBJECTS AND METHODS

The Malmö Preventive Project

The Malmö Preventive Project (MPP) is a prospective, population-based study consisting of 33 346 probands, 22 444 men and 10 902 women, all citizens of the town of Malmö. The MPP started at the Section of Preventive Medicine, Department of Medicine, Malmö University Hospital in 1974. The aim of the project at the start was to examine this mostly middle-aged population, to find high-risk individuals suitable for preventive interventions on cardiovascular risk factors, alcohol abuse and impaired glucose tolerance [190-195]. All individuals born in previously chosen specified years (range1921-1949) were invited to participate in this project, and 72 % of the invited population joined the study [194]. Mean age at the baseline investigation was 44 (range 27-61) years for men and 50 (range 28-58) years for women. The inclusion period for men was 1974 to 1984 (10 years) and for women 1977 to 1992 (15 years). Beyond the original aims of the project it provides data for evaluation of other common public health conditions such as fracture and diabetes. The probands were followed prospectively until the end of 1999, with a mean follow-up of 19 years (range 7-25 years) for men and 15 years (7-22 years) for women for fractures and mortality (Figure 2).

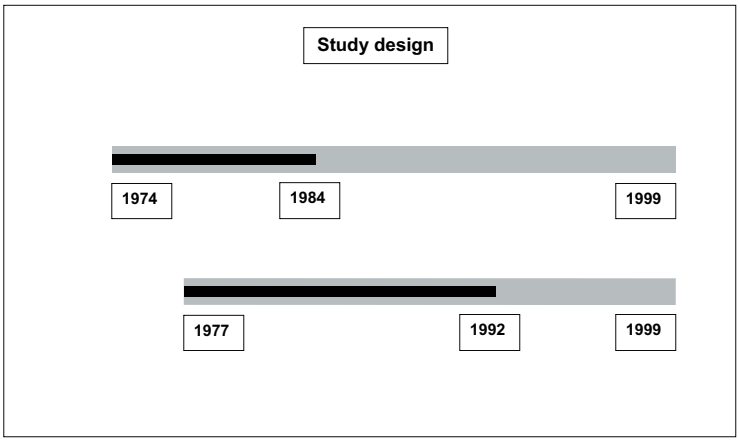


Figure 2
The Malmö Preventive Project started in 1974. The inclusion period for men was from 1974 to 1984 with a mean follow-up of 19 years, and for women from 1977 to 1992 with a mean follow-up of 15 years.

Clinical examinations

At baseline the probands underwent a physical examination including measurements of body height (cm) and body weight (kg), allowing for calculation of body mass index (BMI) (kg/m^2). Additional specific organ system assessments, such as blood pressure (mmHg), pulse rate (beats/minute) and lung capacity were performed in the entire cohort. Blood pressure and pulse rate were measured twice after a 10 minutes rest and a mean figure was recorded. Lung function was evaluated using spirometry.

Questionnaire

At baseline the probands completed a comprehensive, self-administered questionnaire of approximately 260 questions. The questionnaire focused on family history of cardiovascular disease, hypertension and diabetes, presence of signs of cardiovascular disease, use of cardiovascular medication, previous and present smoking habits, social background characteristics, alcohol drinking habits (including screening questions for alcoholism), physical activity both during work and during leisure time, and medical history and status. For women, questions about reproductive history and menopausal status were also included.
For the majority of questions the possible alternatives were yes or no or deferring from answering. During the extended inclusion period new questions were considered relevant and added, while others were withdrawn. The data for some variables are therefore incomplete.

One of the questions with limited response rate was regarding previous fracture. This question was added in 1983, the later part of the inclusion period. The response rate was 74% for women but only 4% for men. The majority of the women were included in the study in the later part of the inclusion period and the majority of the men at the beginning, which explains the difference in response rate. Another question with limited response rate for women regarded hormone replacement therapy, eliciting a response rate of 74%.
Questions with limited response rate in men concerned treatment for psychical illness, sick leave, appetite disturbances, sleep disturbances, and tightness of the chest, all with 72 % response rate. For those who had the opportunity to respond the response rate was almost 100%.

Laboratory analysis

Morning blood samples were collected from the participants after an over-night fast. A large collection of blood analyses were performed, some of them only in subgroups of the study population. The following analyses were used in our studies; haematoglobin, sedimentation rate (SR), serum creatinine, fasting blood glucose, serum γ -glutamyl transferase (GT), serum triglycerides, serum total cholesterol, serum uric acid and serum phosphate. Due to skewed distribution of serum γ -glutamyl transferase it was logarithmically transformed when used in the analyses.

Diabetes

At study start only a small part of the population was suffering from diabetes, 132 women and 249 men, 1.2 and 1.1 % of the study population. No information of type of diabetes or diabetes treatment was recorded.
Fasting blood glucose (FBG) samples were available for 99 % of the probands, and FBG below 5.5 mmol/L was considered as normal, and 18 605 (83%) men and 9 464 (87%) women had normal FBG. Normally, repeated elevated levels of FBG above 6.1 mmol/L are required for diagnosis of diabetes, however in our study a single FBG above 6.1 mmol/L has been considered indicative of diabetes. This was found in 879 (3.9%) men and 365 (3.4%) women.

Approximately half the study population, 13 056 (58%) men and 5 904 (54%) women, underwent an oral glucose tolerance test (OGTT). The tolerance test was performed after an over-night fast, in randomly selected age cohorts within the study population. Each indi-

vidual was given 30 grams of glucose per m² body surface area dissolved into a 10% aqueous solution and ingested within 5 minutes. In the later part of the study the method of the OGTT changed, and each individual, regardless of body size, was given a dose of 75 grams of glucose dissolved in water that was ingested within 5 minutes. Blood samples were drawn at 0 and 120 minutes after the glucose intake.
Subjects with 2-hour blood glucose levels (OGTT) below 7.0 mmol/L were defined as having normal glucose tolerance, while those with values above 10.0 mmol/L were defined as subjects with indication of diabetes, even if not repeated measurements were used. OGTT was normal in 11 166 men (85%) and 3 585 women (64%), whereas 223 men (1.7%) and 275 women (4.7%) had 2-hour glucose elevated above 10.0 mmol/L.

Single photon absorptiometry

Bone mineral density was measured in a smaller group of women (n=1 294). The BMD measurements were made by single photon absorptiometry (SPA) according to the method of Nauclér et al [57]. The measurements were performed at the forearm, 1 and 6 cm from the radio carpal joint, the distal measurement (BMD1) representing mostly cancellous bone and the proximal (BMD6) mainly cortical bone. BMD was calculated as the average thickness of bone mineral in the path of the beam. Both forearms were measured and the average was calculated. The precision of the SPA measurements, determined by double measurements after repositioning the subject, was 1-2 % [196].

Fracture assessment

The fracture data was obtained by linking the probands included in MPP with the register at the Department of Diagnostic Radiology at Malmö University Hospital. In the city of Malmö all emergency radiographic examinations are performed at the Department of Diagnostic Radiology at Malmö University Hospital, the fractures are recorded and the films are stored and kept infinitely. A previous study has confirmed that at least 97 % of all fractures that the Malmö population endures can be identified this way [197]. The unique 10-digit personal identification number, based on birth date and issued to every Swedish citizen at birth, makes identification of cases easy and precise. The fractures were confirmed through manual search of the medical and radiological files. The confirmed fractures were classified into different categories including forearm, vertebral, proximal humerus, ankle and hip fractures (Table 1). The vertebral fractures registered were those causing clinical symptoms and described in radiographic reports, but also those accidentally found on chest or abdominal x-rays for other causes and described in the radiographic report. The degree of vertebral deformity was not quantified.
The fractures where classified according to degree of high or low-energy trauma (Figure 3 and 4). Fractures caused by falling from standing height or less were classified as low-energy fractures and those caused by high-energy trauma as high-energy fractures (Table 1). The classification was based on information given in the radiographic reports. Of all fractures, 4098 fractures (97.7 %) had adequate information about degree of trauma on their radiology reports. The 98 fractures with insufficient information about trauma were classified as low-energy fractures, based on the experience that it is highly unlikely to omit information from high-energy accidents.
Fractures caused by high-energy trauma according to the radiographic report such as motor accidents or falling from heights were excluded from the analyses, as well as pathological fractures caused by cancer or bone diseases.

Table 1
Distribution of all fractures in 33 346 women and men from inclusion date until follow-up ended December 31, 1999. The mean follow-up time was 15 years for women and 19 years for men. Reported in order of frequency in women. (Reprinted by courtesy of Osteoporosis International from paper III)

	Women			Men		
Fracture type	Fractures	Low-energy fractures	% of all fractures	Fractures	Low-energy fractures	% of all fractures
Forearm	666	662	36.7	379	330	16.7
Ankle	231	223	12.4	292	259	13.1
Vertebral	166	160	8.9	219	168	8.5
Proximal humerus	158	158	8.8	133	123	6.2
Hand and foot	150	144	8.0	466	354	17.9
Hip	143	141	7.8	192	174	8.8
Patella	49	47	2.6	79	70	3.5
Tibial condyle	49	45	2.5	56	35	1.8
Elbow	40	35	1.9	42	33	1.7
Pelvis	41	31	1.7	57	37	1.9
Rib cage	25	22	1.2	129	106	5.4
Clavicle and scapula	30	20	1.1	89	74	3.7
Femur below hip	20	17	0.9	43	31	1.6
Tibia, lower leg	16	13	0.7	40	21	1.1
Radius and ulna	14	12	0.7	17	11	0.6
Diaphyseal humerus	12	12	0.7	22	15	0.8
Scull and face	12	11	0.6	68	53	2.7
Other	56	52	2.9	99	81	4.1
Total	1878	1805	100	2422	1975	100

Figure 3
Fracture distribution among the women participating in The Malmö Preventive Project. The figures refer to the number of individuals suffering one or more fractures during follow-up.

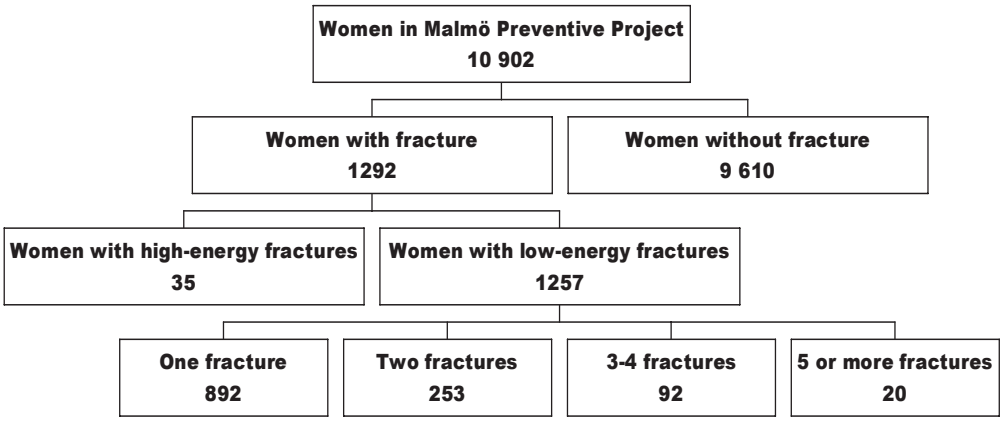
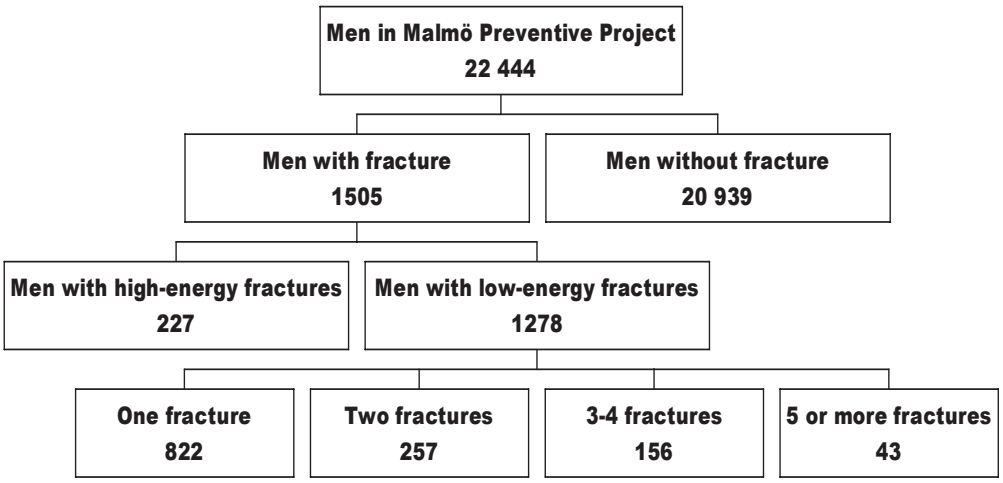


Figure 4
Fracture distribution among the men participating in The Malmö Preventive Project. The figures refer to the number of individuals suffering one or more fractures during follow-up.



SUMMARY OF PAPERS

Paper I

Forearm bone mineral density in 1 294 middle-aged women – a strong predictor of fragility fractures

Research question
Can a single bone mineral density (BMD) measurement of the distal forearm, a relatively cheap and simple method, predict the risk of future fragility fractures in middle-aged women?

Material and Methods
This study involves a subgroup consisting of 1 294 women, included in the later part of the main study. BMD measurements were performed at inclusion, using single photon absorptiometry (SPA) of the forearms. Measurements were made of both forearms at two sites; the distal and ultradistal radius. The mean of the bone mineral density measurements was calculated for each measurement site. The follow-up time for these women was on average 9 years regarding fractures. The data were analysed in a Cox regression model for low energy fractures in general, but also for specified types of fractures, such as forearm, vertebral, shoulder and ankle fractures.

Results
During the follow-up, 65 women had 86 fractures. Two fractures were excluded from the analysis due to high-energy trauma. The women with BMD measurements were on average 3.6 years older and 1.8 kg heavier compared with the entire study cohort. The BMD was significantly lower at both the distal and ultradistal measurement sites in the women who sustained a fracture, compared with those without fracture. One standard deviation (SD) decrease of BMD at the ultradistal measurement site of the radius doubled the relative risk of fracture (relative risk RR 2.02, confidence interval 95 % CI 95% 1.56-2.61, p=0.0001), whereas the same SD decrease at the distal measurement site increased the risk 1.5 times (RR 1.62, CI 95 % 1.26-2.08, p=0.0002). The most common fracture type was the forearm fracture, with 41 fractures recorded. Using the same model, one SD decrease in BMD almost doubled the risk of forearm fracture (RR 1.77-1.98) regardless of measurement site.

Conclusions
A single BMD measurement of the forearm in a 53-year old woman can predict fracture risk at least 9 years prospectively. The measurement can also specifically predict the risk of forearm fractures. Our study shows that forearm bone mineral density measurements may be useful as a screening method in middle-aged women to identify individuals where preventive measure would be useful. The health economic consequences, in terms of gain or costs, were not investigated in this study.

Paper II

Risk factors for hip fractures in a middle-aged population – a study of 33 000 men and women

Research questions
Is it possible to identify factors associated with the risk of hip fracture in middle-aged men and women? If yes, is the risk factor pattern different between men and women, between cervical and trochanteric hip fractures?

Material and Methods
This study is based on the entire study cohort. The follow-up time regarding hip fracture is 19 and 15 years for men and women, respectively. Biologically interesting data with potential

effect on hip fracture risk have been analysed in a Cox regression model. The same statistical methods have been applied on cervical and trochanteric hip fractures.

Results

Low-energy hip fractures occurred in 135 women during the observation period, 93 cervical and 42 trochanteric hip fractures. Mean age at fracture was 61.5 (SD ± 5.7) years. Of the men 163 suffered in total 81 cervical and 85 trochanteric hip fractures. Mean age for the men at fracture was 62 (SD ± 9.2) years. The mean age of those individuals suffering hip fractures was higher than in the background population. Individuals with trochanteric hip fractures had lower body weight and body mass index compared with the background population.

The factor strongest associated with a future hip fracture in women was a history of previous fracture (RR 4.76, 95 % CI 2.74−8.26, p=0.0001). Diabetes was associated with a more than tripled risk increase (RR 3.44, 95 % CI 1.50−7.87, p=0.003). Low pulmonary function, high serum cholesterol, smoking and poor self-rated health were other factors associated with an increased risk of hip fracture in women.

In men the factor strongest associated with the risk of future hip fracture was suffering from diabetes (RR 6.10, 95 % CI 3.17−11.63, p=0.001). Low pulmonary function, high serum cholesterol, smoking and poor self-rated health were, as in women, associated with an increased risk of hip fracture. Other factors that were associated with an increased risk of hip fracture were elevated γ-glutamyl transferase (GT), high ESR, high resting pulse, high diastolic blood pressure and sleep disturbances.

Conclusions

Our study has identified a number of risk factors for hip fracture in a previously rather unknown group, those who suffer hip fractures already in middle age. Our findings indicate that hip fractures in middle age, especially trochanteric hip fractures, are associated with other adverse health conditions and psychosocial problems in individuals with a weaker body constitution. We have not identified any significant difference in risk factor profile between cervical and trochanteric hip fractures at these ages. Our study underlines the importance of preventive work also in middle-aged individuals, especially among those with a poorer health.

Paper III

Risk factors for fragility fractures in middle age. A prospective population-based study of 33 000 men and women

Research questions

In middle-aged men and women, is it possible to identify factors associated with risk of low energy fractures in general and of specific fracture types, i.e. forearm, vertebral, shoulder and ankle fractures? If yes, does the risk factor pattern differ between men and women or between different fracture types?

Material and Methods

This study is based on the entire study cohort, 33 000 men and women, and using the same research strategy as in the previous study. The follow-up time is 19 and 15 years for men and women, respectively. Biologically interesting data with a potential effect on low energy fractures have been analysed using a Cox regression model. The same analytical methods have been applied on forearm, vertebral, proximal humerus and ankle fractures.

Results

In all, 1 878 fractures were registered in 1 292 women during follow-up. Of these, 1 257 women (97 %) had one or more low-energy fractures (Figure 3). The numbers of the most frequently occurring fractures recorded in this study were 600 forearm fractures, 138 vertebral fractures, 146 proximal humerus fractures and 217 ankle fractures (Table 1). The women with low-energy fractures were older and had a higher prevalence of diabetes compared with the background population.

Among the men 2 422 fractures were registered during follow-up, in 1 505 men. Of these, 1 262 men (84 %) sustained at least one low-energy fracture (Figure 4). The numbers of the most frequently occurring fractures in men in this study were 315 forearm fractures, 156 vertebral fractures, 115 proximal humerus fractures and 250 ankle fractures (Table 1). The men with recorded low-energy fractures were older, had lower body mass index, smoked more, and had a higher prevalence of diabetes as well as of joint and back pain compared to the background population.

In women, the factor most strongly associated with risk of low energy fracture, was a history of previous fracture. This doubled the relative risk of a new fracture (RR 2.00, CI 95 % 1.56-2.58, p=0.001), tripled the relative risk of a vertebral fracture (RR 3.13, CI 95 % 1.65-5.75, p=0.001) and doubled the risk of ankle and forearm fractures. Diabetes doubled the risk of a low energy fracture (RR 1.95, CI 95% 1.33-2.86, p=0.001) and increased the risk of vertebral and ankle fractures more than three times (RR 3.36-3.56).

In men, the factor that had the strongest association with risk of low energy fractures was suffering from diabetes (RR 2.34, CI 95 % 1.58-3.46, p=0.001). A history of hospitalization for mental health problems was the factor with the highest impact on risk of a low-energy fracture in general (RR 1.92, CI 95% 1.47-2.51, p= 0.001), as well as on all specified fracture groups, with a more than doubled risk of forearm, vertebral, proximal humerus and ankle fractures (RR 2.28-3.38).

Conclusions

We have identified a number of factors associated with the risk of sustaining low-energy fractures in general and specified fractures types in middle age, in both women and men. In general, fracture seems to be more prevalent among individuals with poorer health. The identified risk factors are indicators of health problems in the areas of diabetes, mental health and cardiovascular disease. Risk factors in middle age are also linked to life-style such as smoking and alcohol consumption. These identified risk factors may be used to identify individuals with a high risk of future fracture.

Paper IV

The Association Between Hyperglycaemia, Diabetes and Early Fracture Risk in Middle Age. A prospective, population-based study of 22 444 men and 10 902 women

Research question

Do hyperglycaemia and increased glucose tolerance affect fracture risk in middle-aged men and women?

Material and Methods

In this study fasting blood glucose (FBG) was analysed in the entire study cohort, 33 000 men and women. Oral glucose tolerance tests were available in 19 000 men, and women and the 2-hour post –challenge blood glucose value (OGTT) was used in the analyses. The population was divided into quartiles based on their levels of fasting blood glucose and 2-hour blood glucose, respectively. A logistical regression model, with step-wise adjustment for age and BMI, was used to evaluate the influence of fasting blood glucose levels and 2-hour post challenge blood glucose levels on future fracture risk.

Results

Incident fractures were recorded in 1 292 women, with 1 257 classified as low-energy fractures, and in men 1 505 fractures were found, with 1 278 classified as low-energy fractures. At least one osteoporotic fracture was identified in 704 (47%) men and 955 (74 %) women of the total fracture population.

In the quartiles of FBG and of OGTT the same trends were seen, with increasing body weight and BMI in the highest quartiles, in both men and women. The incident fractures were evenly distributed over the quartiles of FBG, whereas a higher proportion of persons with fracture was found in the lowest quartile of OGTT,

especially in women. For OGTT the distribution of current smokers in the quartiles was also uneven, with the highest proportion in the lowest quartiles in both men and women.

A 2-hour post-challenge blood glucose level above 4.2 mmol/L in men and above 5.4 mmol/L in women, i.e. the 2nd to 4th quartile in both sexes, decreased the risk of multiple low-energy fractures, compared to the lowest quartile. In men, a 2-hour blood glucose level between 4.3 and 6.2 mmol/L (2nd and 3rd quartile) and in women above 6.6 mmol/L (3rd and 4th quartile) had significantly decreased risk of osteoporotic fractures, with a risk reduction of up to 65 %. Adjustment for age and BMI had only minor effect on the results, but after adding current smoking to the analyses, the risk reduction effect on osteoporotic fractures disappeared in men, and in the 3rd quartile in women.

Belonging to the higher quartiles of fasting blood glucose was, in men, associated with lower risk of fracture, while in women the highest fasting blood glucose quartile had a slightly increased fracture risk. These associations disappeared after adjustment for age and BMI.

Conclusions

Impaired glucose tolerance, as assessed by 2-hour post-challenge blood glucose in middle-aged men and women, was associated with decreased risk of multiple low-energy fractures as well as of osteoporotic fractures, independent of age, BMI and smoking. These findings indirectly suggest a positive effect on bone from insulin.

GENERAL DISCUSSION

The pattern of risk factors for fracture is complex. It has been extensively examined in elderly populations, but since these studies mostly have excluded middle-aged men and women, the relevance of the identified risk factors in middle age is unknown. A better knowledge regarding fracture risk in middle age may be of use, when planning preventive measures against the increasing number of fractures that starts to occur already in middle age, in particular since previous fracture is a known risk factor in those suffering fractures at old age.

In paper II and III we have examined risk factors for low-energy fractures in general and for specified fracture types; hip, forearm, vertebral, proximal humerus and ankle fractures. Many risk factors were common to all specified types of fracture, although with varying impact.

Low-energy fractures

Low-energy fractures were associated with age and suffering from diabetes in both men and women. Diabetes type 1 has in previous studies been associated with low BMD [151, 160, 161] and increased fracture risk [150, 154, 158, 159, 167, 198], whereas diabetes type 2 has been associated with normal or increased BMD [162-166] and with increased and decreased risk of fracture [155, 158, 165, 167]. Diabetes complications lead to increased risk of falls and can affect the vitamin D and calcium metabolism. Thus, the diabetes disease has a multifactorial impact on fracture risk.

A history of hospitalization for mental health problems was one of the strongest risk factors in men, but had no impact in women. Additional risk factors in men were sleep disturbances, poor self-rated health and poor appetite. These factors are to a certain extent interdependent, but they all indicate that the psychological well-being and the mental health of an individual is of great importance for future fracture risk in men. These factors may of course signify underlying diseases or conditions not recognised in our study, however our study is one of the few identifying these risk factors for fracture. A recent study of the Tromsø population of Norway, with an age range of 25-98 years, showed that psychiatric disorders in both men and women increased the risk of future fracture [114], and an increased fracture risk was also found in a study of elderly women diagnosed with depression [21]. Increased risk of fracture associated with anxiolytics, sedatives and antidepressants [182, 183], and increasing prescriptions of antidepressant medication [184], further emphasise the importance of psychological well-being and mental health as risk factors for future fracture.

Forearm fracture

Forearm fractures have in previous studies of women been associated with low BMD [73, 199-203], and in one study in men [204]. In our study the major risk factors for forearm fractures in both men and women were advancing age and BMI, both risk factors typical of osteoporotic fractures. In our study the incidence of forearm fractures in women is stable up to age 45, thereafter the incidence increases rapidly, in consistency with previous studies in Malmö [205] and Uppsala [206]. The increased incidence after menopause is probably a reflection of the increased post-menopausal bone loss, primarily affecting cancellous bone and increasing fracture risk. In men, no age-related increase in fracture incidence is seen. However, a study of 1 300 men and women, 35 years or older, showed an up to ten-fold increased risk of vertebral fracture after suffering a forearm fracture, demonstrating that a forearm fracture is a signal of increased risk of fracture in both men and women [121].

Forearm fractures and bone mineral density
Low bone mineral density is a known risk factor for fracture in the elderly, and is used as a tool for treatment decision. Our study of 1294 middle-aged, mainly post-menopausal women shows, that a single BMD measurement of the forearm is predictive for future fracture, especially for forearm and clinical vertebral fractures, a finding in agreement with previous studies [207-210]. This supports the notion that BMD measurements could be used in middle age as a screening tool for finding individuals at high risk of suffering future fracture.
However, a large proportion of those with low BMD does not suffer fracture, and information regarding other risk factors for fracture needs to be added to make identification more certain. Thus, the controversy regarding screening remains.

Hip fracture
A fracture of the hip is the type of fracture which generates the gravest and most devastating consequences in both men and women. The mean age of men and women suffering hip fractures in Sweden is approximately 80 years. However in our study, performed in middle age, the mean age at fracture was 62 years for both men and women. Diabetes was, also for hip fractures, the risk factor with the strongest impact in both men and women, with an up to 7 times increased relative fracture risk, and similar to the findings in a Norwegian study [157].
Diabetes was not, in our study, associated with an increased cervical hip fracture risk in women, and had a lower impact on cervical hip fracture risk in men. This could be a reflection of the fact that cervical hip fractures are not as strongly associated with comorbidities as trochanteric hip fractures. Furthermore, body weight in itself had no impact on cervical hip fracture risk in either sex, although high BMI was associated with a decreased risk of cervical hip fracture. This effect was, however, more pronounced in men and women with trochanteric hip fractures. Several studies have shown that patients with trochanteric hip fractures have lower bone density [84, 90, 92, 211-217], and that this fracture type seems to affect individuals with a relatively low body weight and a poor constitution [92-94] compared to cervical hip fractures. These findings fit in well with those of our study, but despite the size of our study and the duration of follow-up, our findings are not definite enough to permit any reliable assumptions to be made.
However, indications are strong that trochanteric hip fractures frequently occur in individuals with a relatively frail constitution, also in middle-aged men and women.

Vertebral fracture
Only about 1/3 of all vertebral fractures noted on radiographs come to medical attention, and less than 10 % are admitted to hospital [218]. They are, nevertheless, associated with increased mortality in both men and women, in women also with increased morbidity [18, 149, 219, 220]. In our study vertebral fractures were, especially in men, associated with factors concerning mental health; poor appetite and self-rated health, sleep disturbances and hospitalization for mental health problems, as well as lifestyle factors; smoking, being on sick-leave and high levels of γ -glutamyl transferase. These factors all indicate that individuals with a frail mental constitution have an increased risk of vertebral fracture. A recent study has shown increased fracture risk with consumption of anxiolytics, sedatives, antidepressants and neuroleptics, further supporting this assumption [182].

Proximal humerus fracture
Increased risk of proximal humerus fractures was in men associated with low BMI, whereas in women a high BMI increased the risk. Chu and co-workers [221], have presented similar findings in a case-control study of both men and women. These findings are in contrast to proximal humerus fracture as a type fracture of osteoporosis. The way you fall is important for what type of fracture you suffer. Younger individuals are quicker and have time to stretch out a hand when falling, thus

sustaining a forearm fracture, while individuals with proximal humerus fractures are older and slower, thus falling directly on the shoulder [222, 223]. A heavy body will increase the force of impact, and may explain high BMI increasing fracture risk in middle age, whereas at older ages low bone mass prevail as a risk factor for fracture. The women with proximal humerus fractures had the highest mean age of all fracture groups, they were three years older than the non-fracture group. Thus, with age bone strength seems to become a more important risk factor for proximal humerus fracture, and this is further supported by a retrospective study of 29 000 women 50-80 years of age [116]. These authors found that after a proximal humerus fracture, the relative 10-year risk o hip and vertebral fractures was increased by more than 2.5 times, in those under as well as over 70 years of age.
In men the risk factor pattern for proximal humerus fractures was similar to that of vertebral and hip fractures, suggesting low bone mass as a major contributor to facture risk in men.

Ankle fracture
Ankle fractures have been less thoroughly investigated in the elderly, than most other fracture types. It may depend on that fracture incidence differs from other fragility fractures, with a peak in the sixth decade followed by a rapid decrease [224]. Thus, ankle fractures are rare in age groups where fragility fractures are common and where most fracture studies are performed. Previous studies have reported gender, obesity, weight gain since age 25, diabetes, falling, and high physical activity as risk factors for ankle fracture [225, 226], whereas BMD was not an independent risk factor [84, 226, 227]. This is consistent with a study of 103 women in Sheffield, 50-80 years of age [228], whose BMD was actually higher in the ankle fracture group. These women also had a higher BMI. Subsequently, weight gain and high BMI seem to be an independent risk factors for ankle fracture [84, 225, 226, 228, 229], the risk probably mediated through falls with higher impact, and greater twisting forces [230]. Our study confirms high BMI to be a risk factor for ankle fracture in women.
In our study, diabetes was also a risk factor for ankle fracture, as was high serum-triglycerides, and these two factors, as well as high BMI, are all connected with the metabolic syndrome. Perhaps the metabolic syndrome in itself should be considered as a risk factor for ankle fracture?

Few studies have been made of middle-aged men with ankle fractures, and most seem to concern fracture incidence [224, 225]. This is probably a reflection of the fact that ankle fractures in men are mostly associated with younger age groups and high-energy trauma. The incidence of ankle fracture in men remains stable throughout life, suggesting no association with low bone mass. This further supports previous suppositions that ankle fractures, especially in men, are questionable as typical osteoporosis fractures [201, 226, 231, 232].

Fracture and diabetes

Our previous studies have shown diabetes as a strong risk factor for low-energy fractures in general and for specified fracture types in both men and women. However, other studies have presented conflicting data, with, increased fracture risk [151, 155, 158, 160, 161, 167], decreased fracture risk [165] and no association between diabetes and fracture risk [233]. Clear differences are seen between diabetes type 1 and 2, with diabetes type 1 always associated with increased fracture risk but type 2 with dissimilar associations. A previous study by de Liefde, including also those with impaired glucose tolerance (IGT) or “pre-diabetes”, showed decreased fracture risk in subjects with IGT, whereas fracture risk was increased in those with diabetes type 2 [234]. In women with IGT we found consistently lower risks of one or multiple low-energy fractures and of osteoporotic fractures. In men with IGT the risk of multiple low-energy fractures were consistently decreased, as well as for part of the population regarding osteoporotic fractures. Adjustment for age and BMI had minor

effects on the results, demonstrating the IGT as an independent predictor of fracture risk. Individuals with IGT have decreased sensitivity to insulin, generating high levels of serum-insulin, while individuals with diabetes type 2 have lower serum insulin levels due to treatment and exhaustion of the beta cells in the islands of Langerhan. Serum insulin levels have been associated with bone density [235], and it has been proposed that insulin has a direct anabolic effect on bone cells, as well as an indirect effect on bone formation trough interaction with the IGF-1 receptor and parathyroid hormone, increasing bone mass [236].

Although our study is based on only one measurement of 2-hour post challenge blood glucose, the evidence is strong that middle-aged men and women with impaired glucose tolerance have a decreased risk of fracture. The underlying explanation for this remains to be further explored.

Strengths and limitations

These studies have strengths and limitation. The studies are based on randomly selected age cohorts, with an attendance rate of 72 %. The population is large, 33 000 men and women, and the follow-up is long. A limitation is the extended inclusion period, especially in women, thus generating differences in follow-up. In an attempt to overcome this, the Cox regression model was used in study two and three. Another dilemma is that some data are incomplete, for example data from the questionnaire. In order not to overextend our interpretations of the data, we have chosen to use those variables for which the data can be regarded to be sufficient.

The population has to some extent been subject to intervention against cardiovascular diseases, diabetes and alcohol abuse. This could possibly affect the fracture incidence. However, the intervention studies did not record any effect on cardiovascular disease, diabetes or alcohol abuse in the study cohort [237]. Therefore an effect on fracture incidence seems unlikely.

The strength in these studies is that, to our knowledge, they constitute some of the first prospective studies evaluating risk factors of common fracture types in middle age in both men and women. Furthermore, the studies have been able to evaluate factors that are not commonly studied, making these studies even more unique.

Can risk factor assessment be improved at middle age?

We have, by aid of this large population-based cohort of urban, middle-aged men and women, been able to identify multiple risk factors for low-energy fracture. We have detected differences in risk factor pattern for each fracture type, albeit with large overlaps. Fracture risk can be assessed by bone mineral density measurements [55], but a combination of risk factors would improve fracture prediction compared to the use of a single risk factor [238-242]. However, management strategies and therapeutic guidelines currently being used are not sufficiently consistent, and lack in specificity and sensitivity [242, 243].

Subsequently, this study has identified risk factors that are often overlooked. These fracture predictors can improve risk assessment, and should be included in intervention algorithms, at least in middle age when the first fracture commonly occurs.

CONCLUSIONS

In this thesis the following conclusions were reached for urban middle-aged men and women:

- In middle-aged men and women, it is possible to identify risk factors for low-energy fractures, as well as for specified fracture types. The risk factors include advancing age, low BMI, diabetes, mental health problems, previous fracture, smoking, γ glutamyl transferase and poor self-rated health.

- Factors associated with mental health and psychological well-being are strong risk factors for low-energy fractures and specified fracture types in middle-aged men.

- Risk factor patterns are similar between hip, vertebral, forearm and proximal humerus fractures, while ankle fractures have a dissimilar risk factor pattern.

- In middle-aged women, a single bone mineral density measurement of the forearm is predictive of future fracture up to 9 years.

- In middle age, risk factors for hip fracture are similar to those in the elderly, but with diabetes identified as a strong risk factor in both sexes.

- Risk factor patterns for cervical and trochanteric hip fractures in middle age seem to differ, implying that trochanteric hip fractures affect individuals with a more frail constitution.

- Impaired glucose tolerance is in middle-aged men and women associated with decreased risk of low-energy fractures.

ACKNOWLEDGEMENTS

This thesis would never have been completed without the help and support of family, colleagues, staff and friends. I thank you all. My special gratitude and reverence I would like to give to:

Kristina Åkesson – a wise and competent, caring tutor. You have with gentle guidance helped me find aim and direction in my research, and been patient with my shortcomings. I hope for further, fruitful cooperation.

Olof Johnell – a man with visions and immense knowledge of research.
You provided the idea and resources for this thesis, thank you!

Birgit Holmberg – my mother, who bore me, raised me and has provided me with a first class "hotel" during the completion of my thesis and my new house. You are my role model.

"My children" – Hjalmar, Albert, Ruben, Ragnar and Astor - you are the sunshine of my life!

Jan-Åke Nilsson for teaching me about statistics, **Peter Nilsson** for teaching me about diabetes, **Annelie Norrby** for putting this thesis together, **Cecilia Rogmark** my room mate who has patiently endured the mess on my desk, and has cheered me up when the difficulties seemed immense, and many, many more. THANK YOU!!!!!!!!!!!!!

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Svensk sammanfattning

Människan har genom evolutionen erhållit ett skelett tillräckligt lätt för snabb förflyttning, och starkt nog för att tåla hög belastning. Men med stigande ålder minskar benets styrka, och risken för fraktur ökar. Sedan årtionden ökar antalet frakturer över hela världen, och i alla ålderskategorier.
Frakturer leder ofta till en längre tids konvalescens, inskränkt rörelseförmåga, sämre livskvalitet, och ibland till döden. Projektet ”Malmö Förebyggande Medicin” är en prospektiv, populationsbaserad studie med 33 346 deltagare, 22 444 män och 10 902 kvinnor, med en medelålder på 44 respektive 50 år. Uppföljningstiden var 19 år för män och 15 år för kvinnor. Studiematerialet ger möjlighet till utvärdering av vanliga folkhälsoproblem t.ex. fraktur och diabetes.

Syftet med denna avhandling var att utvärdera vanligt förekommande riskfaktorer för lågenergi-frakturer hos män och kvinnor i medelåldern, och att identifiera olikheter i riskfaktorprofil, mellan män och kvinnor och mellan olika typer av frakturer. Resultatet ska kunna användas som bas för riskbedömning och modifiering av riskfaktorer för fraktur.

Ett flertal riskfaktorer för fraktur kunde identifieras, med olika inverkan på män och kvinnor, och på olika frakturtyper. De viktigaste riksfaktorerna för fraktur hos kvinnor var stigande ålder, tidigare genomgången fraktur och diabetes. Bland männen var de viktigaste riskfaktorerna stigande ålder, mental ohälsa, högt GT och diabetes. Riskfaktorprofilerna för fotleds- och proximala humerus-frakturer skiljde sig till viss del från de andra frakturtyperna hos både män och kvinnor.
Eftersom diabetes visade sig vara en stark risk faktor för fraktur i medelåldern utvärderades även effekten av förhöjt blodglukos på frakturrisk. Sänkt glukostolerans, diagnostiserad med hjälp av en oral glukosbelastning, minskade risken för multipla frakturer och osteoporosfrakturer hos både män och kvinnor, oberoende av ålder, BMI och rökning. Den exakta orsaken till att hyperglykemi hos icke-diabetiker kan minska frakturrisk, har inte undersökts.
I en substudie av 1294 kvinnor med en medelålder på 53 år, gjordes en bentäthetsmätning i handleden. Denna mätning kunde prediktera frakturrisk 9 år framåt, speciellt för handledsfrakturer.

Denna avhandling har identifierat multipla riskfaktorer för lågenergifrakturer hos medelålders män och kvinnor, med diabetes och mental ohälsa som speciellt viktiga riskfaktorer i denna åldersgrupp. Olikheter i riskfaktorprofil för olika frakturtyper har också påvisats.
Nuvarande behandlingsstrategier och läkemedelsrekommendationer inkluderar inte flera av de nu identifierade riskfaktorerna. Man bör, för att förbättra bedömningen av frakturrisk, addera dessa riskfaktorer till de interventionsalgoritmer som används i medelåldern.

Summary in English

The skeleton is vital for animal life on Earth. In humans of both genders, bone becomes weaker and more susceptible to fracture with advancing age. The number of fractures is increasing worldwide, at all ages. Fractures frequently cause long-term disability, impaired quality of life and sometimes death. The Malmö Preventive Project, a population-based, prospective study, including 22 444 men and 10 902 women, mean age 44 and 50 years respectively, provides data for the evaluation of common public health problems, such as fracture and diabetes. The follow-up period was 19 years for men and 15 years for women.

In this study, risk factors for common low-energy fractures were evaluated in women and men as a mean to create a basis for risk assessment and risk factor modification. A further objective was to identify differences in risk between men and women, and between typical fragility fractures.

Multiple risk factors for fracture were identified. These factors had a different impact in men and women, and differed between fracture types.
In women, the most important risk factors for fracture were; advancing age, previous fracture and diabetes. In men, the most important risk factors for fracture were advancing age, mental health problems, a high level of γ glutamyl transferase - an indicator of liver dysfunction or alcoholism, and diabetes. In both men and women risk factors for ankle fracture and proximal humerus fracture differed to a certain extent from risk factors for other fragility fractures.
Identification of diabetes as a significant risk factor for fracture in middle age, led to the evaluation of possible effects on long-term fracture risk, in relation to glucose tolerance.
Impaired glucose tolerance in middle-aged men and women, evaluated through an oral glucose tolerance test, was associated with a decreased risk of multiple fractures as well as of osteoporotic fractures, independent of age, BMI and smoking. The exact mechanism by which the hyperglycaemic status in non-diabetics protects against fracture remains to be explored.
A substudy of 1294 women, at an average age of 53 years, confirmed that a single bone mineral measurement of the ultradistal forearm could predict fragility fractures for up to 9 years, and specifically forearm fractures.

This thesis has identified multiple risk factors for low-energy fracture, in both men and women, highlighting diabetes and mental health problems as major contributors in this age group. The study has identified differences in risk factor pattern for each fracture type, albeit with large overlaps. Current management strategies and therapeutic guidelines are not addressing a number of the identified risk factors. Subsequently, risk assessment can be substantially improved by adding these risk factors to intervention algorithms for middle-aged individuals.