TILBURG ◆ UNIVERSITY

Tilburg University

Guidelines and bio-psychological aspects in fracture risk management

Verdijk, N.A.

Publication date:
2009

Citation for published version (APA):
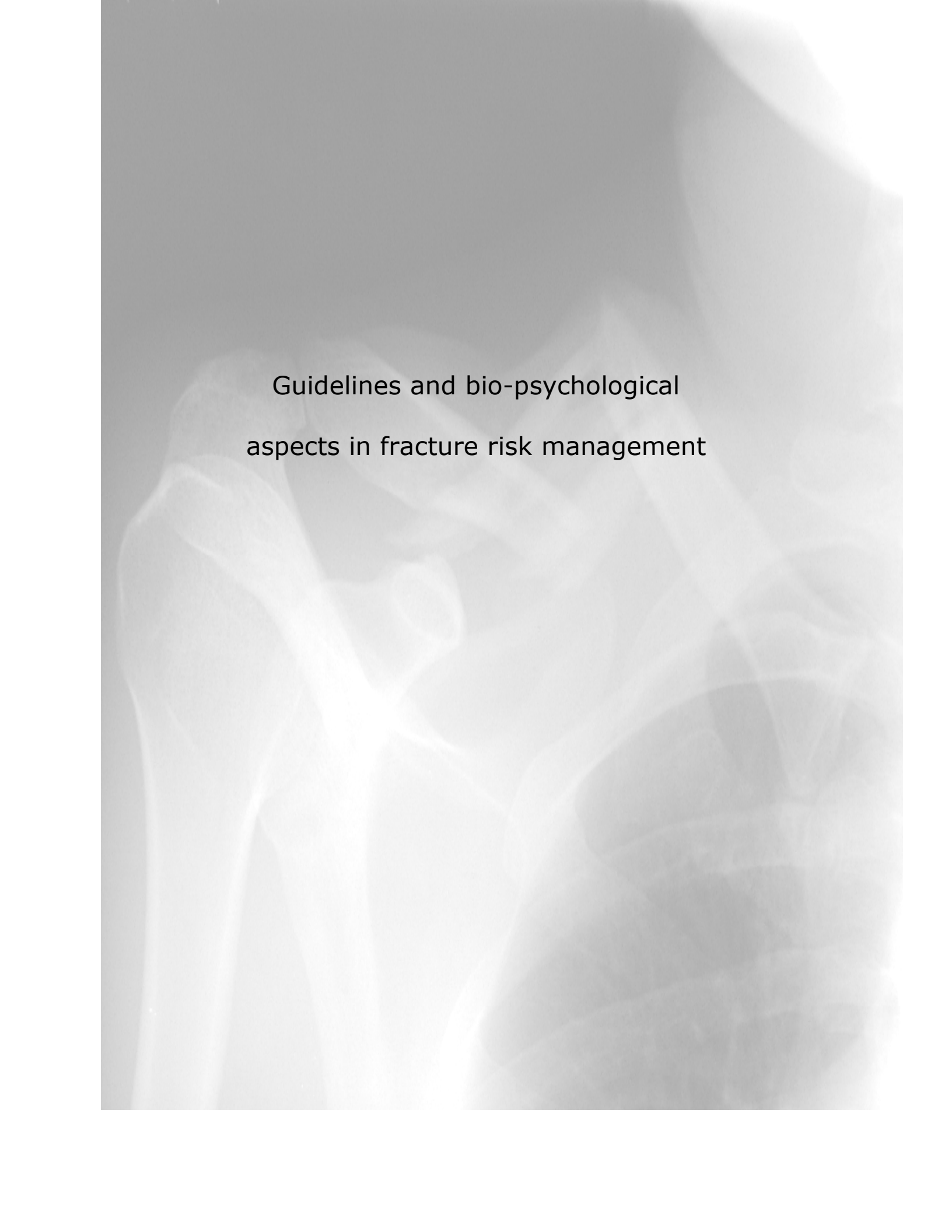Verdijk, N. A. (2009). *Guidelines and bio-psychological aspects in fracture risk management*. Prismaprint.

Guidelines and bio-psychological aspects in fracture risk management

Cover adapted from:

http://images.google.nl/imgres?imgurl=http://injuryupdate.com.au/images/clavicle_

fracture.JPG&imgrefurl=http://injuryupdate.com.au/injuries/shoulder/fractured_clavi

cle.php&usg=__I8KeIPrBKqKL5jtZhXA3wWUz6i0=&h=960&w=1280&sz=425&hl=nl&

start=4&um=1&tbnid=UT_ajxsvbkz_0M:&tbnh=113&tbnw=150&prev=/images%3Fq

%3Dclavicle%2Bfracture%26hl%3Dnl%26rlz%3D1T4SUNA_enNL262NL262%26sa%

3DN%26um%3D1

Guidelines and bio-psychological aspects in fracture risk management

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit van Tilburg op gezag van de rector magnificus, prof. dr. Ph. Eijlander, in het openbaar te verdedigen ten overstaan van een door het college voor promoties aangewezen commissie in de aula van de Universiteit op vrijdag 11 december 2009 om 10.15 uur,

door Noortje Annemarie Verdijk

geboren op 28 december 1981 te 's-Hertogenbosch

Promotor

Prof. dr. V.J.M. Pop

Copromotores

Dr. G.L. Leusink

Dr. R.J. Erdtsieck

DANKWOORD

Op dit proefschrift staat mijn naam, maar dat wil niet zeggen dat ik alles alleen heb gedaan. Ik wil een aantal mensen bedanken zonder wier inspanningen ik dit proefschrift nooit had kunnen afronden.

In de eerste plaats wil ik mijn promotor, prof. dr. Victor Pop bedanken. Beste Victor, ondanks dat ik met mijn afstudeeronderzoek geen hoge ogen gooide zag jij mogelijkheden en heb jij me deze kans geboden. Je tomeloze enthousiasme heeft er zeker toe bijgedragen dat dit proefschrift nu echt af is. Daarnaast heb je me niet alleen geïntroduceerd in de wereld van het wetenschappelijk onderzoek, maar ook bij PoZoB en daar ben ik je zeer dankbaar voor. Ook wil ik mijn copromotores dr. Geraline Leusink en dr. Ronald Erdtsieck bedanken. Geraline, bedankt voor het delen van je uitgebreide kennis over osteoporose en de gezondheidszorg in het algemeen. Je persoonlijke betrokkenheid was erg prettig en ik heb veel van je geleerd. Ronald, jouw feilloze kennis en oog voor detail zijn erg belangrijk geweest voor de kwaliteit van dit proefschrift. Zonder de tijd die je steeds voor me vrij maakte had dit proefschrift er zeker anders uit gezien.

Heel veel dank ben ik schuldig aan Martha Caers. Martha, de lange periode van dataverzameling viel mij soms zwaar, maar werd met jouw hulp een heel stuk dragelijker. Met een gerust hart kon ik de dataverwerking aan je overlaten; ik ken weinig mensen die zo nauwgezet en precies werken. Bedankt ook voor je gezelligheid in de afgelopen jaren en ik ben er gerust op dat je tijdens de verdediging achter me staat. Nimf Liesbeth, dat geldt natuurlijk ook voor jou!

Marscha Schröder, Monique Vos en Riekie Beers: bedankt voor jullie input en medewerking vanuit de Fractuur en Osteoporose poliklinieken van het Maxima Medisch Centrum en Catharina Ziekenhuis Eindhoven. Zonder

jullie hulp was dit proefschrift niet mogelijk geweest. Dr. Marion Blonk, bedankt voor de tijd die je nam om mee te denken en te schrijven aan de artikelen, voor je bevlogenheid en kennis. Arnold en Niels, bedankt voor de kans en het vertrouwen die jullie mij hebben gegeven om me de afgelopen jaren ook op ander vlak te ontwikkelen. Naast al wat ik er van (ge)leer(d heb), bood het mij de afwisseling die ik nodig had om mijn proefschrift tot een goed einde te brengen. Thomas, bedankt voor de prachtige omslag die je voor mijn proefschrift hebt ontworpen en je flexibiliteit in dit proces. Pieter, last but no least wil ik jou bedanken: je weet wel waarvoor.

Noortje Verdijk,

September 2009

Contents

Chapter 1

General Introduction
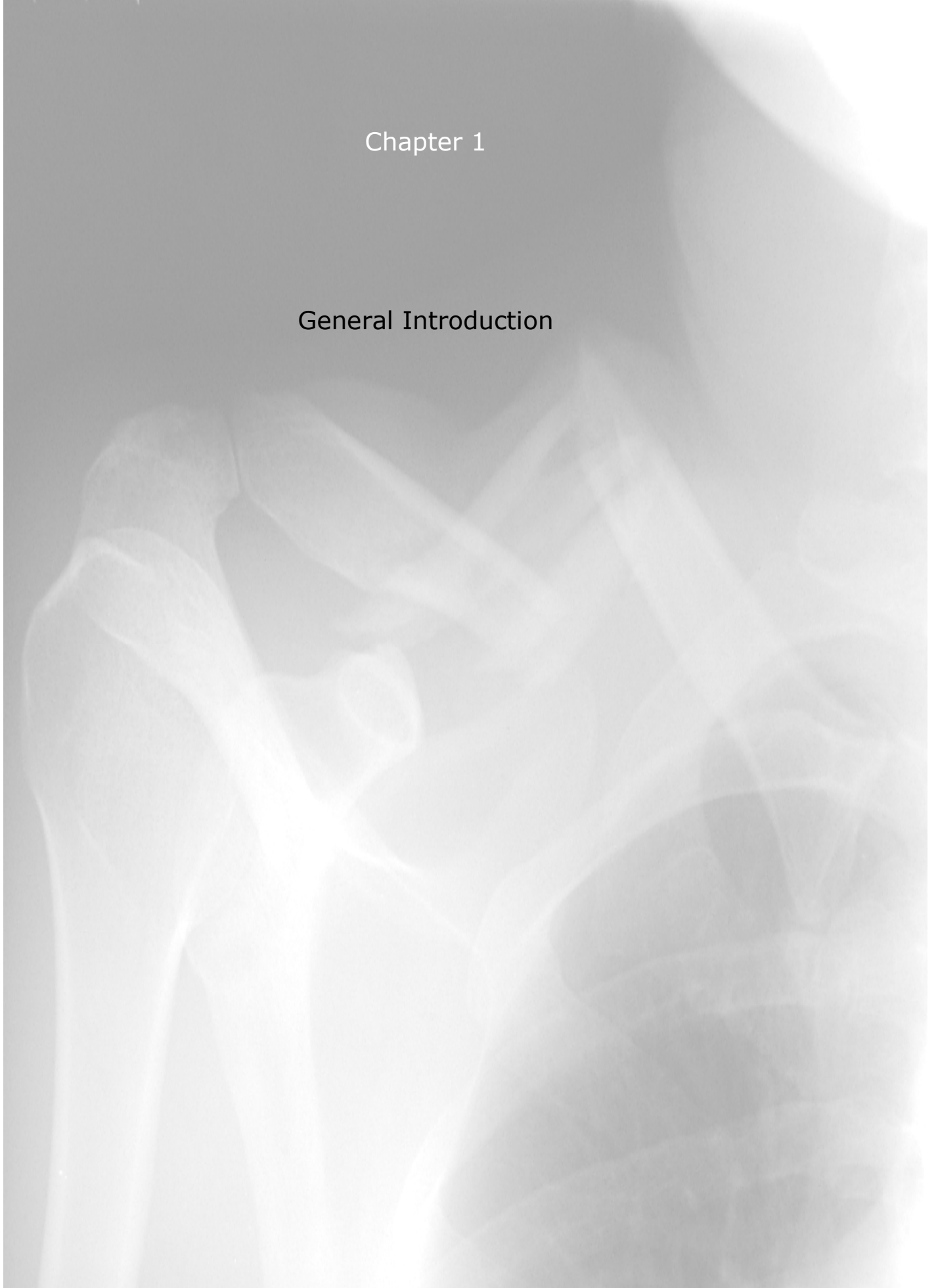
1. INTRODUCTION

Elderly represent the fastest growing population in the world. Within thirty years, the population of people of 65 years or older is about to double and even triple in some countries[1]. In 2007, 14% of the Dutch population was 65 years or older and it has been estimated that this will rise to 24% by 2050[2]. Figure 1 represents the burden of chronic diseases due to ageing and growth of the population[3]. As can be seen, the largest absolute increase between 2005 and 2025 is expected in patients with diabetes and osteoporosis. In 2005, about 640,000 women and 210,000 men suffered from osteoporosis in the Netherlands. Based on demographic changes, an overall increase of 41% is expected between 2005 and 2025 (37% in women and 50% in men), implying that by 2025 over 1 million persons will suffer from osteoporosis[3].

Figure 1. Absolute increase in the prevalence of chronic diseases in the Netherlands 2005-2025[3].
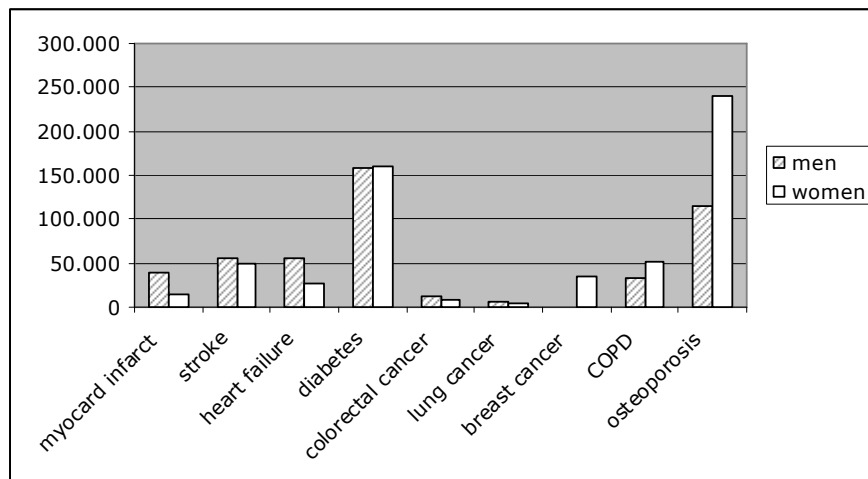
2. DEFINITION OF OSTEOPOROSIS

About 150 years ago, Sir Astley Cooper was the first to observe a relationship between bone fragility and (hip) fracture. The first medical discussions about this subject occurred in the 19th century when French and German physicians described the histologic appearance of osteoporotic bone[4]. In clinical practice, osteoporosis is described as a systemic skeletal disease characterized by low bone mass and microarchitectural derangements, resulting in an increased fracture risk. The World Health Organization (WHO) has defined osteoporosis in bone mineral density (BMD) T-scores[5]. T scores describe the number of standard deviations (SD) by which an individuals BMD value (expressed in grams of mineral per square centimetre) differs from the mean BMD value of the healthy adult population. The WHO classifies patients into three categories, based on T scores: patients with normal BMD have a score higher than −1.0 SD. A T-score between −1.0 SD and −2.5 SD is the criterion for osteopenia (low bone mass). Osteoporosis is defined in case of a T-score ≤ -2.5 SD. When osteoporosis is accompanied by a fragility fracture, established or severe osteoporosis is diagnosed. In addition, a Z-score has been defined, which compares the individual BMD value with the mean BMD value of an age and sex adjusted referential group. Because T-scores may be blunted by other medical ageing conditions in the oldest elderly, the Dutch guidelines recommend the use of Z-scores for the diagnoses of abnormal bone density in patients over 70 years[6,7]. Abnormal bone density is defined as a Z score of -1.0 SD or less.

Osteoporosis can be subdivided into primary and secondary osteoporosis. Primary osteoporosis includes cumulative bone loss or senile osteoporosis and postmenopausal bone loss. In women, declining bone density reaches thresholds for the diagnosis of osteoporosis from menopause[8]. In

12

secondary osteoporosis, accelerated bone loss is caused by chronic medical conditions such as endocrine, haematological, gastrointestinal or connective tissue diseases[9]. Although the exact prevalence of secondary osteoporosis in unknown there are indications that the prevalence is higher than generally assumed[10,11]. The clinical relevance of primary as well as secondary osteoporosis lies in the fractures that arise.

3. THE BURDEN OF FRACTURES

During lifetime, osteoporotic fractures affect one out of two women and one out of five men[12]. In 2000, about 9 million people suffered from osteoporotic fractures worldwide, of which 3.8 million in the European Union[13]. In the Netherlands about 83,000 people aged over 55 years suffer from a fragility fracture each year[6,14]. The burden of these fractures can be discussed at different levels. On the one hand, society is faced with increasing costs resulting from fractures. On the other hand, fractures can have a major impact on individual patients by its physical, psychological and social consequences.

The financial burden related to fractures includes direct and indirect medical costs as well as direct and indirect non-medical costs, such as loss of productivity[15]. Due to variation in resource use, price levels, the application of diagnostic and therapeutic tools and economical differences, the financial burden of osteoporosis varies between regions. Available information regarding the costs of osteoporosis and fractures mainly concerns the Western world[16]. The National Osteoporosis Foundation reported that the financial burden of osteoporotic fractures in the US in 2005 was $19 billion (€13 billion), and is expected to exceed $25 billion (€17 billion) by the year 2025[17]. In the UK, the costs have been estimated

at £1.7 billion (€2.4 billion) each year[18]. In 2000, the financial burden of osteoporotic fractures in the European Union was estimated at 31.7 billion euro's[19]. By 2050, the direct cost of fractures in Europe will be more than €75 billion. In the Netherlands, the current annual medical costs due to osteoporotic fractures are estimated at € 500 million[14]. It is expected that these costs will exceed one billion euro's by the year 2025. Worldwide, the expenditures for osteoporotic fractures are rising faster than general economic inflation[12].

In addition to financial consequences, osteoporotic fractures can majorly affect a patient's life by physical, psychological and social consequences. Of all osteoporotic fractures, hip fractures are believed to be the most severe as they carry the highest morbidity and mortality. Hip fractures immediately cause loss of daily functioning and often necessitate hospitalisation. Mortality rates after a hip fracture have been estimated at 20% in the first year and about 30% of hip fracture patients requires nursing home care. Less than one third regains their original level of physical functioning[20,21]. The expectations are similar for vertebral fractures[22], and may additionally include physical consequences such as back pain and kyphosis. Although wrist fractures have not been associated with mortality[23], only half of the patients will regain good functioning six months after fracture[24]. The above consequences of osteoporotic fractures can easily turn autonomous individuals into dependent patients[25], as they affect interpersonal relationships and social roles: inadequacy in performing simple daily tasks may result in feelings of incapability, low self-esteem, decreased well-being and decreased quality of life. Research showed that feelings of hopelessness, worthless and dissatisfaction are strongly related to fractures[26] and that depressive feelings may occur after hip fracture[27]. In Europe, osteoporotic fractures account for more

14

Disability Adjusted Life Years lost than common cancers, with the exception of lung cancer[13].

4. DEFINITION OF FRACTURES

Osteoporosis is commonly defined by assessing BMD using Dual X-ray Absorptiometry (DXA). The problem however is that despite a high specificity, the sensitivity to predict a fracture is low[28]. Hence, a substantial amount of fractures occurs in persons without osteoporosis[29]. The sensitivity of bone mass measurement to predict fractures can be markedly improved by the integration of other risk factors, without a negative effect on specificity[30]. Because the burden of osteoporosis lies in the fractures that arise, it is currently argued that attention should go out to identifying patients at high fracture risk rather than to patients with low BMD/ osteoporosis[31].

The shifting focus from osteoporosis towards fractures as a health problem demands an accurate definition of fractures as an outcome variable in research. However, the literature is rather unclear about the definition of fractures. Common sites for fractures that are associated with osteoporosis are the hip, spine, distal forearm and humerus[31]. These fractures are generally referred to as osteoporotic fractures, even in the absence of bone densitometry, and have been studied intensively[32]. As osteoporotic fractures also occur at many other sites, several cohort studies on osteoporotic fractures have additionally included fractures of the pelvis, tibia and fibula (in women), ribs, clavicle, scapula, and sternum[32,33]. Furthermore, other cohort studies on osteoporotic fractures rather refer to low trauma fractures[22,23], which have been defined as various types of fractures caused by a fall from standing height or less.

Because the burden of fractures goes beyond fractures of the hip, spine and arms[22,32], and because the risk of a subsequent fracture is increased after any type of prior fracture[34], we defined fractures as low trauma fractures within the studies of this thesis.

5. PATHOPHYSIOLOGY OF FRACTURES

Fractures not only result from low bone mass. In addition, bone architecture, the risk of falling and force of impact are important aspects in fracture risk.

5.1 Bone strength

It is estimated that between 75 and 90% of variance in bone strength is related to bone mineral density[35]. The other part is determined by bone quality, which comprises bone architecture, damage accumulations (micro fractures), bone turnover and mineralization. Bone architecture is characterized by geometry (size and shape) and micro-architecture of the bones (trabecular thickness, connectivity and cortical thickness/ porosity, collagen composition). The skeleton grows continually from birth to the end of the teen years and reaches a maximum strength and size (peak bone mass) in the early adulthood, around the mid-20s. However, the replacement of 'old' bone tissue by new bone continues throughout life. This process is called bone turnover, and determines the balance between bone formation (construction) and bone resorption (destruction). Bone metabolism is affected by hormones, genetic predisposition, and life style habits such as vitamin D and calcium intake, physical activity and smoking.

5.2 Force of impact

About 70% of fractures result from falls[36]. However, in subjects aged 55 years or older, only 1-6% of falls result in a fracture[37]. This implies that the mechanism of falling is also important. For example, research showed that specific floors, such as carpet, may reduce femoral impact force up to 50% by providing a modest degree of force[38]. In addition to energy absorption, the type of fall and protective responses also determine the force of impact. With the exception of spontaneous vertebral fractures, the force of impact of a fall increases as the ability to properly react to falls diminishes.

5.3 Falls

The risk of falls is affected by several factors, which will be discussed below. Impaired mobility, which includes impaired balance, gait, and muscular strength increases the risk for falls[37,39]. Although all aspects of mobility are associated with increased risk of falls, impaired balance has been most often and strongest related with falls[37]. Impaired mobility is an important aspect in fall prevention as it can be affected by training and (physio)therapeutic interventions[40]. Furthermore, a history of falls is a predictor for future falls[41]. Another risk factor is the use of cardiovascular and psychotropic medications, which includes the use of hypnotics, tranquillisers, benzodiazepines, anti-depressant drugs, neuroleptics, sedatives, and antipsychotics. Mechanisms by which drugs may increase the risk of falling are related to central nervous/neuromuscular and blood pressure lowering effects. Particularly polypharmacy has frequently been related to falls[42]. In addition, physical activity has repeatedly been associated with falls. Physical activity is often expressed in the amount of time or intensity spent on daily activities such as walking, cycling,

gardening and household. So far there is no consensus on the nature of this relationship. On the one hand, high levels of physical activity may positively affect balance and muscle strength and may therefore reduce the risk for falling. On the other hand, people with high levels of physical activity may be more prone to high-risk situations[43]. Furthermore, the intensity of physical activity may also play a role. Several joint related diseases have also been identified as a risk factor for falls. Patients with joint related diseases have a two to three times higher risk of falling than patients without joint related diseases, as joint related diseases may result in impaired gait[37]. Another risk factor for falls is impaired sight, which includes impaired depth perception and visual acuity[44]. Moreover, urine incontinence may increase the risk of falls[45]. This relationship might be explained as urine incontinence is assumed to represent overall vulnerability in elderly as well as decreased neuromuscular function. Parkinson's disease has also been identified as a risk factor for falls[46], because patients often develop gait and balance problems which may increase the risk to fall. In addition, depressive symptoms have been associated with an increased risk for falls. It has been suggested that impaired physical activity, decreased attention for the environment and the use of psychotropic medications may play a role[26]. Finally, cognitive dysfunctions have been associated with falls. It is assumed that impaired cognitive functioning is among others expressed in loss of focus and attention[47].

6. CLINICAL RISK FACTORS OF FRACTURES

As discussed before, low bone density is an important aspect in fracture risk. Research showed that for each standard deviation fall in BMD fracture risk increases about 1.5-3.0 fold[31,48]. However, the predictive value of absorptiometric techniques to predict fractures is low and can be improved by concurrent consideration of other factors that affect fracture risk[30]. Several risk factors have been identified that affect fracture risk over and above BMD, age and sex. These risk factors will be discussed below.

6.1 Low body weight

A low body weight is considered as a characteristic of frailty and has been associated with increased fracture risk in several studies[49]. For example, a recent study on the estimation of fracture probability in a sample of 4157 Dutch women showed that a body weight below 64 kilos was associated with increased fracture risk[50]. Others rather defined low body mass index (BMI) as a factor in fracture risk. It has been shown that the risk for a hip fracture is increased in subjects with a BMI of 20 kg/m^2 or less[51].

6.2 History of fragility fracture

Research showed that a fragility fracture is an important risk factor for subsequent fractures. It is estimated that about 40% to 60% of elderly will suffer a subsequent fracture within 10 years after a primary fracture[34]. Moreover, Klotzbuecher et al. reported that the risk for a hip or vertebral fracture is about 2 times greater in subjects with any prior fractures than in subjects without any prior fracture[52]. The increase for a subsequent vertebral fracture after a prior vertebral fracture is even more marked[53].

6.3 Family history of fragility fractures

A family history of fragility fractures has been identified as a significant risk factor that is largely independent of BMD. Moreover, a family history of hip fracture is a stronger risk factor than a family history of other osteoporotic fractures[54].

6.4 Smoking

Current smokers have a significantly increased risk of any fracture compared to non-smokers, independently of BMD, age and sex. A higher risk has been observed for hip fractures, especially in men. Although a history of smoking also increases fracture risk, risk ratios for current smoking are stronger[55].

6.5 Alcohol use

The relation that exists between alcohol usage and fracture risk is dose-dependent. Moderate alcohol intake has been associated with higher levels of BMD in postmenopausal women. However, a daily alcohol intake of 3 or more units has been associated with an increased fracture risk. It has been suggested that high alcohol intake is associated with low BMD by affecting osteoblasts or endogenous secretion of calcitonin. Furthermore, excessive alcohol intake has been associated with poor nutrition regarding the intake of calcium and vitamin D and may additionally increase the risk for falls. Moreover, it may negatively affect the response after falling[56].

6.6 Longterm use of glucocorticosteroids

The use glucocorticosteroids in elderly is estimated at 2.5%, with an average treatment period of 1.3 years and is associated with a decrease in BMD in about 50% of the users. Bone loss especially occurs within the

first six months after usage, and may cause secondary osteoporosis. The effect of corticosteroids on BMD dependents upon the duration and dose[57]. In the Dutch guidelines for general practitioners[7], a threshold of 7.5 mg per day during a period of at least 3 months has been described as a 'high dose' that may affect bone density. Based on a meta-analysis, it has been shown that prior and current systematic use of corticosteroids increased fracture risk, independently of BMD, age and sex[58].

6.7 Rheumatoid arthritis

As discussed before, secondary osteoporosis can be described as accelerated bone loss caused by chronic medical conditions. Several medial conditions have been identified that may increase fracture risk, such as inflammatory bowel disease and endocrinological disorders. Rheumatoid arthritis has been shown to independently affect fracture risk, after correction for corticosteroid use and BMD. For other diseases it remained unclear to what extend the medical conditions affect fracture risk[58].

6.8 Other risk factors

In addition to the above, other risk factors have been related to fractures, however not independently of low BMD. Commonly described factors are genetic factors, sex hormones (early menopause), vitamin D deficiency, endocrine diseases (Cushing's syndrome, hyperparathyroidism), low calcium intake and physical inactivity[4].

7. PSYCHOLOGICAL RISK FACTORS

During the last decennia, character traits, behavioural patterns, and psychiatric disorders have been associated with the onset and course of

several chronic medical conditions, such as coronary artery disease and diabetes. Although psychological factors are not considered as primary risk factors for osteoporosis and fractures, there are indications that fear of falling and depression may play a role.

7.1 Fear of falling

Fear of falling is highly prevalent among elderly[59,60] and has been associated with restricted and reduced levels of physical and daily activity[61,62]. Furthermore they have been related to depressive disorders, symptoms of depression and feelings of anxiety[62,63]. In a population-based prospective study, Friedman et al. showed that falls are an independent predictor for fear of falling after 20 months and moreover, that fear of falling at baseline is an independent predictor for falls at 20 months[64]. Although only five percent of falls results in a fracture[65,66], approximately 70% of fractures are caused by a fall[36]. Luukinen et al. showed that frequent fear of falling was a risk factor for fracture-causing falls in elderly women[67].

7.2 Depression

Depressive disorders are the fourth most important cause of disability worldwide and are expected to have become second by 2020[68]. Regarding the prevalence and definition of depression, a difference must be made between depressive syndrome and symptoms. Depressive syndrome (major depressive disorder; MDD) refers to a set of symptoms with at least one of the major signs of depression (low mood or loss of interest)[69], and several symptoms such as sleeping problems, cognitive dysfunction or eating problems. These symptoms have to be prominent for at least two weeks, with a major negative impact on daily activities. Patients with sub-

threshold depression have symptoms of depression, but do not meet DSM-IV criteria for major depression[70]. In the general elderly population, the prevalence of depressive syndrome is 1 to 3%[71], whereas clinically relevant symptoms of depression occur in 8 to 16%[72]. Depressive disorders are often chronic and have been associated with a wide range of physiological changes and poor health conditions, also in the elderly[70,72]. Chronic depression more often occurs at symptom than at syndrome level[73]. Nevertheless, depressive symptoms affect well-being and psychosocial functioning with nearly the same degree of impairment as depressive syndromes[71,74].

From the 1980s on, researchers first started to investigate the relation between depression and osteoporosis. Subsequent studies pursued a distinct perspective and investigated depression as a risk factor for bone loss and fractures[75]. Several biological processes have been suggested to explain this association, of which hyperactivity of the hypothalamic pituitary-adrenal (HPA) axis and resulting hypercortisolism are most often referred to. From behavioural perspective it has been suggested that the use of psychoactive drugs and poor health behaviour, such as physical inactivity, nutritional deficiencies, comorbidity, excessive alcohol use and smoking may negatively affect bone strength and therefore increase the risk of falls and fractures. Furthermore, it has been shown that depression as an adverse outcome of osteoporotic fractures may negatively affect recovery after fracture[76,77].

8. DISEASE MANAGEMENT

Nutrition and exercise are known to affect peak bone mass and bone turnover. For the prevention of osteoporosis sufficient physical activity

and intake of calcium and vitamin D can be promoted to achieve maximum peak bone mass in youth: physical inactivity has been related to low BMD and increased (prior and subsequent) fracture risk[43]. There are indications that increased physical activity positively affects BMD and may reduce the risk for falls[43,78]. However, there is no strong evidence that it reduces fracture risk. In addition to adequate nutrition and exercise, prevention from smoking and excessive alcohol intake may also have a positive affect on bone density. The above lifestyle factors for building strong bones are also applicable to adults to prevent excessive cumulative bone loss.

Regarding the prevention of fractures, a difference can be made between primary and secondary prevention. Primary fracture prevention is aimed the prevention of a prior fracture in patients with osteoporosis. During the last decades, several national and international case-finding methods have been designed to prevent prior fractures by the identification of patients with osteoporosis[79]. In 2005, the Dutch College of General Practitioners published guidelines for general practitioners including a case-finding method to select patients at risk for osteoporosis for bone densitometry[7]. Recently, case finding methods have been designed which primarily focus on the identification of subjects with a high risk profile for fractures instead of osteoporosis: in 2008, the WHO introduced the FRAX® tool to estimate fracture risk by clinical risk factors with or without the integration of BMD value[80]. In addition, a Dutch tool has been designed to estimated fracture risk in the elderly[81].

Secondary prevention is aimed at the prevention of subsequent fractures in patients with an established fragility fracture. According to the guidelines of the CBO it has been recommended that fractured patients should be evaluated for osteoporosis[6]. Because the implementation of this

policy showed to be poor[82], fracture and osteoporosis outpatient (F&O) clinics have been introduced to increase adequate identification of osteoporosis. After a fragility fracture, all patients over 50 years receive Dual X-ray Absorptiometry (DXA) measurement and are screened for clinical risk factors. Research on Dutch F&O clinics showed that they are effective and useful for the identification of patients with osteoporosis[82-84]. According to the CBO guidelines[6], pharmacological treatment is recommended to patients with osteoporosis based on the DXA outcome. According to the European Guidance for the diagnosis and management of osteoporosis in postmenopausal women, pharmacological treatment is recommended in all women with a prior fragility fracture, irrespective of their bone density[31]. Effective treatment options are available that have been shown to maintain bone density and reduce fracture risk in patients with osteoporosis within one year. Common treatments are bisphosphonates (alendronate, ibandronate, risedronate), calcitonin, raloxifene, strontium ranelate, teriparatide and tibolone[17]. Calcium and vitamin D supplements may additionally be prescribed to ensure adequate intake, and to ensure maximum effectiveness of the pharmacological treatment. In addition, exercise programs have been defined[43]. As was discussed before, physical activity may further increase bone strength and prevent from falls. Moreover, hip protectors have been developed which can be used for additional fracture prevention[85].

9. AIM OF THE THESIS

This thesis concerns primary and secondary fracture prevention. The aims are to study (i) the current use of risk factors for primary and secondary fracture prevention in general practice and fracture clinics in the

Netherlands and (ii) the value of psychological factors for fracture risk estimation. Hence, the research questions of this thesis are as follows:

Part I: guidelines in fracture risk management.

The aim of this part is to study the current use of risk factors for primary and secondary fracture prevention in general practice and fracture clinics in the Netherlands. The research questions are as follows:

1. How valid are the guidelines of the Dutch College of General Practitioners to identify by case-finding patients at high risk for osteoporosis and is alternative usage advisable?

2. Is the current treatment policy in fracture clinics accurate for subsequent fracture prevention?

Part II: bio-psychological aspects of fracture risk management.

This part is aimed at the investigation of psychological factors as risk factors for fractures and includes the following research questions:

1. Are depression, osteoporosis and fractures related according to literature?

2. Is assessment of depressive symptoms in older fractured women advisable?

3. Are there psychological risk factors which should be included in the risk profile for subsequent fractures?

To answer these questions, two health care projects on osteoporosis were conducted. The first project is part of a larger project called FRACture PREvention Zuid Oost-Brabant (FRACPREZOB) and has therefore been named FRACPREZOB-II. The second projects is the Eindhoven Subsequent

Fracture and Osteoporosis Reduction Project (ESFOR-p). The research designs of these projects will be discussed below.

10. RESEARCH DESIGN

10.1 FRACPREZOB-II

In 2006 and 2007, a large project on osteoporosis, called Fracture Prevention Zuid Oost Brabant (FRACPREZOB), took place in the South East of the Netherlands. According to the guidelines of the Dutch College of General Practitioners[7], case-finding was conducted in the general practitioners' population. Over 21,500 patients were included in this project, who received a questionnaire regarding the risk factors for osteoporosis according to the case-finding method, in interrogative form. For 17,500 subjects who returned the questionnaire (response rate 81%), a sum score was calculated based on the weighted scores described in the case-finding method of the Dutch guidelines. Over 1800 subjects were invited for DXA measurement, of which 1100 subjects responded (61%). Of these, 203 were diagnosed with osteoporosis according to DXA measurement.

This thesis describes a part of the FRACPREZOB project, called FRACPREZOB-II, which was especially designed to assess the validity of the case-finding procedure as recommended by the guidelines of the Dutch College of General Practitioners. Therefore, the population of one general practice was screened for osteoporosis. Because this project was conducted as a part of a regular health care project (FRACPREZOB), ethical approval was not applicable. However, patients were informed about the goal of the FRACPREZOB-II project and were requested to sign

informed consent for inclusion in data analysis. The participation of subjects in the FRACPREZOB and FRACPREOB-II projects is described in a flowchart (figure 2). As can bee seen, 444 patients (345 women and 99) of a Dutch general practice (without known diagnosis of osteoporosis or terminal illness) were invited for DXA measurement in the FRACPRERZOB-II project, during a period of six months in 2006. Eligible were all female patients between 50 and 85 years and male patients between 65 and 85 years. These cut offs were based on the knowledge that declining bone mineral density reaches thresholds that indicate osteoporosis from the age of 50 years in women and from the age of 65 years in men[8,17]. Bone mineral density measurements were collected at the total hip, femoral neck and lumbar spine using DXA technology (hologic QDR 4500W, version 12.4).

Figure 2. Flowchart of participation in the FRACPREZOB projects

FRACPREZOB   FRACPREZOB II

FRACPREZOB	FRACPREZOB II
21736 questionnaires sent	444 questionnaires sent
17566 questionnaires returned (RR 81%)	293 returned questionnaires (RR 66%)
1819 invitations for DXA measurement	
1117 DXA's performed (RR 61%)	296 DXA measurements (RR 67%)

203 osteoporosis (18%)	331 osteopenia (30%)	583 normal BMD (52%)

RR = response rate

28
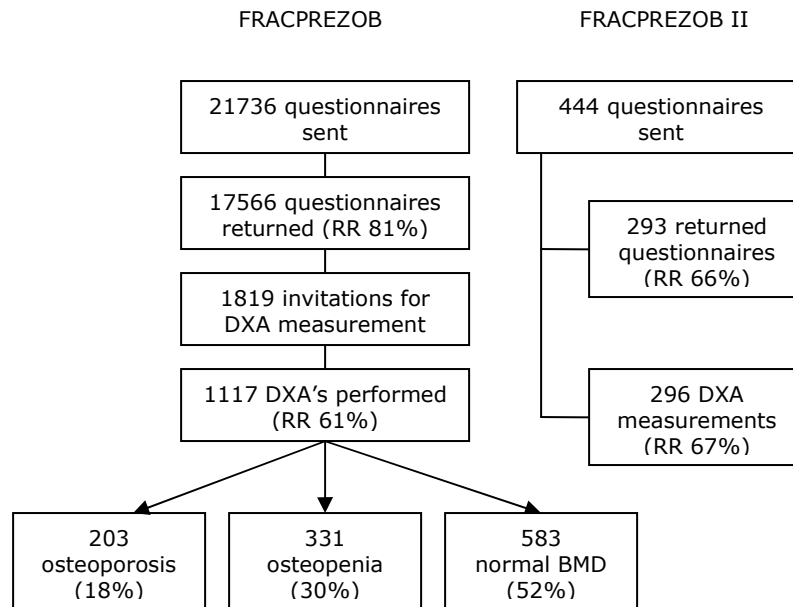
Values were expressed in T scores and Z scores based on the NHANES database references for the hip and hologic database references for the spine. In addition, participants were asked to fill in a purpose-designed questionnaire, including demographic characteristics and questions regarding the risk factors according to Dutch case-finding method in interrogative form. Written informed consent was received from 234 women and 65 men (response rate 67%). This loss was not selective as there were no significant differences in sex, age and socio-economic status between the non-responders and the participants (data not shown). Only participants who completed both DXA measurement and the questionnaire were included for analyses: 226 women and 64 men. Table 1 summarises the characteristics of the research population.

Table 1. Patients' characteristics of the FRACPREZOB-II project

	Total (N=290)		Females (n=226)		Males (n=64)	
	n	%	n	%		
Mean age (SD)	63 (9)		61 (8)		72 (5)	
Risk factors guidelines						
Vertebral fracture	4	1	2	1	2	3
Long-term use of high dose corticosteroids	17	6	14	6	3	5
Fracture after age of 50 yrs	26	9	23	10	3	5
Age >70 yrs	65	22	32	14	33	52
Age >60 yrs	109	38	78	35	31	48
Hip fracture 1st degree family member	41	14	28	12	13	20
Weight <60 kg	44	15	41	18	3	5
Severe immobility	28	10	19	8	9	14
Risk score ≥ 4	43	15	38	17	5	8
DXA outcome						
Osteoporosis[a]	41	14	32	14	9	14
Osteopenia	146	50	117	52	29	45
Normal bone density	103	36	77	34	26	41

10. 2 ESFOR-p

In the period between October 2006 and July 2008, all eligible patients of the fracture and osteoporotic (F&O) outpatient clinics of two hospitals in the South of the Netherlands were invited to participate in a prospective cohort study on the effects and processes of osteoporosis and subsequent fractures, called the Eindhoven Subsequent Fracture and Osteoporosis Reduction-project (ESFOR-p). Subjects with low BMD (osteoporosis or osteopenia) were randomly divided in an intervention group (A1) and control group (A2). Subjects with normal BMD were allocated to a separate control group (B). Participants in the intervention group were visited at home by researchers each six months, and were telephonically contacted in between the visits, during a period of two years at maximum. At the visits, information regarding risk factors and (psycho)social consequences of fractures was collected using standardized interviews, tests and questionnaires. Subjects of the control groups received the same set of questionnaires by post, with an interval of 12 months. Inclusion criteria were defined as follows: (1) age of 50 years or over, (2) a recent low trauma fracture, (3) sufficient knowledge of the Dutch language and (4) sufficient cognitive abilities. The follow-up period ends in December 2009. The Medical Ethical Committee of the Maxima Medical Centre approved this study.

All patients who visited the F&O clinics were informed about the study by the fracture nurses and were handed an information letter. Patients who were willing to participate gave permission to be telephonically contacted by the researchers for further outlines of the study and to inform on their final decision regarding participation. A flowchart of participation is described in figure 3. As can be seen, 1339 patients visited the clinics (mean age 66 years (SD=9.5); 40% osteoporosis, 37% osteopenia and

22% normal BMD). Of these, 738 patients were interested to participate (mean age 66 years (SD=8.7); 42% osteoporosis, 36% osteopenia and 21% normal BMD) of which 534 patients signed informed consent and met the inclusion criteria. Table 2 presents their characteristics. Despite the low response rate (40%) there were no significant differences in mean age and incidence of osteoporosis, osteopenia and normal BMD between our population and the overall population that visited the clinics between October 2006 and July 2008.

Figure 3. Flowchart of the participation in ESFOR-p

patients of the F&O clinic
1339

Not interested
601

Interested
738

Available
720

Exclusion criteria
18

A1
306

A2
267

B
147

Not interested
99

Not interested
61

Not interested
26

A1
207

A2
206

B
121
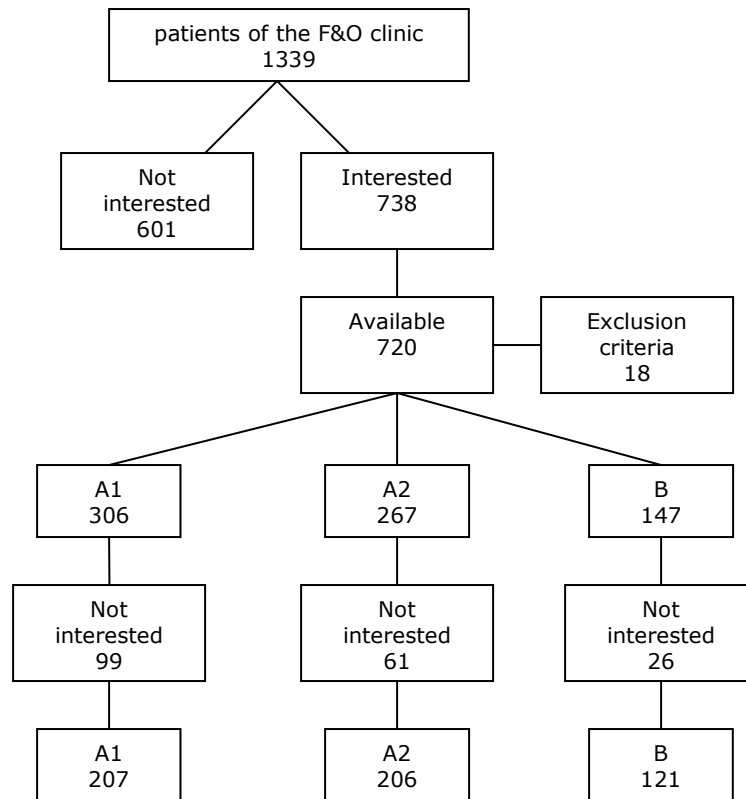
Table 2. Characteristics of 534 patients of the Dutch Fracture & Osteoporosis clinics

N=534		Mean	SD	N	%
Sex	Women			441	83
	Men			93	17
Age		66	9		
Race	Caucasian			529	99
	Other			5	1
Educational level	Low			278	52
	Moderate			196	37
	High			58	11
Social status	Married/ living together			385	72
	Living apart together			5	1
	Widowed/ divorced			144	27
Economic status	Low (< €1000/month)			158	30
	Moderate (€1000-3000/month)			342	64
	High (>€3000/month)			34	6
Type of fracture	Hip fracture			47	9
	Vertebral fracture			27	5
	Wrist fracture			145	27
	Other fractures[a]			311	58
	Multiple fractures[b]			4	1
DXA outcome	Osteoporosis			222	42
	Osteopenia			193	36
	normal BMD			119	22
Risk factors	Weight (kg)	72	13		
	BMI (kg/m^2)	26	4		
	Parental history of hip fracture			96	18
	Current smoking			81	15
	Use of high dose corticosteroids			21	4
	Rheumatoid arthritis			35	7
	Alcohol units ≥3/day			46	9
Psychological	Depressive symptoms (≥12 points)			92	17
characteristics	Fear of falling (<80% confidence)			178	33

[a]*hand, forearm, elbow, clavicle, ankle, foot.* [b] *1x hip and vertebral fracture; 1x vertebral and wrist fracture; 1x wrist and vertebral fracture; 1x wrist and other fracture.*

11. OUTLINE OF THE THESIS

Part I

Chapter 2 concerns a study on the validity of the case-finding method for general practitioners to select patients at risk for osteoporosis for dual energy x-ray absorptiometry, as has been published by the Dutch College of General Practitioners in 2005[7]. They defined clinical decision rules consisting of eight risk factors with weighted scores. Although these guidelines are widely used in the Netherlands, the case-finding method has never been validated. In chapter 3, alternative usage of the case-finding method will be discussed. Chapter 4 concerns the evaluation of the current intervention policy of the Dutch F&O clinics by the estimation of subsequent fracture risk. According to the Dutch guidelines, pharmacological treatment is recommended to patients who have been diagnosed with osteoporosis according to DXA measurement. In contrast, international guidelines have recommended to treat all fractured women irrespective of their DXA outcome.

Part II

Research on the relation between depression and osteoporosis describes contradictory results. This is not remarkable regarding the different levels of depression (syndrome and symptoms) and different research designs that have been studied. In chapter 5 a review is presented which discusses literature on the relationship between depression, osteoporosis and fractures, while making a distinction between depressive symptoms and depressive syndrome, and cross-sectional and longitudinal research. Chapter 6 describes the validity and optimal usage of the Edinburgh Depression Scale to assess depressive symptoms in older fracture women.

The Edinburgh Depression Scale is a highly accepted and user-friendly questionnaire in research on depressive symptoms. However, it has never been validated in elderly fractured females so far. Based on indications that psychological risk factors may affect fracture risk, chapter 7 describes a study on depressive symptoms and fear of falling as risk factors for subsequent fractures in women after 12 months of follow-up.

In chapter 8 the general discussion is presented, in which the main findings of the empirical studies are summarized and evaluated. Moreover, implications of the findings are discussed and recommendations for further research are described. In the appendix, a Dutch article is presented which has been adapted from chapter 2 and 3.

REFERENCES

1. Kinsella K, Velkoff VA. An aging World: 2001. International Population Reports. U.S. Government Printing Office, Washington D.C., USA, 2001; p.128

2. De Hollander AEM, Hoeymans N, Melse JM, *et al.* Zorg voor gezondheid: volksgezondheid toekomst verkenning 2006. Rijksinstistiuut voor Volksgezondheid en Milieu, Bilthoven. Bohn Stafleu van Loghum, Houten, 2006.

3. Blokstra A, Verschuren WMM, Baan CA, *et al.* Vergrijzing en toekomst van ziektelast. Prognose chronische ziekteprevalentie 2005-2025. Rijksinstistiuut voor Volksgezondheid en Milieu, Bilthoven, 2007.

4. Jordan KM, Cooper C. Epidemiology of osteoporosis. *Best Pract Res Clin Rheumatol* 2000; **16:**795-806.

5. World Health Organization (WHO) Working Group: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. *World Health Organ Tech Rep Ser.* 1994; **843:**1-129.

6. Kwaliteitsinstituut voor de gezondheidszorg CBO. Osteopose: tweede herziene richtlijn. Alphen a/d Rijn: Van Zuiden Communications, 2002.

7. Elders PJ, Leusink GL, Graafmans WC, *et al.* NHG standaard osteoporose. *Huisarts Wet* 2005; **48:**559-570.

8. Poole K & Compston J. Osteoporosis and its management. *BMJ* 2006; **333:**1251-1256.

9. Boling EP. Secondary Osteoporosis: underlying disease and the risk for glucocorticoid-induced osteoporosis. *Clin Ther* 2004; **26:**1-14.

10. Wagman RB, Marcus R. Beyond bone mineral density-navigating the laboratory assessment of patients with osteoporosis. *J Clin Endocrinol Metab* 2002; **87:**4429-4430.

11. Tannenbaum C, Clark J, Schwartzman K, *et al.* Yield of laboratory testing to identify secondary contributors to osteoporosis in otherwise healthy women. *J Clin Endocrinol Metab* 2002; **87:**4431-4437.

12. Cummings SR, Melton III R. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002; **359:**1761-1767.

13. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006; **17:**1726-1733.

14. http://cognosserver.prismant.nl/cognos7/cgi-bin/ppdscgi.cgi?DC =Q&E=/Prisma-Landelijke-LMR/Landelijke+LMR-informatie+-+ Diagnosen

15. Sedrine WB, Radican L, Reginster JY. On conducting burden-of-osteoporosis studies: a review of the core concepts and practical issues. A study carried out under the auspices of a WHO Collaborating Center. *Rheumatology* 2001; **40:**7-14.

16. Kanis JA, Borgstrom F, De Laet C, *et al.* Assessment of fracture risk. *Osteoporos Int* 2005; **16:**581-589.

17. The National Osteoporosis Foundation (NOF) *Clinician's Guide to prevention and treatment of osteoporosis 2008.* Washington, DC, US: National Osteoporosis Foundation, 2008.
http://www.nof.org/professionals/NOF_Clinicians_Guide.pdf

18. Woolf AD, Akesson K. Preventing fractures in elderly people. *BMJ* 2003; **327:**89-95.

19. Kanis JA, Johnell O. Requirements for DXA for the management of osteoporosis in Europe. *Osteoporos Int* 2005; **16:**229-238.

20. Leibston CL, Tosteson AN, Gabriel SE, *et al.* Mortality, disability, and nursing home use in persons with and without hip fracture: a population-based study. *J Am Geriatr Soc* 2002; **50:**1644-1650.

21. Braithwaite RS, Col NF, Wong JB. Estimating hip fracture morbidity, mortality and costs. *J Am Geriatr Soc* 2003; **51:**364-370.

22. Bliuc D, Nguyen TV, Milch VE, *et al.* Mortality risk associated with low-trauma osteoporotic fracture in men and women. *JAMA* 2009; **301:**513-521.

23. Center JR, Nguyen TV, Schneider D, *et al.* Mortality after all major types of osteoporotic fractures in men and women: an observational study. *Lancet* 1999; **353:**878-882.

24. Kaukonen JP, Karaharju EO, Porras M, *et al.* Functional recovery after fractures of the distal forearm. Analysis of radiographic and other factors affecting the outcome. *Ann Chir Gynaecol* 1988; **77:**27-31.

25. Gold DT. The nonskeletal consequences of osteoporotic fractures. Psychologic and social outcomes. *Rheum Dis Clin North Am* 2001; **27:**255-262.

26. Whooley MA, Kip KE, Cauley JA, *et al.* Depression, falls, and risk of fracture in older women. Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 1999; **159:**484-490.

27. Kamholz B, Unützer J. Depression after hip fracture. *J AM Geriatr Soc* 2007; **55:**126-127.

28. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone density predict occurrence of osteoporotic fractures. *BMJ* 1996; **312:**1254-1259.

29. Sornay-Rendu E, Munoz F, Garnero P, *et al.* Identification of osteopenic women at high risk of fracture: the OFELY study. *J Bone Min Res* 2005; **20:**1813-1819.

30. Kanis JA, Oden A, Johnell O, *et al.* The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 2007; **18:**1033-1046.

31. Kanis JA, Burlet N, Cooper C, *et al.* European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2008; **19:**399-428.

32. Kanis JA, Oden A, Johnell O, *et al.* The burden of osteoporotic fractures: a method for setting intervention thresholds. *Osteoporos Int* 2001; **12:**417–427.

33. Jackson SA, Tenenhouse A, Robertson L. Vertebral fracture definition from population-based data: preliminary results from the Canadian Multicenter Osteoporosis Study (CaMos). *Osteoporos Int* 2000; **11:**680-687.

34. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. *JAMA* 2007; **297:**387-394.

35. Lauritzen JB. Hip fractures: incidence, risk factors, energy absorption and prevention. *Bone* 1996; **18:**S65-75.

36. Appleby PN, Allen NE, Roddam AW, Key TJ. Physical activity and fracture risk: A prospective study of 1898 incident fractures among 34.696 British men and women. *J Bone Min Metabol* 2008; **26:**191-198.

37. Kwaliteitsinstituut voor de gezondheidszorg CBO. Preventie van valincidenten bij ouderen. Alphen a/d Rijn: Van Zuiden Communications, 2004.

38. Laing AC, Robinovitch SN. Low stiffness floors can attenuate fall-related femoral impact forces by up to 50% without substantially impairing balance in older women. *Accid Anal Prev* 2009; **41:**642-650.

39. Muir SW, Berg K, Chesworth B, Klar N, Speechley M. Quantifying the magnitude of risk for balance impairment on falls in community-dwelling older adults: a systematic review and meta-analysis. *J Clin* Epidemiol 2009; Epub ahead of print.

40. Sherrington C, Whitney JC, Lord SR, *et al*. Effective exercise for the prevention of falls: a systematic review and meta-analysis. *J Am Geriatr Soc* 2008; **56:**2234-2243.

41. Pluijm SM, Smit JH, Tromp EA, *et al*. A risk profile for identifying community-dwelling elderly with a high risk of recurrent falling: results of a 3-year prospective study. *Osteoporos Int* 2006; **17:**417-425.

42. Cooper JW, Burfield AH. Medication interventions for fall prevention in the older adult. *J Am Pharm Assoc* 2009; **49:**e70-82.

43. Moayyeri A. The association between physical activity and osteoporotic fractures: a review of the evidence and implications for future research. *Ann Epidemiol* 2008; **18:**827-835.

44. Lord SR. Visual risk factors for falls in older people. *Age Ageing* 2006; **35:**ii42-ii45.

45. Morris V, Wagg A. Lower urinary tract symptoms, incontinence and falls in elderly people: time for an intervention study. *Int J Clin Pract* 2007; **61:**320-333.

46. Pickering RM, Grimbergen YA, Rigney U, A meta-analysis of six prospective studies of falling in Parkinson's disease. *Mov Disord* 2007; **22:**1892-1900.

47. Härlein J, Dassen T, Halfens RJ, Heinze C. Fall risk factors in older people with dementia or cognitive impairment: a systematic review. *J Adv Nurs* 2009;**65:**922-933.

48. Glüer CC. Quantative ultrasound techniques for the assessment of osteoporosis: expert agreement on current status. The International Quantative Ultrasound Consensus Group. *J Bone Min Res* 1997; **12:**1280-1288.

49. Ensrud KE, Ewing SK, Stone KL, *et al.* Intentional and unintentional weight loss increase bone loss and hip fracture risk in older women. *J Am Geriatr Soc* 2003; **51:**1740.

50. Pluijm SMF, Bart Koes, de Laet C, *et al.* A Simple Risk Score for the Assessment of Absolute Fracture Risk in General Practice Based on Two Longitudinal Studies. *J Bone Min Res* 2009; **24:**768-774.

51. De Laet C, Kanis JA, Oden A, *et al.* Body mass index as a predictor of fracture risk: a meta-analysis. *Osteoporos Int* 2005; **16:**1330–1338.

52. Klotzbuecher CM, Ross PD, Landsman PB, *et al.* Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res* 2000; **15:**721–739.

53. Lindsay R, Silverman SL, Cooper C, *et al.* Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001; **285:**320-323.

54. Kanis JA, Johansson H, Oden A, *et al.* A family history of fracture and fracture risk: a meta-analysis. *Bone* 2004; **35:**1029–1037.

55. Kanis JA, Johnell O, Oden A, *et al.* Smoking and fracture risk: a meta-analysis. *Osteoporos Int* 2006; **16:**155–162.

56. Kanis JA, Johansson H, Johnell O, *et al.* Alcohol intake as a risk factor for fracture. *Osteoporos Int* 2005; 16:737–742.

57. Walsh LJ, Wong CA, Pringle M, Tattersfield AE. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. *BMJ* 1996; **313:**344-346.

58. Kanis JA, Johansson H, Oden A, *et al.* A meta-analysis of prior corticosteroid use and fracture risk. *J Bone Miner Res* 2000; **19:**893–899.

59. Deshpande N, Metter EJ, Bandinelli S, *et al.* Psychological, physical, and sensory correlates of fear of falling and consequent activity restriction in the elderly. *Am J Phys Med Rehabil* 2008; **87:**354-362.

60. Zijlstra GAR, van Haastregt JCM, van Eijk JThM, *et al.* Prevalence and correlates of fear of falling, and associated avoidance of activity in the general population of community-living older people. *Age Ageing* 2007; **36:**304-309.

61. Walker JE, Howland J. Falls and fear of falling among elderly persons living in the community: occupational therapy interventions. *Am J Occup Ther* 1991; **45:**119-112.

62. van Haastregt, JCM, Zijlstra GAR, van Rossum E, *et al.* Feelings of anxiety and symptoms of depression in community-living older persons who avoid activity for fear of falling. *Am J Geriatr Psychiatry* 2008; **16:**186-193.

63. Gagnon N, Flint AJ, Naglie G, Devins GM. Affective correlates of fear of falling in elderly persons. *Am J Geriatr Psychiatry* 2005; **13:**7-14.

64. Friedman SM, Munoz B, West SK, *et al.* Falls and fear of falling: Which comes first? A longitudinal prediction model suggests strategies for primary and secondary prevention. *J Am Geriatr Soc* 2002; **50:**1329-1335.

65. Nachreiner NM, Findorff MJ, Wyman JF, McCarthy TC. Circumstances and consequences of falls in community-dwelling older women. *J Womens Health* 2007; **16:**1437-1446.

66. Berg WP, Alessio HM, Mills EM, Tong C. Circumstances and consequences of falls in independent community-dwelling older adults. *Age Ageing* 1997; **26:**261-268.

67. Luukinen H, Koski K, Laippala P, Kivelä SL. Factors predicting fractures during falling impacts among home-dwelling older adults. *J Am Geriatr Soc* 1997; **45:**1302-1309.

68. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997; **349:**1498-1504.

69. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition - Text Revision

(DSMIV-TR), 4th ed. Washington, DC: American Psychiatric Press, 2000.

70. Cuijpers P, Smit F. Subthreshold depression as a risk indicator for major depressive disorder: a systematic review of prospective studies. *Acta Psychiatr Scand* 2004; **109:**325-331.

71. Beekman A, Deeg D, Van Tilburg T, *et al.* Major and minor depression in later life: a study of prevalence and risk factors. *J Affect Disord* 1995; **36:**65-75.

72. Cole M, Dendukuri N. Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *Am J Psychiatry* 2003; **160:**1147-1156.

73. Judd L, Akiskal H, Maser J, *et al.* A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. *Arch Gen Psychiatry* 1998; **55:**694-700

74. Wagner H, Burns B, Broadhead W, *et al.* Minor depression in family practice: functional morbidity, co-morbidity, service utilization and outcomes. *Psychol Med* 2000; **30:**1377-1390.

75. Gold D, Solimeo S. Osteoporosis and depression: a historical perspective. *Curr Osteoporos Rep* 2007; **4:**134-139.

76. Holmes J, House A. Psychiatric illness predicts poor outcome after surgery for hip fracture: a prospective cohort study. *Psychol Med* 2000; **30:**921-929.

77. Fredman L, Hawkes WG, Black S, *et al.* Elderly patients with positive affect have better functional recovery over 2 years. *J Am Geriatr Soc* 2006; **54:**1074-1081.

78. Moayerri A. The association between physical activity and osteoporotic fractures: a review of the evidence and Implications for future research. *Ann Epidemiol* 2008; **18:**827-835.

79. Schmitt NM, Schmitt J, Dören M. The role of physical activity in the prevention of osteoporosis in post-menopausal women – an update. *Maturitas* 2009; **63:**34-38.

80. Cadarette SM, Jaglal SB, Murray TM, *et al.* Evaluation of decision rules for referring women for bone densitometry by dual-energy x-ray absorptiometry. *JAMA* 2001; **286:**57-63.

81. Kanis JA, Johnell O, Oden A, *et al.* FRAX and the assessment of fracture probability in men and women in the UK. *Osteoporos Int* 2007; **19:**385-397.

82. Pluijm SM, Koes B, de Laet C, *et al*. A simple risk score for the assessment of absolute fracture risk in general practice based on two longitudinal studies. *J Bone Miner Res* 2009; **24:**768-774.

83. van Helden S, Cauberg E, Geusens P, *et al.* The fracture and osteoporosis outpatient clinic: an effective strategy for improving implementation of an osteoporosis guideline. *J Eval Clin Pract* 2007; **13:**801-805.

84. Blonk M, Erdtieck R, Wernekinck M, Schoon E. The fracture and osteoporosis clinic: 1-year results and 3 months-compliance. *Bone* 2007; **40:**1643-1649.

85. Hegeman JH, Willemsen G, van Nieuwpoort J, *et al.* Effective tracing of osteoporosis at a fracture and osteoporosis clinic in Groningen: an analysis of the first 100 patients. *Ned Tijdschr Geneesk* 2004; **148:**2180-2185.

44

86. Kannus P, Parkkari J, Niemi S, *et al.* Prevention of hip fracture in elderly people with use of a hip protector. *N Engl J Med* 2000; **23:**1506-1513.

Part I:

Guidelines in fracture risk

management

Validation of the Dutch case-finding method to identify patients at risk for osteoporosis

Noortje A Verdijk[1], Arnold C Romeijnders[2], Jos J Ruskus[3], Corien van der Sluijs[3], Victor J Pop[1]

1. the Centre Of Research for Psychology in Somatic diseases, Medical Psychology and Neuropsychology, Tilburg University
2. Coordination Centre of Nurse Practitioners for South East Netherlands
3. Primary Health Care Centre Riethoven

ABSTRACT

Objective: In Europe, a case-finding strategy for osteoporosis is recommended above widespread population based screening. However, no universally accepted policy exists. In 2005, the Dutch College of General Practitioners published guidelines for General Practitioners including a case-finding method to select patients at risk for osteoporosis for dual energy x-ray absorptiometry (DXA). We aimed to evaluate the sensitivity, specificity and predictive value of the Dutch case-finding method to select subjects at risk for osteoporosis for DXA measurement.

Design of Study: cross-sectional.

Setting: 345 females aged over 50 years (mean age = 62 years, standard deviation [SD] = 8.3) and 99 males aged over 65 years (mean age = 72 years, SD = 5.2) of a Dutch general practice.

Methods: Calculation of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the Dutch case-finding method for selecting subjects at risk for osteoporosis for DXA measurement.

Results: sensitivity was 20%, specificity 86%, PPV 19%, and NPV 87%.

Conclusion: the Dutch case-finding method is unreliable in detecting people at risk for osteoporosis.

INTRODUCTION

Osteoporosis is a major public health issue; osteoporotic fractures affect one out of two females and one out of five males aged over 50 years[1]. In 2000, the number of osteoporotic fractures in the European Union was estimated at 3.8 million, equalling a financial burden of €31.7 billion[2]. It is expected that by 2050, the direct costs of fractures in Europe will exceed €75 billion. The annual incidence of fractures in the UK is estimated at 310,000 with costs of €2.4 billion[3]. In 2005 about 850,000 patients had osteoporosis in the Netherlands[4] and each year about 83,000 people aged over 55 years have a fragility fracture[5].

Considering the growing incidence, early diagnosis of osteoporosis is of great importance, especially since adequate pharmacological treatment of osteoporosis is available, which has been shown to be cost-effective irrespective of age[6]. Diagnosis of osteoporosis is currently based on bone densitometry, usually by dual energy x-ray absorptiometry (DXA). Case-finding strategy has been shown to be more cost-effective than population-based screening of bone density[2,6] and is advocated by the World Health Organisation[7] and in Europe[2,5]. To date, several case finding instruments to identify patients with osteoporosis have been developed and validated[8-19]. However, there is no universally accepted policy.

In 2005, the Dutch College of General Practitioners published guidelines for General Practitioners (GPs) for the diagnosis and therapy of osteoporosis[20]. Based on recommendations for case-finding of the Dutch Institute for Health Care Improvement[5], they defined clinical decision rules, consisting of eight risk factors with weighted scores (Table 1). When a cut-off score of 4 is reached, referral for bone densitometry is advised. Although this case-finding method is part of the Dutch national guidelines for general practitioners, it has never been validated. Therefore we aim to

investigate the sensitivity, specificity and predictive value of the Dutch case-finding method for selecting patients at high risk for osteoporosis for bone mineral density testing by DXA.

METHODS

Participants

Over a period of six months, 444 patients aged over 50 years (345 females and 99 males) of a Dutch general practice (without known diagnosis of osteoporosis or terminal illness) received a written invitation for DXA measurement. Eligible patients were all female patients aged 50-85 years and male patients aged 65-85 years. These cut-offs were based on the knowledge that declining bone mineral density in females reaches thresholds that indicate postmenopausal osteoporosis from the age of 50[1,6]. For males, a cut off of 65 years was defined because, in general, fracture risk increases greatly after this age[6,20] Bone mineral density measurements were collected at the total hip, femoral neck and lumbar spine using DXA technology (Hologic QDR 4500W, version 12.4). Values were expressed in T scores (that is, using standard deviations [SD] from the young adult normal mean) and Z scores (that is, using SDs from the age- and sex-adjusted mean) based on the National Health and Nutrition Examination Survey database references for the hip and Hologic database references for the spine. In addition, participants were asked to fill in a questionnaire, consisting of ten questions regarding the risk factors for osteoporosis according to Dutch case-finding method, in interrogative form. For example, 'Have you suffered from a fracture after the age of 50

years? (yes/no)'. In addition, information was gathered on demographic characteristics.

Measurements

A total risk score of the questionnaire was calculated based on the weighted scores of the Dutch case-finding method (Table 1). According to the Dutch case-finding method, the cut-off score was defined at four points. First, bone mineral density was defined according to World Health Organisation criteria as normal (T score ≥ -1.0 SD), osteopenic (T-score <-1.0 SD and > -2.5 SD) or osteoporotic (T score ≤ -2.5 SD)[21]. Second, bone density was defined according to Dutch guidelines[5,20]. In patients aged below 70 years the WHO criteria were used; in patients aged over 70 years, a Z score below -1.0 SD was used to define abnormal bone density. Based on the diagnosis according to bone mineral density levels and the risk score according to the Dutch case-finding method, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Ninety-five percent confidence Intervals (95% CI) were calculated using binomial expansion. Statistical analyses were performed using SPSS software (version 14.0). All analyses were carried out on the total research population, and for males and females separately.

Table 1. Dutch case-finding method to identify subjects at risk for osteoporosis: Dual Energy X-ray Absorptiometry measurement is recommended if the total risk score ≥4[20].

Risk factor	Score	Sex
Established vertebral fracture	4	M,F
Long-term use of high dose of corticosteroids (>3 months; >7.5 mg/day)	4	M,F
Fracture after age of 50 years	4	F
Age >70 years	2	F
Age >60 years	1	F
Hip fracture in first-degree family member	1	F
Weight <60 kg	1	F
Severe immobility	1	F

RESULTS

Written informed consent was received from 234 females and 65 males (response rate 67%). This loss was not selective as there were no significant differences in sex, age, and socioeconomic status between the non-responders and participants (data not shown). Two hundred twenty-eight females and 65 males filled out the questionnaire; 232 females and 64 males underwent DXA measurement. Only participants who completed both DXA measurement and the questionnaire were included for analyses: 226 females and 64 males. Table 2 summarises their characteristics. Of all participants, 15% (43/290) scored at least four points on the questionnaire - 38 females and 5 males. According to the DXA results and WHO criteria, 14% (41/290) of all participants suffered from osteoporosis (32 females and nine males). Osteopenia was found in 50% (146/290) of

the participants (117 females and 29 males). Of all participants, 36% (103/290) had normal bone mineral density: 77 females and 26 males. Of the 41 osteoporotic patients, eight (20%) scored at least four points on the questionnaire (seven females and one man). The results are summarized in Table 3 for the whole population, females and males.

Table 2. Patients' characteristics: mean age, prevalence of risk factors according to the case-finding method and DXA outcome.

	total population (n=290)		females (n=226)		men (n=64)	
Mean age (SD)	63 (9)		61 (8)		72 (5)	
Risk factors case- finding method	n	%	n	%	n	%
established vertebral fracture	4	1	2	1	2	3
long-term use high dose corticosteroids	17	6	14	6	3	5
fracture after age of 50 yrs	26	9	23	10	3	5
age >70 yrs	65	22	32	14	33	52
age >60 yrs	109	38	78	35	31	48
hip fracture 1st degree family member	41	14	28	12	13	20
weight <60 kg	44	15	41	18	3	5
severe immobility	28	10	19	8	9	14
risk score ≥ 4	43	15	38	17	5	8
DXA outcome						
Osteoporosis	41	14	32	14	9	14
Osteopenia	146	50	117	52	29	45
normal bone density	103	36	77	34	26	41

Table 3. Total risk score according to the case-finding method and DXA outcome

	Osteoporosis	No osteoporosis	n
Total population			
risk score ≥4	8	35	43
risk score <4	33	214	247
N	41	249	290
Females			
risk score ≥4	7	31	38
risk score <4	25	163	188
N	32	194	226
Males			
risk score ≥4	1	4	5
risk score <4	8	51	59
N	9	55	64

In Table 4, the sensitivity, specificity, PPV and NPV of the case-finding method are shown using a cut off score ≥4. Regarding the WHO diagnostic criteria for osteoporosis, the case-finding instrument had a sensitivity of 20%, a specificity of 86%, a PPV of 19% and NPV of 87%. Analyses based on the Dutch diagnostic criteria for osteoporosis (using Z scores for DXA results from participants aged ≥70 years) resulted in rather similar findings for the total population (sensitivity 17%, specificity 86%, PPV 14% and NPV 88%), and for females as well as for males (data not shown).

Table 4. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the Dutch case-finding method to select patients at risk for osteoporosis for DXA measurement

	sensitivity % (95% CI)	specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Total population	20	86	19	87
(n=290)	(7 - 32)	(82 - 90)	(7 - 30)	(77 - 97)
Males	11	93	20	86
(n=64)	(-9 - 32)	(86 - 100)	(-15 - 55)	(56 - 116)
Females	22	84	18	87
(n=226)	(8 - 36)	(79 - 89)	(6 – 31)	(76 - 98)

DISCUSSION

In this study, the sensitivity, specificity and predictive value of the Dutch case-finding method for the selection of patients at risk for osteoporosis for DXA measurement have been evaluated. Although specificity (86%) and NPV (87%) were appropriate, sensitivity and PPV were low: 20% and 19% respectively.

The low value of PPV indicates that the change is low that a patient, who scores ≥4 points, indeed suffers from osteoporosis. An instrument with moderate PPV can be used in practice if the sensitivity is high and (thus) the majority of patients with a high risk profile are identified. However, as both the PPV and sensitivity of the Dutch case-finding method are low, it can be concluded from this study that the case-finding method is unreliable in detecting people at risk for osteoporosis. In fact, for every patient that was diagnosed with osteoporosis after referral for DXA based

on a high-risk score, about four patients with osteoporosis remained undiscovered (in males this were eight patients).

As mentioned before, other case-finding instruments to select patients for DXA measurement have been developed and validated. In Table 5, the construct validity of some of these is shown and compared to that of the current study[8-19]. Although sensitivity of the majority of these instruments is high, most are limited by moderate specificity and PPV. The Osteoporosis Self-assessment Tool (OST) has also been validated in a Dutch and Belgian population with a sensitivity of approximately 90% and 92% respectively, using a cut off of 2 points[13,16]. Compared to literature, the Dutch case-finding instrument showed the poorest outcomes.

There are several explanations for the poor validity of the Dutch case-finding method. First, the definition of several risk factors that have been included may contribute to the low validity. For example, one may speculate what the relevance is of asking a patient whether he or she suffers from a vertebral fracture, knowing that up to two-thirds of vertebral fractures are clinically unrecognized[22]. Moreover, the question concerning severe immobility has not been quantified. Neither items are used in other case-finding instruments. Furthermore, being aged between 60 and 70 years is regarded as a small risk for osteoporosis in the Dutch case-finding method, while in other instruments the factor 'age' received much more weight.

Another explanation for the low validity might be the definition of the weighted scores in the Dutch case-finding method: the definitions of the weighted scores have been based on the relative risk of certain factors for hip and vertebral *fractures* (as recommended by the Dutch Institute of Health Care Improvement[5]), instead of risk factors for *osteoporosis*.

58

Table 5. Sensitivity (sens), specificity (spec), positive predictive value (PPV), and negative predictive value (NPV) of case-finding methods to identify patients at risk for osteoporosis.

Case-finding method	1st author, year of publication	sens %	spec %	PPV %	NPV %
Dutch method[20]	Elders, 2005	20	86	19	87
ABONE[8]	Cadarette, 2001	93	48	-	-
OPERA[9,a]	Salaffi, 2005	88-90	61-64	29-39	96-97
ORAI[10]	Cadarette, 2000	94	41	18	-
OSIRIS[11,12]	Sedrine, 2002	79	51	-	-
	Reginster, 2004	85	39	42	83
OST[13-17,]	Geusens, 2008 [a]	92	16	18-65 [b]	-
	Richy, 2004[a]	86	40	41	86
	Adler, 2003 [a]	82	74	38	97
	Geusens, 2002 [a]	88	52	-	-
	Koh, 2001[a]	91	45	-	-
SCORE[18]	Sedrine, 2001	82	42	41	83
Weight criterion[19,c]	Michaëlsson, 1996	89-94	36-38	21-33	91-97

[a] Cut-off< 2.0. [b] Depending on fracture risk. [c] T scores of lumbar spine and femoral neck separately. ABONE = Age, BOdy, No Estrogen use. OPERA = Osteoporosis Prescreening Risk Assessment. ORAI = Osteoporosis Risk Assessment Instrument. OSIRIS = Osteoporosis Index of Risk. OST = Osteoporosis Self-assessment Tool. SCORE = Simple Calculated Osteoporosis Risk Estimation.

The clinical impact of our findings is important because the Dutch guidelines are used on a large scale in general practice. In the same period and in the same area as the present study, a large osteoporosis project was conducted supported by health insurance. Within this project,

GPs used the Dutch case-finding method to detect patients at high risk for osteoporosis and referred them for DXA measurement. Over 21,500 participants were included. By using the Dutch case-finding method, it can be concluded from the current study that the majority of patients with osteoporosis have been missed and are thus denied appropriate treatment.

A strength of our study is that a response rate of 67% suggests no recall bias. However, we included the population of only one general practice, which comprised a rural area and only white patients. On average, relatively young participants participated. This might explain why the prevalence of osteoporosis in the research population is rather low compared to the overall prevalence of osteoporosis. Hence, the results cannot be generalized to the Dutch population. Another limitation of the study is that, due to its cross-sectional design, no information is provided on the usefulness of the Dutch case-finding method in enhancing fracture prevention. In addition, only 64 males were included. Therefore no definite conclusions regarding data of this subgroup can be drawn. It might be argued that the Dutch College of General Practitioners never meant their guidelines to be used as a case-finding method, especially not on a large scale. However, by introducing an instrument with weighted scores and a cut-off score above which patients should be referred for DXA, the Dutch strategy resembles a diagnostic tool rather than general guidelines. Moreover, whether or not the Dutch case-finding method is used for an individual patient or a large population, the likelihood of missing patient with osteoporosis remains equal.

It can be concluded that the Dutch case-finding method, which is part of the Dutch national guidelines for general practitioners, is of little value for selecting patients at risk for osteoporosis for DXA measurement. The

growing incidence of osteoporosis reflects the urge for an active strategy. Further research is needed to develop a more appropriate policy to detect patients at risk for osteoporosis and to evaluate the usefulness of the case-finding method for the prevention of fractures.

REFERENCES

1. Poole K, Compston J. Osteoporosis and its management. *BMJ* 2006; **333:**1251-1256.

2. Kanis JA, Johnell O. Requirements for DXA for the management of osteoporosis in Europe. *Osteoporos Int* 2005; **16:**229-238.

3. Woolf AD, Akesson K. Preventing fractures in elderly people. *BMJ* 2003; **327:**89-95.

4. Blokstra A, Verschuren WMM, Baan CA, *et al.* Vergrijzing en toekomst van ziektelast. Prognose chronische ziekteprevalentie 2005-2025. Rijksinstistiuut voor Volksgezondheid en Milieu, Bilthoven, 2007.

5. Kwaliteitsinstituut voor de gezondheidszorg CBO. Osteopose: tweede herziene richtlijn. Alphen a/d Rijn: Van Zuiden Communications, 2002.

6. Kanis JA, Burlet N, Cooper C, *et al.* European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2008; **19:**399-428.

7. Genant HK, Cooper C, Poor G, *et al*. Interim report and recommendations of the World Health Organization Task-Force for Osteoporosis. *Osteoporos Int* 1999; **10:**259-264.

8. Cadarette SM, Jaglal SB, Murray TM, *et al.* Evaluation of decision rules for referring women for bone densitometry by dual-energy x-ray absorptiometry. *Jama* 2001; **286:**57-63.

9. Salaffi F, Silveri F, Stancati A, Grassi W. Development and validation of the osteoporosis prescreening risk assessment

(OPERA) tool to facilitate identification of women likely to have low bone density. *Clin Rheumatol* 2005; **24:**203-211.

10. Cadarette SM, Jaglal SB, Kreiger N, *et al*. Development and validation of the Osteoporosis Risk Assessment Instrument to facilitate selection of women for bone densitometry. *CMAJ* 2000; **162:**1289-1294.

11. Sedrine WB, Chevallier T, Zegels B, *et al*. Development and assessment of the Osteoporosis Index of Risk (OSIRIS) to facilitate selection of women for bone densitometry. *Gynecol Endocrinol* 2002; **16:**245-250.

12. Reginster JY, Ben Sedrine W, Viethel P, *et al.* Validation of OSIRIS, a prescreening tool for the identification of women with an increased risk of osteoporosis. *Gynecol Endocrinol* 2004; **18:**3-8.

13. Geusens P, Dumitrescu B, van Geel T, *et al*. Impact of systematic implementation of a clinical case finding strategy on diagnosis and therapy of postmenopausal osteoporosis. *J Bone Miner Res* 2008; **23:**812-818.

14. Richy F, Gourlay M, Ross PD, *et al.* Validation and comparative evaluation of the osteoporosis self-assessment tool (OST) in a Caucasian population from Belgium. *QJM* 2004; **97:** 39-46.

15. Adler RA, Tran MT, Petkov VI. Performance of the Osteoporosis Self-assessment Screening Tool for osteoporosis in American men. *Mayo Clin Proc* 2003; **78:**723-727.

16. Geusens P, Hochberg MC, van der Voort DJ, *et al.* Performance of risk indices for identifying low bone density in postmenopausal women. *Mayo Clin Proc* 2002; **77:**629-637.

17. Koh LK, Sedrine WB, Torralba TP, *et al.* Osteoporosis Self-Assessment Tool for Asians (OSTA) Research Group. A simple tool to identify asian women at increased risk of osteoporosis. *Osteoporos Int* 2001; **12:**699-705.

18. Sedrine BW, Devogelaer JP, Kaufman JM, *et al.* Evaluation of the simple calculated osteoporosis risk estimation (SCORE) in a sample of white women from Belgium. *Bone* 2001; **29:**374-380.

19. Michaëlsson K, Bergström R, Mallmin H, *et al.* Screening for osteopenia and osteoporosis: selection by body composition. *Osteoporos Int* 1996; **6:**120-126.

20. Elders PJ, Leusink GL, Graafmans WC, *et al.* NHG standaard osteoporose. *Huisarts Wet* 2005; **48:**559-570.

21. World Health Organization (WHO) Working Group: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. *World Health Organ Tech Rep Ser.* 1994; **843:**1-129.

22. Kanis JA, McCloskey EV. Epidemiology of vertebral osteoporosis. *Bone* 1992; **13:**S1-S10.

Improving the sensitivity of the Dutch case-finding method to identify subjects at risk for osteoporosis

Noortje A Verdijk[1], Geraline L Leusink[2], Ronald J Erdtsieck[3], Victor J Pop[1]

1. the Centre Of Research for Psychology in Somatic diseases, Medical Psychology and Neuropsychology, Tilburg University
2. Stichting Zuidwester
3. Maxima Medical Centre

RESEARCH LETTER

In a previous paper we reported on the poor validity of the Dutch case finding method for GPs to identify patients at risk for osteoporosis for Dual Energy X-ray Absorptiometry (DXA) measurement[1,2], as the sensitivity was 20% and positive predictive value (PPV) was 19%. We suggested that a more appropriate tool is needed for accurate case-finding of patients at risk for osteoporosis. The problem however is that many GPs have poor knowledge of the different case-finding methods that are available[3]. Therefore, alternative use of current guidelines may be preferred above the design of a new method. The aim of this study is to evaluate alternative use of the case-finding method, as recommended by the Dutch College of General Practitioners.

We performed receiver operating characteristic (ROC) curves to evaluate whether the recommended cut-off score of four points is the best cut-off score to be used. As only 64 men were included, data analyses were performed on 226 females. Osteoporosis was diagnosed according to the World Health Organisation (WHO) guidelines (T score $\leq$ -2.5 SD) [4] and, in addition, according to the Dutch guidelines[2,5], using the WHO criteria in patients younger than 70 years and Z-scores in patients over 70 years ($\leq$ -1.0 SD) to define osteoporosis. Osteopenia was not defined within this age group. We calculated sensitivity, specificity, and predictive value of the guidelines using varying cut-offs. Ninety-five percent confidence intervals (95% CI) were calculated using binomial expansion. Statistical analyses were performed using SPSS software (version 16.0).

The sensitivity, specificity and predictive value according to the ROC analysis are shown in Table 1.

66

Table 1. Sensitivity (sens), specificity (spec), positive predictive value (PPV) and negative predictive value (NPV) of the Dutch case-finding method in 226 females

cut-off	criteria[a]	sens % (95% CI)	spec % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
1	WHO	88	40	18	94
		(76 - 99)	(35 - 46)	(12 - 24)	(91 - 98)
	Dutch	83	39	13	95
		(68 - 98)	(34 - 45)	(8 - 18)	(91 - 98)
2	WHO	63	63	22	91
		(46 – 79)	(57 – 70)	(14 – 31)	(85 - 97)
	Dutch	50	61	13	91
		(30 - 70)	(54 - 68)	(6 - 20)	(85 - 97)
3	WHO	38	80	24	89
		(21 - 54)	(74 - 86)	(12 - 35)	(80 - 97)
	Dutch	30	78	14	90
		(11 - 47)	(73 - 84)	(4 - 23)	(82 - 98)
4	WHO	22	84	18	87
		(8- 36)	(79 - 89)	(6 - 31)	(76 - 98)
	Dutch	21	84	13	90
		(5 - 37)	(79 - 89)	(2 - 24)	(80 - 100)

a WHO criteria: DXA outcome is based on T-scores for all ages. Dutch criteria: DXA outcome is based on T-scores if age<70 years and on Z-scores of age≥70 years.

 As can be seen, the best cut-off of the current Dutch case finding method is one point. Using this cut-off and the WHO criteria for osteoporosis, sensitivity improved to 88%, specificity was 40%, PPV 14% and NPV 97%. Slightly lower values were calculated if DXA outcome was based on

the Dutch criteria of osteoporosis (using Z-scores in patients aged over 70 years).

The use of one point as a threshold would imply screening from the age of 60 years. Weighted scores The US guidelines have recommended screening in females over 65 years, based on cost-effectiveness analysis[6]. In addition, treatment of females with risk factors other than a prior fracture is cost-effective after the age of 65 years according to the European Guidance[7]. Therefore, we investigated the validity of the Dutch case-finding method in females, after changing the original model: in the original method, one risk point is given for the age 60-70 years and two points for the age over 70 years. Instead, we now gave one risk point for the age over 65 years. The original and adapted case-finding methods are shown in Table 2.

Table 2. The original (O) and adjusted (A) Dutch case-finding methods to select females at high risk for osteoporosis for bone densitometry

Risk factor	Score (O)	Score (A)
Established vertebral fracture	4	1
Long-term use of high dose of corticosteroids (>3 months; >7·5 mg/day)	4	1
Fracture after age of 50 years	4	1
Age > 70 years	2	-
Age > 60 years	1	-
Age ≥ 65 years	-	1
Hip fracture in first-degree family member	1	1
Weight <60 kg	1	1
Severe immobility	1	1

Sensitivity, specificity and predictive value of the adjusted case-finding method for females are summarised in Table 3.

Table 3. Sensitivity (sens), specificity (spec), positive predictive value (PPV) and negative predictive value (NPV) of the adjusted Dutch case-finding method in 226 females

cut-off	criteria[a]	sens % (95% CI)	spec % (95% CI)	PPV[b] % (95% CI)	NPV[b] % (95% CI)
1	WHO	84	44	20	94
		(72 – 97)	(37 – 51)	(13 - 27)	(91 - 98)
	Dutch	79	42	14	94
		(63 - 95)	(35 - 49)	(8 - 20)	(91 - 98)
2	WHO	47	82	30	90
		(30 - 64)	(77 - 87)	(17 - 43)	(82 - 99)
	Dutch	42	80	20	92
		(22 - 61)	(75 - 86)	(9 - 31)	(85 – 100)
3	WHO	24	89	19	87.3
		(10 - 39)	(86 - 93)	(70 – 31)	(70 – 105)
	Dutch	25	89	14	90
		(8 - 42)	(85 - 92)	(4 - 25)	(74 - 106)
4	WHO	21	91	19	92
		(7 - 35)	(88 - 94)	(7 - 32)	(83 - 101)
	Dutch	21	90	14	94
		(5 - 37)	(87 - 94)	(3 - 25)	(9 - 102)

a WHO-criteria: DXA outcome is always based on T-scores. Dutch-criteria: DXA outcome is based on T-scores if age<70 years and on Z-scores of age≥70 years

As can be seen, values were slightly higher if WHO criteria were used to define osteoporosis instead of the Dutch criteria. Furthermore there was little benefit if age as a risk factor was defined as 65 years or older instead of 60 years. However, when taking into account cost-effectiveness, the use of an age over 65 years as a risk factor may be recommended[5].

We showed that the clinical performance of the Dutch case finding method majorly improves with alternative use: based on the WHO criteria for the diagnosis of osteoporosis, the sensitivity in females largely increases from 22% to 88%. Instead of missing four patients with osteoporosis for each patient that is found[1], only one female patient is missed for each six female patients that are found. This implies that the majority of female patients with osteoporosis will be properly referred for DXA. However, PPV remained low. This can be explained by the low prevalence of osteoporosis in our relatively young population. As we discussed in our previous paper[1], an instrument with high sensitivity may be of great practical interest in primary care, even if PPV is low. However, the specificity was modest and alternative usage would imply screening from a certain age (60 or 65 years). Therefore, additional research is needed to investigate the clinical and economical consequences of alternative usage of the Dutch case-finding method.

Based on our results, we suggest that the Dutch College of General Practitioners revises her policy on the case-finding of patients at risk for osteoporosis.

REFERENCES

1. Verdijk N, Romeijnders A, Ruskus J, *et al.* Validation of the Dutch guidelines for dual X-ray absorptiometry measurement. *Br Gen Pract* 2009; **59:**256-261.

2. Elders PJ, Leusink GL, Graafmans WC, Bolhuis AP, *et al.* NHG standaard osteoporose. *Huisarts Wet* 2005; **48:**559-570.

3. Schwartz E. and Steinberg D. Prescreening tools to determine who needs DXA. *Current Osteoporosis Reports* 2006, **4:**148-152.

4. World Health Organization (WHO) Working Group: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. *World Health Organ Tech Rep Ser.* 1994; **843:**1-129.

5. Kwaliteitsinstituut voor de gezondheidszorg CBO. Osteopose: tweede herziene richtlijn. Alphen a/d Rijn: Van Zuiden Communications, 2002.

6. The National Osteoporosis Foundation (NOF) Clinician's Guide to prevention and treatment of osteoporosis 2008*.* Washington, DC, US: National Osteoporosis Foundation, 2008. http://www.nof.org/professionals/NOF_Clinicians_Guide.pdf

7. Kanis JA, Burlet N, Cooper C, *et al*. European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporosis Int* 2008; **19:**399-428.

Evaluation of the Dutch intervention policy

in fractured females using the FRAX®

Noortje A Verdijk[1], Martha van den Berg[2], Geraline L Leusink[3], Marion C Blonk[4], Ronald J Erdtsieck[5], Victor J Pop[1]

1. Centre of Research on Psychology in Somatic diseases (CoRPS), Medical Psychology and Neuropsychology, Tilburg University
2. Coordination Centre of Nurse Practitioners for South East Netherlands
3. Stichting Zuidwester
4. Catharina Hospital Eindhoven
5. Maxima Medical Centre

ABSTRACT

Objective: In contrast with international guidelines that recommend treatment of all fractured females irrespective of BMD, the current intervention policy of Dutch Fracture and Osteoporosis (F&O) clinics recommends treatment of only osteoporotic patients. We aim to evaluate the accuracy of the current intervention policy of Dutch F&O clinics for fracture prevention by assessing the 10-year fracture probability in fractured patients according to the FRAX®

Design of study: cross-sectional.

Setting: 396 female patients of two Dutch F&O clinics.

Methods: calculation of the 10-year major osteoporotic fracture probabilities according to the FRAX®.

Results: Based on the current policy of the Dutch F&O clinics, 43% of the female patients were recommended pharmacological treatment. The average 10-year major osteoporotic fracture probabilities were 21% and 17%, with and without the integration of BMD respectively. These values exceeded the UK cost-effective and interventions thresholds. On individual level however, a substantial amount of females had a fracture probability below the intervention thresholds.

Conclusion: the current intervention policy of the Dutch F&O clinics is not accurate towards women without osteoporosis in terms of fracture risk. Based on the average fracture probability, treatment of all fractured females seems appropriate and cost-effective. However, this can be questioned from a risk-benefit and ethical point of view. Estimation of fracture probability may improve the current intervention policy of the F&O clinics. However, further research is needed to gain insight in fracture probabilities in the Dutch population, as well as the effect of pharmacological intervention in subjects without osteoporosis.

INTRODUCTION

Fractures are a major health issue, affecting one in two females and one in five men aged over 50 years[1]. Subsequent fracture risk is majorly increased by the occurrence of a prior fragility fracture and low bone density (osteoporosis)[1-3]. In the guidelines on osteoporosis of the Dutch Institute for Healthcare (CBO) it has been recommended that fractured patients should be evaluated for osteoporosis[4]. Because the implementation of this policy showed to be poor[5], fracture and osteoporosis outpatient (F&O) clinics have been introduced to increase adequate identification of osteoporosis. After a fragility fracture, all patients over 50 years receive Dual X-ray Absorptiometry (DXA) measurement and are screened for clinical risk factors. Research on Dutch F&O clinics showed that they are effective and useful for the identification of patients with osteoporosis[5-7]. According to the CBO guidelines, pharmacological treatment is recommended to patients with osteoporosis based on DXA outcome. This comprises about 40-48% of the patient population of the F&O clinics[5,6]. In contrast, the European Guidance and UK National Osteoporosis Guideline Group have recommended that *all* fractured females should receive pharmacological treatment, irrespective of their DXA outcome[8,9], as the treatment of fractured females has been shown to be cost-effectiveness for all ages.

Because the aim of intervention is to prevent fractures, treatment of fractured patients should concern those at highest risk for a subsequent fracture. In 2008, The World Health Organization (WHO) Collaboration Center for Metabolic Bone Diseases at Sheffield, UK, introduced an algorithm to estimate fracture probability by integration of BMD and clinical risk factors, called the FRAX® [10]. In addition to BMD and age the FRAX® includes low Body Mass Index (BMI), a previous fragility fracture, a

history of parental hip fracture, current smoking, systemic use of glucocorticosteroids, 3 or more units of alcohol per day and diagnosis of secondary osteoporosis (type I diabetes, hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or chronic liver disease). The FRAX® can be used to compute the 10-year probability of both hip fractures and major osteoporotic fractures (clinical spine, hip, forearm or humerus fractures) and is available online at http://shef.ac.uk/FRAX. The health economic threshold for intervention has been estimated at a major osteoporotic fracture probability of 7% in the UK and 7.5% in Europe, for all ages[8,9]. In addition, intervention thresholds have been set for the UK[10]. These differ from the health economic threshold because a single intervention threshold would result in under-treatment of younger people and over-treatment of older people[9]. Instead, intervention thresholds have been set at the fracture probability equivalent to females with a prior fracture, depending on age. As a result, intervention thresholds vary between 7.5% in females of 50 years and 30% in females of 80 years.

The intervention policy of Dutch F&O clinics to treat osteoporotic patients is in large contrast with the policy to treat all fractured females, as has been recommended by international guidance. To evaluate the accuracy of the current intervention policy of Dutch F&O clinics for fracture prevention, we aim to assess the 10-year fracture probability in fractured patients according to the FRAX®.

METHODS

Participants

In the period between October 2006 and July 2008, all patients of two F&O clinics in the South of the Netherlands were invited to participate in a prospective cohort study on osteoporosis and fractures, called the Eindhoven Subsequent Fracture and Osteoporosis Reduction-project (ESFOR-p). Inclusion criteria were defined as follows: (1) age 50 years or over, (2) a recent fragility fracture (resulting from a fall of standing height or less), (3) sufficient knowledge of the Dutch language and (4) sufficient cognitive abilities. The Medical Ethical Committee of the Maxima Medical Centre approved this study. Of the 1339 patients who visited the clinics, 756 were interested to participate, of which 534 signed informed consent and met the inclusion criteria (89 men and 419 females (mean age 66 SD=8.8)). Despite the low response rate (40%) our population accurately reflects the population of the F&O clinics: there were no significant differences in mean age and incidence of osteoporosis, osteopenia and normal BMD between our population and the overall population that visited the F&O clinic during the same period. As the recommendations of the international guidelines mainly concern females, only female subjects were included in this study. Due to missing data, 23 subjects were excluded, resulting in a research population of 396 fractured females. Their characteristics are presented in table 1.

Table 1. Characteristics of 396 female patients of the Dutch Fracture & Osteoporosis clinics

N=396	Mean	SD	N	%
FRAX® risk factors				
Age	66	9		
BMI (kg/m^2)	26	5		
Previous fracture			396	100
Parental hip fracture			74	19
Current smoking			57	14
Glucocorticoids			12	3
Rheumatoid arthritis			25	6
Secondary osteoporosis			81	21
Alcohol units ≥3/day			30	8
Type of fracture				
Hip fracture			31	8
Vertebral fracture			15	4
Wrist fracture			118	30
Humerus fracture			30	8
Other fractures[a]			198	50
Multiple fractures[b]			4	1
DXA outcome				
Osteoporosis			169	43
Osteopenia			147	37
normal BMD			80	20

[a]*hand, forearm, elbow, clavicle, ankle, foot.* [b] *1x hip and vertebral fracture; 1x vertebral and wrist fracture; 1x wrist and vertebral fracture; 1x wrist and other fracture.*

Measurements

Using the FRAX® algorithm, fracture probabilities of major osteoporotic fractures were calculated, because the use of major osteoporotic fracture probability has been recommended above of hip fracture probability for intervention policy[10]. The results and utilization of the FRAX® have been described by Kanis et al[11]. The identification of risk factors is based on twelve international population-based cohorts, comprising over 60,000 subjects. This population was studied for a quarter of a million person/years and included about 5500 fractures, of which nearly 1000 hip fractures. Using Poisson regression model, fracture probabilities have been estimated for different combinations of risk factors[12-14]. Separate models have been developed for men and females. Subsequently, the algorithm was validated in 11 other cohort studies[13].

The FRAX® has been developed from population-based cohort studies in Europe, the US, Asia and Australia. So far, references are available for France, Italy, the UK, Spain, Sweden, Turkey, the US (Caucasian, Black, Hispanic and Asian), China and Japan. Because no references for the Dutch population are available, we used the UK references for this study as has been recommended by the European Guidance as a surrogate for countries with high fracture risk, such as the Netherlands[8]. Probabilities were calculated with and without BMD of the femoral neck. Using SPSS software (version 16.0) descriptive statistics were obtained for the overall population and for subgroups based on age and DXA outcome. Paired-samples T-tests were conducted to evaluate the contribution of BMD on participants' scores on the FRAX®.

RESULTS

According to the current intervention policy of the Dutch F&O clinics, treatment is recommended to patients with osteoporosis. Based on DXA measurement and spinal radiographs, pharmacological intervention was recommended in 169 females (43%).

The mean 10-year fracture probability of a major osteoporotic fracture according to the FRAX® was 21% (standard deviation [SD] = 9.8; range 5-57). When BMD value was taken into account, the mean fracture probability was significantly lower (p<0.01): 17% (SD 9.1; range 5-58). The average fracture probabilities in females of different ages are shown in figure 1. As expected, fracture probability increased with age. The average fracture probabilities exceeded the 7% (UK) and 7.5% (Europe) health-economic thresholds[8,9].

Figure 1. Average major osteoporotic (MO) fracture probability according to the FRAX® in 396 Dutch fractured females, computed with (+) and without (-) BMD value
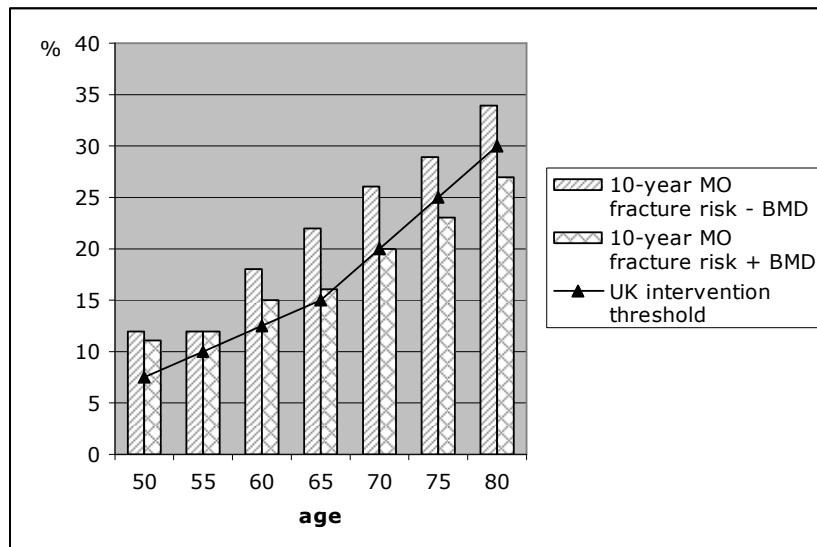
In addition, they exceeded the UK intervention thresholds in fractured females of all ages[10] if BMD value was not taken into account. After the integration of BMD, the average fracture probabilities significantly decreased ($p<0.01$). In females aged over 70 years, the average fracture probability decreased below the intervention thresholds.

In figure 2a-b, the fracture probabilities of individual patients with osteoporosis, osteopenia and normal BMD are shown with and without the inclusion of BMD to estimate fracture probability. If BMD was *not* included, values *above* the intervention thresholds were calculated for patients with (n=141) and without (n=162) osteoporosis. Furthermore, 93 subjects (23%) had a fracture probability *below* the intervention thresholds, of which 28 females with osteoporosis. After the inclusion of BMD, 103 patients with osteoporosis and 83 patients without osteoporosis had a fracture probability *above* the intervention thresholds. Two hundred ten subjects (53%) had a fracture probability *below* the intervention thresholds, of which 66 had osteoporosis.

DISCUSSION

In this study, the 10-year major osteoporotic fracture probability was assessed in fractured females to evaluate the current intervention policy of the Dutch F&O clinics. According to the FRAX® 10-year fracture probability, the current policy of the Dutch F&O clinics is accurate towards fractured females with osteoporosis, however not those without. Based on the average FRAX® 10-year fracture probabilities the treatment of all fractured females may be appropriate and cost-effective in the Dutch population. However, about a substantial amount of females had a fracture probability below the intervention thresholds.

Figure 2a. The 10-year fracture probability without BMD in fractured females with osteoporosis, osteopenia and normal BMD
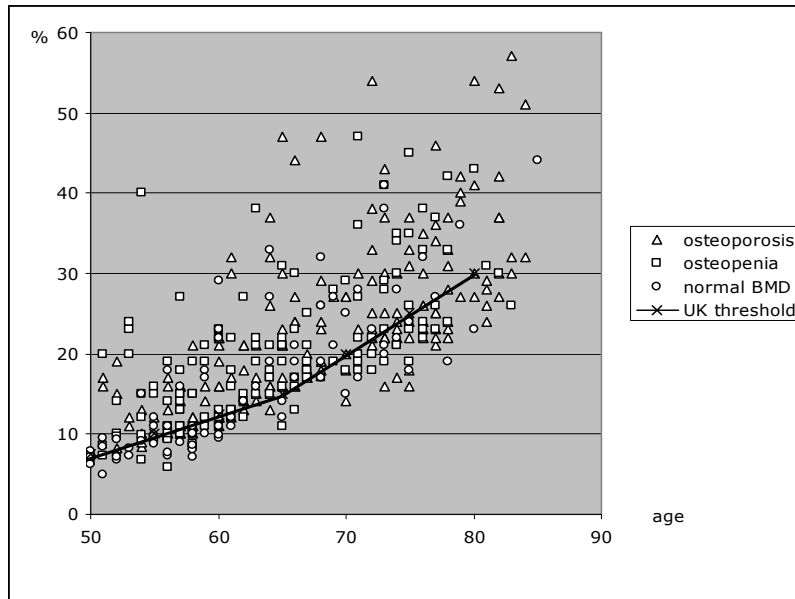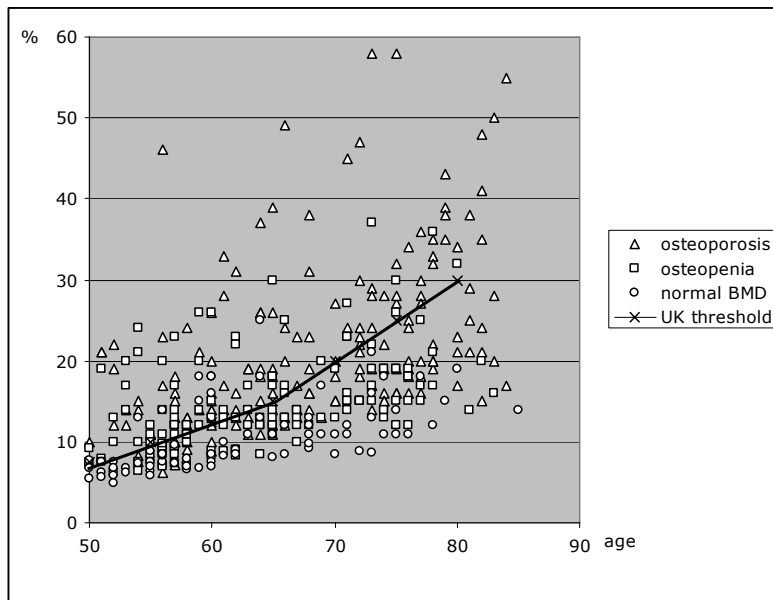

Figure 2b. The 10-year fracture probability with BMD in fractured females with osteoporosis, osteopenia and normal BMD

According to our results, a high fracture probability was not limited to females with osteoporosis. Based on the risk factors included in the FRAX, fracture probabilities above the cost-effectiveness and intervention thresholds were also calculated for patients with higher levels of BMD. In females aged over 70 years, fracture probabilities decreased below the intervention threshold if BMD was included. This might be explained because the FRAX® fracture risk probability is based on femoral BMD, whereas the diagnosis of osteoporosis is based on the lowest BMD of either the spine or the hip, including the total hip as well as the femoral neck and trochanter. In accordance with previous reports on the F&O clinics[6] the oldest elderly were underrepresented in our population. The inclusion of relatively healthy elderly in this study may have resulted in higher average levels of BMD in the subjects over 70 years and also explains the underrepresentation of hip fractures in our population (8%).

The average fracture probabilities in fractured females exceeded or closely approached the UK intervention and cost-effectiveness thresholds for all ages. Therefore our findings support the intervention policy as recommended by the European Guidance, to treat all fractured postmenopausal females irrespective of their BMD. However, there are several reasons to question the treatment of all fractured females in the Netherlands. First, different intervention thresholds have been set for different ages in the UK to prevent from under-treatment of younger people and over-treatment of older people when using a single threshold. However, the recommendation to treat all fractured females has been solely based on cost-effectiveness and comprises a threshold which is equal for all ages. According to our results, overtreatment may also occur in individual fractured females based on their risk profile, especially if BMD is included. A substantial amount of females (54% and 23% with and

without the inclusion of BMD respectively) had a fracture probability *below* the intervention thresholds, especially younger females with higher BMD. If BMD was included this additionally concerned women over the age of 70 years. Second, although treatment of all fractured females might be cost-effective, it remains unclear if pharmacological intervention in patients without osteoporosis reduces fracture risk. The majority of research on the effect of drug treatment on fracture risk concerns patients with low BMD. One study on the effect of alendronate showed that it significantly reduced the fracture risk among females with osteoporosis but not among females with normal BMD[15]. Moreover, pharmacological treatment does not address other risk factors included in the FRAX® such as low bodyweight, alcohol use and smoking. Treatment with oral bisphosphonates should only be prescribed if it is expected to decrease fracture risk because they have been associated with adverse events from the upper gastrointestinal tract and several other events such as acute phase response, hypocalcaemia, secondary hyperparathyroidism, muscoskeletal pain, osteonecrosis of the jaw and ocular events[16]. Third, no research has been conducted on fracture probabilities and cost-effectiveness in the Netherlands. Further insight in the Dutch population is necessary to draw definite conclusions on the treatment of all fractured females in the Netherland.

If the treatment policy of fractured females should not be solely based on BMD value, nor on a single risk factor (prior fragility fracture), it might be suggested that the implementation of (FRAX®) fracture risk estimation, which integrates BMD and risk factors, may improve the current intervention policy of the Dutch F&O clinics. The question remains if the BMD value should be in- or excluded for the estimation of fracture risk. Measurement of BMD value may be especially important females with

higher levels of BMD, which is more frequent in females of younger ages. The UK guidelines recommended that bone densitometry may sometimes be appropriate in fractured females, particularly in younger postmenopausal females[9]. We suggest that the clinician should profess the incorporation of BMD. Furthermore, the clinicians' view is of great importance because the risk of falls is not included in the FRAX®, nor in the DXA outcome. Recently, it has been discussed that falls are more important in determining fracture risk than low BMD[17].

A strength of our study is that we investigated fracture probability in a population of relatively young fractured women. Insight in fracture probability in this group is important because it has been estimated that 40% to 60% of elderly will suffer a subsequent fracture within 10 years after a prior fracture[2]. Our study also comprises several limitations. First, no references of the FRAX® fracture probability are available for the Dutch population. However, the European Guidance recommended that the UK references can be used as a proxy for countries with a high average fracture risk, such as the Netherlands. Recently, another fracture risk calculation tool has been designed based for the Dutch population. However, this has not been validated yet. Second, only 40% of the patients of the original F&O clinics participated in our study. Despite the low response rate, our population accurately reflected the population of the F&O clinics because there were no significant differences in mean age and incidence of osteoporosis, osteopenia and normal BMD between our population and the overall population that visited the F&O clinic during the same period. Third, our sample was too small to perform separate analyses for different types of fractures. Therefore insight on the intervention policy regarding different types of fractures could not be provided. Fourth, men were not included in this study.

We conclude that the current policy of the F&O clinics is accurate towards fractured females with osteoporosis, however not those without. Treatment of all fractured females seems appropriate and cost-effective based on average population-based values but can be questioned from a risk-benefit and ethical point of view. The current policy of the F&O clinics may be improved by the estimation of fracture probability. Further research is warranted to provide Dutch references for the estimation of fracture probabilities and cost-effectiveness. In addition, the effect of pharmacological treatment on fracture risk reduction in patients without osteoporosis should be further investigated.

REFERENCES

1. Poole K, Compston J. Osteoporosis and its management. *BMJ* 2006; **333:**1251-1256.

2. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. *JAMA* 2007; **297:**387-394.

3. Klotzbuecher CM, Ross PD, Landsman PB, *et al.* Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res* 2000; **15:**721–739.

4. Kwaliteitsinstituut voor de gezondheidszorg CBO. Osteopose: tweede herziene richtlijn. Alphen a/d Rijn: Van Zuiden Communications, 2002.

5. van Helden S, Cauberg E, Geusens P, *et al.* The fracture and osteoporosis outpatient clinic: an effective strategy for improving implementation of an osteoporosis guideline. *J Eval Clin Pract* 2007; **13:**801-805.

6. Blonk M, Erdtieck R, Wernekinck M, Schoon E. The fracture and osteoporosis clinic: 1-year results and 3 months-compliance. *Bone* 2007; **40:**1643-1649.

7. Hegeman JH, Willemsen G, van Nieuwpoort J, *et al.* Effective tracing of osteoporosis at a fracture and osteoporosis clinic in Groningen: an analysis of the first 100 patients. *Ned Tijdschr Geneesk* 2004; **148:**2180-2185.

8. Kanis JA, Burlet N, Cooper C, *et al.* The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). European Guidance for diagnosis and management of

osteoporosis in postmenopausal women. *Osteoporos Int* 2008; **19:**399-428.

9. Kanis JA, Compston J, Cooper A, *et al.* on behalf of the National Osteoporosis Guideline Group. Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 in the UK. http://www.shef.ac.uk/NOGG/

10. Kanis JA, McCloskey E, Johansson H, *et al.* on behalf of the National Osteoporosis Guideline Group. Case finding for the management of osteoporosis with FRAX® - assessment and intervention thresholds for the UK. *Osteoporos Int* 2008; **19:**1395-1408.

11. Kanis JA, Johnell O, Oden A, *et al.* FRAX™ and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008; **19:**385-397.

12. Kanis JA, Johnell O, De Laet C, *et al.* A meta-analyses of previous fracture and subsequent fracture risk. *Bone* 2004; **35:**375-382.

13. Kanis JA, Oden A, Johnell O, *et al.* The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 2007; **18:** 1033-1046.

14. Oden A, Dawson A, Dere W, *et al*. Lifetime risk of hip fracture is underestimated. *Osteoporos Int* 1998; **8:**599–603.

15. Cummings SR, Black DM, Thompson DE, *et al.* Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998; **280:**2077–2082.

16. Papapetrou PD. Bisphosphonate-associated adverse events. *Hormones* 2009; **8:**96-110.

17. Järvinen TL, Sievänen H, Khan KM, *et al.* Shifting the focus in fracture prevention from osteoporosis to falls. *BMJ* 2008; **336:**124-126.

Part II:

Bio-psychological aspects in fracture

risk management

CHAPTER 5

Osteoporosis and fractures in relation to depression: a systematic review

Noortje A Verdijk[1], Maarten JM van Son[2], Victor J Pop[1]

1. the Centre Of Research for Psychology in Somatic diseases, Medical Psychology and Neuropsychology, Tilburg University
2. Department of Clinical and Health Psychology, Utrecht University

ABSTRACT

Objective: previous reviews on depression and osteoporosis described contradictory results, to be partially explained by the lack of differentiation between osteoporosis and fractures and by substantial differences in definition of depression and research designs. Therefore, we studied literature on depression in relation to osteoporosis and fractures, while making further distinctions between depressive syndrome and symptoms, and cross-sectional and longitudinal studies.

Design of Study: systematic review.

Methods: Using Pubmed and PsychInfo, a literature search was conducted on all papers published since 1990 on depression as a risk factor in osteoporosis and fractures.

Results: twenty-nine studies were included. Seventeen studies concerned depressive syndrome in relation to BMD and/ or BTM, of which 16 cross-sectional and one longitudinal study. Twelve studies investigated depressive symptoms. Of these, four had a longitudinal design and four concerned fractures.

Conclusion: Depressive syndrome and symptoms are associated with low bone density. However, the nature and clinical relevance of this relationship remains unclear. Longitudinal studies showed that depressive symptoms increase fracture risk, independently of BMD. Further insight in the relation between depression and osteoporosis is of great importance considering the high prevalence of both diseases. Even a weak link might result in a major health impact. Hence, further research is necessary.

INTRODUCTION

Depressive disorders are the fourth most important cause of disability worldwide and are expected to have become second by 2020[1]. Regarding the prevalence and definition of depression, a difference must be made between depressive syndrome and depressive symptoms. Depressive syndrome (major depressive disorder; MDD) refers to a set of symptoms with at least one of the major signs of depression (low mood or loss of interest) and several symptoms such as sleeping problems, cognitive dysfunction or eating problems[2]. These symptoms have to be prominent for at least two weeks, with a major negative impact on daily activities. Patients with sub-threshold depression have symptoms of depression, but do not meet DSM-IV criteria for major depression[3]. In the general elderly population the prevalence of depressive syndrome is 1 to 3%[4], whereas clinically relevant symptoms of depression occur in 8 to 16%[5]. Depressive disorders are often chronic and have been associated with a wide range of physiological changes and poor health conditions[6], also in the elderly[7,8]. Chronic depression more often occurs at symptom than at syndrome level[9]. Depressive symptoms affect well-being and psychosocial functioning with nearly the same degree of impairment as depressive syndromes[4,10].

Like depression, osteoporosis is a very common disorder, especially among elderly. During lifetime, osteoporotic fractures affect one out of two women and one out of five men[11]. Osteoporosis is commonly defined by assessing bone mineral density (BMD) using bone densitometry. According to the World Health Organization (WHO), osteoporosis is diagnosed if the bone mineral density (BMD) level is more than 2.5 times below reference measurement[12]. In addition, bone turnover markers

(BTM) may provide information on the future risk for bone loss, and are used as indices of therapeutic alternatives[13,14]. BMD is an important predictor of future fractures: for each standard deviation fall in BMD fracture risk increases about 1-3 fold[15,16]. However, as the predictive value of absorptiometric techniques to predict fractures is rather low[17], an important amount of fractures occurs in subjects without osteoporosis[18,19]. Therefore, it is important to differentiate between osteoporosis and fractures when studying risk factors.

From the 1980s on, researchers first started to investigate the relation between depression and osteoporosis, and showed that depression is an adverse outcome of osteoporotic fractures. Subsequent studies pursued a distinct perspective and investigated depression as a risk factor for bone loss and fractures[20]. Several biological explanations have been suggested to explain this association, of which overactivity of the hypothalamic pituitary-adrenal (HPA) axis, resulting in hypercortisolism, is most often referred to. From behavioural perspective it has been suggested that the use of psychoactive drugs and poor health behaviour, such as physical inactivity, nutritional deficiencies, excessive alcohol intake and smoking may negatively affect bone strength and increase the risk of falls and fractures.

So far, several reviews on depression and osteoporosis have been published[20-22]. However, no clear distinction has been made between osteoporosis and fractures, different levels of depression (syndrome and symptom) and different research designs (cross-sectional or longitudinal). In addition, more studies have been published recently. Therefore, the aim of this paper is to update and review the literature on the relation between osteoporosis and depression on the one hand and fractures and depression on the other hand, while further differentiating between

depressive syndrome and symptoms, and cross-sectional and longitudinal research design.

METHODS

Using Pubmed and PsychInfo, a literature search was conducted on all papers published since 1990 on depression as a risk factor for osteoporosis and fractures using the following keywords: depression, depressive syndrome, depressive symptoms, osteoporosis, osteopenia, bone mineral density, bone metabolism, bone turnover, bone turnover markers, and fractures. Only human studies, investigating the relation between (i) osteoporosis (by means of bone mineral density (BMD) and/ or bone turnover markers (BTM)) or fractures and (ii) depressive syndrome or symptoms, measured using valid and appropriate instruments, and that were written in English, were included. The included studies were first subdivided based on the investigation of osteoporosis (bone density and/ or bone turnover) versus fractures. Second, studies were subdivided based on the level of depression. Studies that used clinical interviews to define depression according to DSM-IV criteria were defined as measuring depression at syndrome level, whereas studies that used self-rating scales were defined as assessing depression at symptom level. Third, a distinction was made between cross-sectional and longitudinal studies. Studies in which data were collected at one point in time were referred to as cross-sectional. Studies describing repeated measures were labeled as longitudinal.

RESULTS

A total of 29 studies were included. Sixteen cross-sectional studies on BMD and depressive syndrome were found, of which 8 additionally assessed the relation between BTM and depressive syndrome. One study only investigated BTM and depressive syndrome. One longitudinal study on BMD and depressive syndrome was found. A total of 9 studies on BMD and depressive symptoms were found, of which 1 longitudinal and 8 cross-sectional. In addition, 4 studies on fractures and depressive symptoms were found, of which 1 cross-sectional and 3 longitudinal. The results are summarized in Tables 1a-c.

Table 1a. Characteristics of studies on the relationship between depressive syndrome bone density, and bone turnover

Depressive syndrome and BMD: cross-sectional design						
1st author, year of publication	N	mean age	sex	control group	location DXA	significant relation
Amsterdam, 1998	11	40	♀♂	yes	S	No
Altindag, 2007	77	41	♀	yes	S, H	Yes
Eskandari, 2007	133	35	♀	yes	S, H	Yes
Halbreich, 1995	68	39	♀♂	yes	S, H	Yes
Kahl, 2005a	58	27	♀	yes	S, H, F	Yes
Kahl, 2005b	26	28	♀	yes	S, H, F	Yes
Kahl, 2006	83	30	♀	yes	S, H, F	Yes
Kavuncu, 2002	84	36	♀	yes	S, H	No
Michelson, 1996	48	41	♀	yes	S, H, F	Yes
Mussolino, 2004	5171	30	♀♂	yes	H	Yes
Özsoy, 2005	65	36	♀♂	yes	S, H	No
Petronijvić, 2008	120	41	♀	yes	S, H	Yes
Schweiger, 1994	137	61	♀♂	yes	S	Yes
Yazici, 2003	40	31	♀	yes	S, H	Yes
Yazici, 2005	65	45	♀	yes	S, H	No

S = spine; H = hip; F = forearm

98

Table 1a. Characteristics of studies on the relationship between depressive syndrome bone density, and bone turnover

Depressive syndrome and bone turnover markers: cross-sectional design

1st author, year of publication	N	mean age	sex	control group	location DXA	significant relation
Altindag, 2007	77	41	♀	yes	S, H	Yes
Herran, 2000	38	44	♀	yes	-	Yes
Kahl, 2005 a	58	27	♀	yes	S, H, F	Yes
Kahl, 2005 b	26	28	♀	yes	S, H, F	Yes
Kahl, 2006	83	30	♀	yes	S, H, F	Yes
Kavuncu, 2002	84	36	♀	yes	S, H	No
Michelson, 1996	48	41	♀	yes	S, H, F	Yes
Petronijvić, 2008	120	41	♀	yes	S, H	Yes
Yazici, 2003	40	31	♀	yes	S, H	Yes

Depressive syndrome and BMD: longitudinal design

Schweiger, 2000	39	62	♀♂	yes	S	Yes

Table 1b. Characteristics of studies on the relationship between depressive symptoms and bone density

1st author, year of publication	N	mean age	sex	control group	location DXA	significant relation

Depressive symptoms and BMD: cross-sectional design

1st author, year of publication	N	mean age	sex	control group	location DXA	significant relation
Coehlo, 1999	102	58	♀	no	S, H	Yes
Furlan, 2005	19	64	♀	yes	S	Yes
Jacka, 2005	78	53	♀	no	S, H	Yes
Laudisio, 2008	306	79	♀♂	no	A	Yes
Reginster, 1999	121	63	♀	no	S, H	No
Robbins, 2001	1552	74	♀♂	no	H	Yes
Whooley, 1999	7414	73	♀	yes	S, H	No
Wong, 2004	1999	72	♂	no	S, H	Yes

Depressive symptoms and BMD: longitudinal design

Whooley, 2004	515	65	♂	yes	S, H	No

S = spine; H = hip; F = forearm; A = achilles

Table 1c. Characteristics of studies on the relation between depressive symptoms and fractures

1st author, year of publication	N	mean age	sex	control group	fracture type	sign. relation
Depressive symptoms and fractures: cross-sectional design						
Silverman, 2007	3789	67	♀	No	V	yes
Depressive symptoms and fractures: longitudinal design						
Mussolino, 2005	6195	49	♀♂	No	H	yes
Sprangler, 2008	93676	64	♀	No	A	yes
Whooley, 1999	7414	73	♀	No	A	yes

V = vertebral fracture; H = hip fracture; A = any fracture

OSTEOPOROSIS

Depressive syndrome

The first study on osteoporosis and depression concerned a cross-sectional study on the relation between BMD and depressive syndrome and was conducted in 1994[23]. Spinal BMD was approximately 15% lower in patients with Major Depressive Disorder (MDD) than in healthy controls. Factors such as weight, physical activity, smoking, medical history and duration of depression and previous episodes, did not affect this relation. Comparable results were found by Michelson et al.[24], who showed that premenopausal women with a single or recurrent episode of depression had about a 6% lower level of BMD at the spine and 10-14% at the hip than healthy women. About a third of the depressed women even had an average BMD of 2 SD below the expected norm; values which are frequently reported in postmenopausal women. The average activity levels and mean body weight did not differ between depressed and non-depressed participants and treatment with antidepressants was not related to BMD. These findings applied to women with a current or a past

episode of depression. In accordance, other studies found BMD at the spine and hip to be significantly lower in depressed than in healthy women[25-27], independently of severity or duration of depression. Yazici et al.[27] suggested that bone loss might even occur in very early stages of depression because the depressed women who were included in their study had not had any previous depressive episode. Petronijvić et al.[28] also found BMD to be significantly lower in depressed women compared to controls. However, they showed that the decrease in BMD was correlated with the duration of the depression. No influence of (psychotropic) medication on bone metabolism was found. The N-HANES III study showed that major depression was associated with low BMD[29]. Interestingly, this association was only found in young men; not in women. In addition, Halbreich et al.[30] concluded that psychiatric patients (among which depressed patients) had lower BMD levels than healthy controls, particularly males. The patients' psychiatric diagnosis (MDD or schizophrenia) appeared not to be related with BMD, nor specific medications that were used. Kahl et al. investigated the association between depression[31], borderline personality disorder (BPD) and BMD and showed that low BMD is related to depression above BPD or health status. Subsequently, they showed that low BMD is stronger associated with depressive disorder in combination with BPD than with depression alone[32]. In a study among young female patients with depressive syndrome and anorexia nervosa, Kahl et al. showed that over 50% of the patients had osteopenia[33]. Although the mean BMD reduction was mild in comparison to healthy controls, they concluded that young depressed patients with anorexia may be at high risk to develop osteoporosis early in life.

In contrast to these findings, other cross-sectional studies found no association between depressive syndrome and BMD: Amsterdam and

Hooper found similar BMD values in young depressed patients (male and female) and healthy participants[34]. However, this study was limited by a small sample size. Kavuncu et al. found no difference in mean BMD values at all sites when comparing depressed and healthy women[35]. Öszoy et al. compared BMD at the spine and hip in young major depressed male and female patients and in healthy controls and found no significant differences between both groups[36]. In addition, Yazici et al. found no differences in average BMD level between depressed premenopausal women and healthy controls[37].

In addition to BMD, cross-sectional research on bone turnover markers and depressive syndrome has been conducted to provide insight in the relation between osteoporosis and depressive syndrome. Bone turnover markers measure the rate of bone turnover and reflect the functioning of osteoblasts (bone formation) and osteoclasts (bone resorption). Receptors, growth factors and cytokines, enzymes, bone-associated proteins and miscellaneous, which indirectly affect bone turnover are not discussed in this review. Bone formation markers that have been widely used in clinical research are osteocalcin, alkaline phosphatase and type 1 collagen propeptides. Petroijević et al., Kahl et al., and Herrán et al. found elevated levels in depressed participants[28,31-33,38], whereas Altindag et al. and Michelson et al. found decreased levels[24,25]. Yazici et al. and Kavuncu et al. found no differences in osteocalcin level between depressed and non-depressed participants[27,35,37]. No significant differences in alkaline phosphatase and type 1 collagen propeptides have been found in depressed patients compared to healthy controls[24,32,33,35,37,38]. Important markers of resorption are deoxyperydinoline and type 1 collagen telopeptides. Elevated levels of deoxypiridinoline have repeatedly been found in depressed patients compared to healthy controls[27,31,35,38].

102

However, Michelson et al. found decreased levels of deoxypiridinoline in depressed patients[24]. Increased levels of type 1 collagen telopeptides have been reported in depressed participants[25,38], however not unequivocally[24,37].

So far, only one longitudinal study has been conducted on depressive syndrome and BMD: Schweiger et al. assessed BMD[39], measured over a period of at least 2 years, in 18 depressed patients and 21 healthy controls. They showed that the average, yearly bone loss was significantly greater in depressed patients than in healthy subjects. Interestingly, bone loss in depressed men was about 6% greater than in depressed women.

Depressive symptoms

Research on BMD and depressive symptoms is mainly population-based and cross-sectional. Coehlo et al. investigated the relationship between BMD and depressive symptoms by comparing self reported symptoms of depression of women with and without osteoporosis[40], based on DXA measurement of the lumbar spine and femur. Osteoporotic women showed significantly higher levels of depressive symptoms than women without osteoporosis. Robbins et al. carried out a population-based study in which the measurement of depressive symptoms preceded BMD measurement with an interval of two years[41]. No repeated measures were conducted. They showed a significant association between depressive symptoms and BMD after two years in elderly women. Jacka et al. assessed BMD in perimenopausal women[42], within 12 months after filling in a questionnaire on depression. They found that, after adjustment for age, weight and hormone therapy, self-reported depression was associated with lower BMD at the hip, however not at the spine. Wong et al. found comparable results in elderly Asian men[43]; the average BMD

level was 2.1% lower in subjects with depressive symptoms than in healthy controls. Depression was a 1.4-fold risk for a T-score equal to or less than −1.0 SD. Furlan et al. showed that women with a self-reported history of depression had significantly lower BMD Z-scores in the spine and hip than women who had never been depressed[44]. In contrast with the above findings, Reginster et al. found no significant association between depressive symptoms and BMD in postmenopausal women[45]. In a large prospective cohort study, Whooley et al. measured depressive symptoms and BMD at base-line[46]. Mean BMD was similar in women with and without self-reported depression. However, after adjustment for several potential confounders, women in the highest percentile of body mass index and with depressive symptoms, had 4.6% lower levels of BMD in the spine was and 2.6% lower in the hip than women without depressive symptoms.

Only one longitudinal study on BMD and depressive symptoms was found; Whooley et al. conducted a prospective cohort study on depression[47], falls and fracture risk. They reported no significant difference in the annual change in BMD between men with and without self-reported depression.

FRACTURES

Research on fractures is limited to depressive symptoms. One cross-sectional study was found. The prevalence of depressive symptoms was investigated among postmenopausal women with osteoporosis, with and without a vertebral fracture. There was an absolute increase of 2.5% in the prevalence of depressive symptoms in women with a vertebral fracture (6.6%) compared to those with no fracture (4.1%). Three studies longitudinally investigated depressive symptoms as a risk factor for

fractures. Spangler et al. investigated self-reported depressive symptoms and fractures in 93,676 postmenopausal women[48]. No significant differences were found in adjusted risk for hip, wrist of spine fractures between women with and without depressive symptoms. However, depressive symptoms were associated with a minimal increased risk of any fracture. Women with serious emotional problems and mental illness were excluded from this study. The NHANES I study showed that depressive symptoms were prospectively associated with an increased risk of hip fracture after adjustment for confounding factors[49]. In accordance with these findings, Whooley et al. reported a significant association between depressive symptoms and fracture risk in older women[46]. Women who reported high depressive symptomatology at baseline, had a 40% increased non-vertebral fracture rate per year of follow-up compared to women with low depressive symptomatology at baseline. Moreover, women with depressive symptoms had a 40% increased propensity to fall. Falls appeared to only partially explain the relation between depressive symptoms and fracture risk. So far, no research on depressive syndrome and fractures was found in literature.

DISCUSSION

The aim of this paper is to accurately update and review literature on depression, osteoporosis and fractures by making a distinction between depressive syndrome and symptoms and cross-sectional and longitudinal studies. From cross-sectional research there are indications that depressive syndrome and symptoms are associated with decreased BMD, and that depressive syndrome is associated with deviant bone metabolism. Longitudinal research provides evidence for depressive symptoms as a risk factor for fractures, however not for depressive syndrome as no longitudinal study could be retrieved.

Research on osteoporosis in relation to depressive syndrome and symptoms mainly concerns cross-sectional studies. The majority of these studies found evidence for a relation between BMD and depressive symptoms and syndrome. The nature of the relationship remains unclear because only two longitudinal studies have been performed, with contradictory results. Moreover, the results of these two studies cannot be compared as one study concerns depressive syndrome and one study concerns depressive symptoms. Moreover, it remains unclear if the relationship that was found between depressive syndrome, symptoms and BMD is limited to depression or whether it concerns psychiatric diseases in general. Halbreich et al. found significant lower levels of BMD in psychiatric patients with different syndromes[30], compared to healthy controls. Although Kahl et al. found no significant relation between BMD and BPD alone[32], they showed that depression in combination with BPD was stronger associated with low BMD than depression alone. With the exception of one study, no studies investigated the relation between depression and osteoporosis, according to the diagnostic criteria.

106

Therefore, the clinical relevance of the relation between osteoporosis and depressive syndrome and symptoms remains unclear.

Low BMD has been suggested to result from the effect of depression on bone metabolism. Most cross-sectional studies found indications for deviant bone turnover in patients with depressive syndrome. However, it remains unclear if bone formation and resorption are increased or decreased in depressed subjects. Conflicting findings may be explained by the fact that cross-sectional data do not adequately represent duration and intensity of the effects of bone metabolises.

Research on fractures is limited to depressive symptoms. Only few studies have been conducted. However, they are all population-based and included large samples. From these studies it can be concluded that depressive symptoms increase the risk for fractures. It was found that low BMD cannot explain this relation. On study reported that subjects with depressive syndromes had an increased risk of falls. However, this only partially explained the relationship between depressive symptoms and fractures. Overall, adjustment for smoking, alcohol, physical activity, and antidepressant use did not significantly affect the relation between depressive symptoms and fractures. Therefore, it might be hypothesized that depressive symptoms, not (solely) alter bone remodelling but (also) affect bone architecture, for example by hypercortisolism[34]. So far, bone architecture has not been investigated in relation to depression. Another explanation might be that behavioural symptoms of depression, which have not been investigated in relation to fractures, may play a role: Whooley et al. showed that feelings of hopelessness[46], worthlessness and dissatisfaction were strongest associated with fracture risk. Another explanation might be that abnormal responses to stress in subjects with depressive symptoms may increase fracture risk[44]: depressive symptoms

have been associated chronic stress. Although the relation between stress and fractures is beyond the scope of this review, there are indications that long-term mental distress is a risk factor for osteoporotic fractures in middle-aged women[50,51].

Furthermore, we can conclude from the reviewed studies that there is large heterogeneity in research designs. Although we differentiated between osteoporosis and fractures, depressive syndrome and symptoms and cross-sectional and longitudinal studies, there is still a wide variation in characteristics of patient groups, such as gender, age and menopausal status; factors which are known to interfere with both depression and bone metabolism. Moreover, there are differences in research methods such as the type and location of BMD or bone marker measurement, duration and currency of depression, the use of antidepressant drugs, or the period of time between measurements.

Based on the above, it might be concluded that there is need for well-conducted prospective cohort studies to further explore the relation between depression, osteoporosis and fractures. Insight in the relation between depression, osteoporosis and fractures is of great importance, considering the high prevalence of these diseases. Even a weak link might result in a major health impact. Future studies should be more homogenous is design, accurately define outcome parameters of depression and osteoporosis, and take into account confounders such as sex and age. Moreover, psychiatric controls should be included and remarkable findings, such as the relation between depressive syndrome and BMD in men and younger persons, deserve further investigation.

REFERENCES

1. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997; **349:**1498-1504.

2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition - Text Revision (DSMIV-TR), 4th ed. Washington, DC: American Psychiatric Press, 2000.

3. Cuijper P, Smit F. Subthreshold depression as a risk indicator for major depressive disorder: a systematic review of prospective studies. *Acta Psychiatr Scand* 2004; **109:**325-331.

4. Beekman A, Deeg D, Van Tilburg T, *et al.* Major and minor depression in later life: a study of prevalence and risk factors. *J Affect Disord* 1995; **36:**65-75.

5. Cole M, Dendukuri N. Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *Am J Psychiatry* **160:**1147-1156.

6. Prince M, Patel V, Saxena S, *et al.* No health without mental health. *Lancet* 2007; **370:**859-877.

7. Smit F, Ederveen A, Cuijper P, *et al*. Opportunities for cost-effective prevention of late-life depression: an epidemiological approach. *Arch Gen Psychiatry* 2006; **63:**290-296.

8. Cole M, Bellavance F, Mansour A. Prognosis of depression in elderly community and primary care populations: a systematic review and meta-analysis. *Am J Psychiatry* 1999; **156:**1182-1189.

9. Judd L, Akiskal H, Maser J, *et al.* A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar

major depressive disorders. *Arch Gen Psychiatry* 1998; **55:**694-700.

10. Wagner H, Burns B, Broadhead W, *et al*. Minor depression in family practice: functional morbidity, co-morbidity, service utilization and outcomes. *Psychol Med* 2000; **30:**1377-1390.

11. Cummings SR, Melton III R. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002; **359:**1761-1767.

12. World Health Organization (WHO) Working Group: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. *World Health Organ Tech Rep Ser*. 1994; **843:**1-129.

13. Bonnick SL, Shulman L. Monitoring osteoporosis therapy: bone mineral density, bone turnover markers, or both? *Am J Med.* 2006; **119(4 Suppl. 1):**25-31.

14. Miller P. Bone density and markers of bone turnover in predicting fracture risk and how changes in these measures predict fracture risk reduction. *Curr Osteoporos Rep* 2005; **3:**103-110.

15. Kanis JA, Burlet N, Cooper C, *et al.* European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2008; **19:**399-428.

16. Glüer CC. Quantative ultrasound techniques for the assessment of osteoporosis: expert agreement on current status. The International Quantative Ultrasound Consensus Group. *J Bone Min Res* 1997; **12:**1280-1288.

17. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone density predict occurrence of osteoporotic fractures. *BMJ* 1996; **312:**1254-1259.

18. Sornay-Rendu E, Munoz F, Garnero P, *et al.* Identification of osteopenic women at high risk of fracture: the OFELY study. *J Bone Min Res* 2005; **20:**1813-1819.

19. Wainwright SA, Marshall LM, Ensrud KE, *et al.* Hip fracture in women without osteoporosis. *J Clin Endocrinol Metab* 2005; **90:**2787-2893.

20. Gold D, Solimeo S. Osteoporosis and depression: a historical perspective. *Curr Osteoporos Rep* 2007; **4:**134-139.

21. Cizza G, Ravn, P, Chrousos G, Gold P. Depression: a major, unrecognized risk factor for osteoporosis? *Trends Endocrinol Metab* 2001; **12:**198-203.

22. Ilias I, Alesci S, Gold P, Chrousos G. Depression and osteoporosis in men: association or casual link? *Hormones* 2006; **5:**9-16.

23. Schweiger U, Deutschle M, Körner A, *et al*. Low lumbar bone mineral density in patients with major depression. *Am J Psychiatry* 1994;**151:**1691-1693.

24. Michelson D, Stratakis C, Hill L, *et al.* Bone mineral density in women with depression. *N Engl J Med* 1996; **335:**1176-1181.

25. Altindag O, Altindag A, Asoglu M, *et al.* Relation of cortisol levels and bone mineral density among premenopausal women with major depression. *Int J Clin Pract* 2007; **61:**416-420.

26. Eskandari F, Martinez PE, Torvik S, *et al.* Low bone mass in premenopausal women with depression. *Arch Intern Med* 2007; **167:**2329-2336.

27. Yazici K, Akinci A, Sütçü A, Ozçakar L. Bone mineral density in premenopausal women with major depressive disorder. *Psychiatry Res* 2003; **117:**271-275.

28. Petronijvić M, Petronijvić N, Ivković M, *et al*. Low bone mineral density and high bone metabolism turnover in premenopausal women with unipolar depression. *Bone* 2008; **42:**528-590.

29. Mussolino ME, Jonas B, Looker A. Depression and bone mineral density in young adults: results from NHANES III. *Psychosom Med* 2004; **66:**533-537.

30. Halbreich U, Rojanski N, Plater S, *et al.* Decreased bone mineral density in medicated psychiatric patients. *Psychosom Med* 1995; **57:**485-491.

31. Kahl K, Rudolf S, Stoeckelhuber B, *et al.* Bone mineral density, markers of bone turnover, and cytokines in young women with borderline personality disorder with and without comorbid major depressive disorder. *Am J Psychiatry* 2005a; **162:**168-174.

32. Kahl K, Greggersen W, Rudolf S, *et al.* Bone mineral density, bone turnover, and osteoprotegerin in depressed women with and without borderline personality disorder. *Psychosom Med* 2006; **68:**669-674.

33. Kahl K, Rudolf S, Dibbelt L, *et al.* Decreased osteoprotegerin and increased bone turnover in young female patients with major depressive disorder and a lifetime history of anorexia nervosa. *Osteoporos Int* 2005b; **16:**424-429.

34. Amsterdam J, Hooper M. Bone density measurement in major depression. *Prog Neuropsychopharmacol Biol Psychiatry* 1998; **22:**267-277.

112

35. Kavuncu V, Kuloglu M, Kaya A, *et al.* Bone metabolism and bone mineral density in premenopausal women with mild depression. *Yonsei Med J* 2002; **43:**101-108.

36. Öszoy S, Eşel E, Turan M, *et al.* Is there any alteration in bone mineral density in patients with depression? *Türk Psikiyatri Derg.* 2005; **16:**77-82.

37. Yazici A, Bagis S, Tot S, *et al.* Bone mineral density in premenopausal women with major depression. *Joint Bone Spine* 2005; **72:**540-543.

38. Hérran A, Amado J, García-Unzueta M, *et al.* Increased bone remodeling in first-episode major depressive disorder. *Psychosom Med* 2000; **62:**779-782.

39. Schweiger U, Weber B, Deuschle M, Heuser I. Lumbar bone mineral density in patients with major depression: evidence of increased bone loss at follow-up. *Am J Psychiatry* 2000; **157:**118-120.

40. Coehlo R, Silva C, Maia A *et al.* Bone mineral density and depression: a community study in women. *J Psychosom Res* 1999; **46:**29-35.

41. Robbins J, Hirsch C, Whitmer R, *et al.* The association of bone mineral density and depression in an older population. *J Am Geriatr Soc* 2001; **49:**732-736.

42. Jacka F, Pasco J, Henry M, *et al*. Depression and bone mineral density in a community sample of perimenopausal women: Geelong Osteoporosis Study. *Menopause* 2005; **12:**88-91.

43. Wong SYS, Lau EMC, Lynn H, *et al.* Depression and bone mineral density: is there a relationship in elderly Asian men? Results from Mr. Os (Hong Kong). *Osteoporos Int* 2005; **16:**610-615.

44. Furlan P, Ten Have T, Cary M, *et al.* The role of stress-induced cortisol in the relationship between depression and decreased bone mineral density. *Biol Psychiatry* 2005; **57:**911-917.

45. Reginster JY, Deroisy R, Paul I, *et al.* Depressive vulnerability is nota n independent risk factor for osteoporosis in postmenopausal women. *Maturitas* 1999; **33:**133-137.

46. Whooley M, Kip K, Cauley J, *et al.* Depression, falls, and risk of fracture in older women. Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 1999; **159:**484-490.

47. Whooley MA, Cauley JA, Zmunda JM, *et al.* Depressive symptoms and bone mineral density in older men. *J Geriatr Psychiatry Neurol* 2004; **17:**88-92.

48. Sprangler L, Scholes D, Brunner RL, *et al*. Depressive symptoms, bone loss, and fractures in postmenopausal women. *J Gen Intern Med* 2008; **23:**567-574.

49. Mussolino ME. Depression and hip fracture risk: the NHANES I epidemiologic follow-up study. *Public Health Rep.* 2005; **120:**71-75.

50. Søgaard AJ, Joakimsen RM, Tverdal A, *et al.* Long-term mental distress, bone mineral density and non-vertebral fractures. The Tromso Study. *Osteoporos Int* 2005; **16:**887-897.

51. Forsén L, Meyer HE, Søgaard AJ, *et al.* Mental distress and risk of hip fracture. Do broken hearts lead to broken bones*? J Epidemiol Community Health* 1999; **53:**343-347.

114

Psychometric characteristics of the Edinburgh Depression Scale in older fractured females

Noortje A Verdijk[1], Martha van den Berg[1], Ronald J Erdtsieck[3], Marion C Blonk[4], Geraline L Leusink[5], Victor J Pop[1]

1. Centre of Research on Psychology in Somatic diseases (CoRPS), Medical Psychology and Neuropsychology, Tilburg University
2. Coordination Centre of Nurse Practitioners for South East Netherlands
3. Maxima Medical Centre
4. Catharina Hospital Eindhoven
5. Stichting Zuidwester

ABSTRACT

Objective: Because the assessment of depression is important in fractured females, this study investigates the psychometric aspects of the Edinburgh Depression Scale (EDS) in a sample of older fractured females (55-85 years).

Design of Study: cross-sectional.

Setting: 354 female patients (55-85 years) of two Dutch F&O clinics.

Methods: Construct validity of the EDS is investigated in 354 females using the SCL-90 anxiety subscale, and the psychological domain and the general mental health subscale of quality of life questionnaires, the WHOQOL-bref and SF-36, respectively. Receiver operating characteristic (ROC) curves were obtained for a subsample of 147 females with low bone density to evaluate the best cut-off score of the EDS to predict major depression according to the DSM-IV criteria. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the EDS according to major depression were calculated for different cut-offs.

Results: Chronbachs alpha was 0.86. The EDS was significantly correlated with the other subscales (p<0.001). Using a cut-off of nine points, major depression was predicted with a sensitivity of 83%, specificity of 78%, PPV of 34% and NPV of 97%.

Conclusion: Major depression had a high prevalence in recently fractured elderly females with low bone density. Using a lower cut-off of nine, the EDS is a reliable and valid questionnaire to assess depressive symptoms in older fractured females.

INTRODUCTION

Osteoporotic fractures are a major public health issue, affecting one in two females and one in five men over 50 years[1]. In 2000, about 3.8 million osteoporotic fractures occurred in the European Union, equalling a financial burden of €31.7 billion[2]. By 2050, the direct cost of fractures in Europe will exceed €75 billion. Depressive disorders have been associated with different physiological consequences and poor health conditions[3,4], among which osteoporosis and its fractures[5]. Therefore, appropriate diagnosis and treatment of depression in fractured elderly with low bone mineral density (BMD) is warranted. Moreover, depressive symptoms are known to negatively influence recovery from fractures[6,7].

To overcome the time consuming character and costs of psychiatric interviews to diagnose major depression, assessment of depressive symptoms is often used as a proxy in research, as they affect well-being and psychosocial functioning with nearly the same degree of impairment as major depression[8,9]. Additionally, up to 27% of older persons suffering from depressive symptoms develop major depression within three years[10]. The Edinburgh Depression Scale (EDS) is a highly accepted and user-friendly questionnaire in research of depressive symptoms. It was originally designed as the Edinburgh Postnatal Depression Scale (EPDS), to assess postpartum depression and has been validated in postnatal females[11]. After validation in non-postnatal female community samples and men[12-14], the EPDS has been renamed the Edinburgh depression Scale (EDS). In the Netherlands, the EDS has been validated in postnatal and menopausal females (47-55 years) [15-17]. Recently, the EDS has been validated for internet use in females (mean age 55 years)[18]. However, it has never been validated in elderly females. Therefore, the aim of this

study is to investigate the reliability and validity of the EDS in a sample of older fractured females.

METHODS

Participants

In the period between October 2006 and July 2008, all patients of two Fracture and Osteoporosis (F&O) clinics in the South of the Netherlands were invited to participate in a prospective cohort study on osteoporosis and fractures, called the Eindhoven Secondary Fracture and Osteoporosis Reduction-project (ESFOR-p). The Medical Ethical Committee of the Maxima Medical Centre approved this study. Of the 1339 fractured patients who visited the clinics, 756 were interested to participate, of which 534 patients (mean age 66; SD=9) signed informed consent (93 males and 441 females). This study concerns Caucasian females over 55 years (n=372), in accordance with the definition of Beekman et al. for older subjects[10]. Due missing data, 18 subjects were excluded from analyses, resulting in a population of 354 females in this study. Table 1 summarizes their characteristics. In a subsample of 147 females with low bone density (osteoporosis or osteopenia according to the World Health Organization (WHO) criteria[19]) a structured clinical interview regarding major depression was performed.

Measurements

To measure depressive symptoms, participants filled out the EDS; a ten-item self report questionnaire (range 0-30). Higher scores reflect more depressive symptoms. Generally, a cut-off of 12/13 is recommended[11]. With Cronbach's alpha of at least 0.80, the EDS has good internal consistency[12-14]. Perceived symptoms of anxiety were measured with the anxiety subscale of the Symptom Check List-90 (SCL-90)[20]. The subscale contains ten questions, with a 5 point rating scale, ranging from 'totally not' to 'very much'. The Dutch version has good reliability and validity[21]. The WHOQOL-bref comprises 26 items on a 5-point Likert interval scale and has five domains. Better quality of life corresponds with higher scores. It has been validated in Dutch, with good construct validity and reliability[22,23]. In this study the psychological subscale was used (6 items). The Short Form-36 Health Survey (SF-36) contains 36 questions with standardized response choices, has eight subscales and a total range from 0-100. Higher scores reflect higher quality of life. It has been translated and validated in the Dutch community and diseased populations, with good reliability and validity[24]. We only used the "acute" version of the subscale general mental health (MH; nine items), employing a 1-week time frame. In a subsample of 147 females with low BMD, major depression was diagnosed by two trained psychologists (M.B., N.V.) using the depression section of the Composite International Diagnostic Interview (CIDI) of the WHO[25]. The CIDI is a fully structured interview to identify DSM-IV and ICD-10 symptoms. Reliability is good with a test–retest kappa coefficient of 0.71 and the interrater kappa coefficient of 0.95[26]. We used the one-month prevalence of major depressive episode.

Reliability of the EDS was investigated using Chronbach's alpha and construct validity by calculating Pearson correlations between the EDS,

and the SCL-90 anxiety subscale, psychological domain of the WHOQOL-bref, and general mental health subscale of the SF-36. A *p*-value below 0.001 was considered statistically significant. As a criterion for convergent validity we defined that a correlation should be at least 0.60, implying that over 36% of the variance should be shared. Finally, receiver operating characteristic (ROC) curves were perceived to assess the best EDS cut-off score according to the CIDI. The sensitivity (SN), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV), were calculated for different cut-offs. Ninety-five percent confidence intervals (95% CI) were calculated using binomial expansion. Statistical analyses were performed using SPSS software (version 16.0).

RESULTS

A total of 354 females was included (mean age 67; SD 8) with a mean EDS score of 6 points (SD 5). Chronbach's Alpha was 0.86. Using 12 as a cut-off, the prevalence of depressive symptoms was 16%. The Pearson correlation coefficients between the EDS and subscales of the SF-36, SCL-90, and WHOQOL-bref were -0.72, 0.65 and -0.64 respectively and significant at 0.01 level (two-tailed). In a subgroup of 147 females (mean age 67; SD 8), major depression occurred in 18 subjects (12%). The Area Under the Curve (AUC) was good (0.85). Table 2 shows the validity of the EDS according to the CIDI for different cut-off points. As can be seen, best results were achieved using a cut-off of nine points.

Table 1. Characteristics of 354 Dutch Caucasian fractured females (55-85 years)

	Mean	SD	N	%
Age	67	8		
Marital Status				
Married/ living together			238	67
Living apart together			4	1
Single/ divorced/ widowed			112	32
Educational level				
Low			189	53
Moderate			131	37
High			32	9
Economical status (income/ month)				
Low (< $1300)			111	31
Moderate ($1300-4000)			222	63
High (> $4000)			21	6
Bone density				
Osteoporosis			160	45
Osteopenia			129	36
Normal bone density			65	18
Type of fracture				
Hip			28	8
Vertebral			15	4
Wrist			106	30
Other[a]			201	57
Multiple fractures [b]			4	1

[a]*hand, forearm, elbow, clavicle, ankle, foot.* [b] *1x hip and vertebral fracture; 1x vertebral and wrist fracture; 1x wrist and vertebral fracture; 1x wrist and other fracture.*

Table 2. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the EDS according to the CIDI in 147 Dutch fractured females (55-85 years)

EDS score	sensitivity % (95% CI)	specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
6	89 (74-103)	97 (94-101)	22 (12-31)	55 (32-78)
7	89 (74-103)	60 (52-69)	24 (14-34)	98 (94-101)
8	83 (66-101)	70 (62-78)	28 (16-40)	97 (92-102)
9	**83 (66-101)**	**78 (70-85)**	**34 (20-48)**	**97 (92-102)**
10	72 (52-93)	79 (72-86)	33 (18-47)	95 (89-102)
11	61 (39-84)	83 (77-89)	33 (17-49)	94 (86-102)
12	61 (39-84)	86 (80-92)	38 (20-56)	94 (86-103)
13	56 (33-79)	89 (84-95)	42 (22-61)	94 (84-103)
14	44 (22-67)	92 (88-97)	44 (22-67)	92 (80-105)

DISCUSSION

The aim of this study was to investigate the reliability and validity of the EDS according to major depression, in older fractured females. Internal consistency was good and best validity was achieved using nine points as a cut-off. The EDS showed appropriate internal consistency and construct validity in older females: Cronbach's alpha was 0.86. The EDS correlated highly positive with the anxiety subscale (SCL-90), and highly negative with quality of life subscales of the SF-36 and WHOQOL-bref. All correlations exceeded the value of 0.60.

Previous reports on the validity of the EDS suggested a cut-off of 12 or 13 points to predict major depression[13]. However, based on our results, a lower cut-off (nine points) is recommended in older fractured females. The

validity of the EDS in older women using a cut-off of nine points is comparable with the validity of the EDS in younger females using a cut-off of 12 points; Cox et al. reported a sensitivity of 88%, specificity of 80%, and PPV of 21%[11]. Similar results were found in 951 Dutch Caucasian menopausal females by Becht et al.[17], reporting a sensitivity of 88%, specificity of 85% and PPV of 40%.

The prevalence of depressive syndrome in our sample was high (12%), compared to the general older population (3%)[9]. This might be explained by the inclusion of solely fractured females: 21% of our sample needed surgery, 24% of the females were hospitalized and 54% needed physiotherapy during several months. These are major negative life events which might contribute to co-morbid depression. Studies on depressive syndrome in elderly after hip fractures reported prevalence rates between 9% and 47%[27]. In contrast, the prevalence of depressive symptoms was rather low (16%), based on a cut-off of 12 points. In general, the prevalence of depressive symptoms is more or less twice that of depressive syndrome[28]. Using nine as a cut-off, the prevalence of depressive symptoms in the research population increased to 30%. Compared to 12% prevalence of depression syndrome, this further supports the use of a lower cut-off score in older fractured women.

A limitation of our study is that major depression was assessed in a small subsample (147 females), of which only 18 suffered from major depression. As a result, the confidence interval of the sensitivity, specificity, PPV and NPV were rather wide. However, for prior validation of the EDS in a female community sample, a clinical interview was conducted in 136 non-postnatal females of whom only 8 were diagnosed with major depression[11]. Another limitation is that our results cannot be generalized to the overall elderly population as major depression was only

investigated in females with low BMD. However, our findings are important for the majority of older fractured females as low BMD is highly prevalent in this group (81% in our sample).

From our study it can be concluded that the prevalence of major depression and depressive symptoms is high in older fractured females with low BMD. Assessing depressive symptoms in fractured elderly is important because undiagnosed depression might interfere with appropriate revalidation. We showed that the EDS is a reliable and valid questionnaire to assess depressive symptoms in older fractured females with low BMD. However, a lower cut-off score (nine instead of 12) is recommended.

REFERENCES

1. Cummings SR, Melton III R. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2000; **359:**1761-1767.

2. Kanis JA, Johnell O. Requirements for DXA for the management of osteoporosis in Europe. *Osteoporos Int* 2005; **16:**229–238.

3. Goodwin GM. Depression and associated physical diseases and symptoms. *Dialogues Clin Neurosci* 2006; **8:**259-265.

4. Dinan TG. The physical consequences of depressive illness. *BMJ* 1999; **318:**826.

5. Mezuk B, Eaton WW, Golden SH. Depression and osteoporosis: potential mediating pathways. *Osteopros Int* 2008; **19:**1-12.

6. Kempen GIJM, Sanderman R, Scaf-Klomp W, Ormel J. The role of depressive symptoms in recovery from injuries to the extremities in older persons. A prospective study. *Int J Geriatr Psychiatry* 2003; **18:**14-22.

7. Scaf-Klomp W, Sanderman R, Ormel J, Kempen GIJM. Depression in older people after fall-related injuries: a prospective study. *Age Ageing* 2003; **32:**88-94.

8. Wagner HR, Burns BJ, Broadhead WE, *et al.* Minor depression in family practice: functional morbidity, co-morbidity, service utilisation and outcomes. *Psychol Med* 2000; **30:**1377-1390.

9. Beekman ATF, Deeg DJH, Van Tilburg T, *et al.* Major and minor depression in later life: a study of prevalence and risk factors. *J Affect Disord* 1995; **36:**65-75.

10. Beekman ATF, Geerlings SW, Deeg DJH, *et al*. The natural history of late-life depression. *Arch Ger Psychiatry* 2002; **59:**605-611.

11. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal

Depression Scale (EPDS) in non-postnatal women. *Br J Psychiatry* 1987; **150:**782-786.

12. Matthey S, Barnett B, Kavanagh DJ, Howie P. Validation of the Edinburgh Postnatal Depression Scale for men, and comparison of item endorsement with their partners. *J Affect Disord* 2001; **64:**175-184.

13. Cox JL, Chapman G, Murray D, Jones P. Validation of the Edinburgh Postnatal Depression Scale in non-postnatal women. *J Affect Disord* 1996; **39:**185-159.

14. Murray L, Carothers AD. The validation of the Edinburgh Post-natal Depression Scale on a community sample. *Br J Psychiatry* 1990; **157:**288-290.

15. Pop VJ, Komproe IH, van Son MJ. Characteristics of the Edinburgh Post Natal Depression Scale in the Netherlands. *J Affect Disord* 1992; **26:**105-110.

16. Nyklíček I, Scherders MJ, Pop VJ. Multiple assessment of depressive symptoms as an index of depression in population-based samples. *J Psychiatry Res* 2004; **128:**111-116.

17. Becht MC, van Erp CF, Teeuwisse TM, *et al*. Measuring depression in women around menopausal age: towards a validation of the Edinburgh Depression Scale. *J Affect Disord* 2001; **63:**209-213.

18. Spek V, Nyklíček I, Cuijpers P, Pop VJ. Internet administration of the Edinburgh Depression Scale. *J Affect Disord* 2008; **106:**301-305.

19. World Health Organization (WHO) Working Group: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. *World Health Organ Tech Rep Ser.* 1994; **843:**1-129.

20. Derogatis LR, Lipman RS, Covi L. SCL-90, an outpatient psychiatric rating scale. *Psychopharmacol Bull* 1973; **9:**13-28.

21. Nederlands Instituut voor Psychologen : SCL-90, 1981-1986. In: Evers, A., Van Vliet-Mulder JC, Groot JC. Documentation of Tests and Testresearch in the Netherlands. Assen, van Gorcum, 2000.

22. Masthoff ED, Trompenaars FJ, Van Heck GL, *et al.* Validation of the WHO Quality of Life assessment instrument (WHOQOL-100) in a population of Dutch adult psychiatric outpatients. *Eur Psychiatry* 2005; **20:** 465-473.

23. Trompenaars FJ, Masthoff ED, Van Heck GL, *et al*. Content validity, construct validity, and reliability of the WHOQOL-Bref in a population of Dutch adult psychiatric outpatients. *Qual Life Res* 2005; **14:**151-160.

24. Aaronson NK, Muller M, Cohen PDA, *et al*. Translation, Validation, and Norming of the Dutch Language Version of the SF-36 Health Survey in Community and Chronic Disease Populations. *J Clin Epidemiol* 1998; **51:**1055–1068.

25. World Health Organization, 1997. *Composite International Diagnostic Interview, version 2.1.* WHO, Geneva.

26. Wittchen HU. Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): A critical review. *J Psychiatr Res* 1994; **28:**57-84.

27. Holmes JD, House AO. Psychiatric illness in hip fracture. *Age Ageing* 2000; **29:**537-546.

28. Cole MG, Dendukuri N. Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *Am J Psychiatry* 2003; **160:**1147-1156.

Low fear of falling affects subsequent

fracture risk in women

Noortje A Verdijk[1], Martha van den Berg[2], Ronald J Erdtsieck[3], Geraline L Leusink[4], Victor J Pop[1]

1. Centre of Research on Psychology in Somatic diseases (CoRPS), Medical Psychology and Neuropsychology, Tilburg University
2. Coordination Centre of Nurse Practitioners for South East Netherlands
3. Maxima Medical Centre
4. Stichting Zuidwester

ABSTRACT

Objective: to investigate fear of falling and depressive symptoms as risk factors for subsequent fractures in women.

Design of study : longitudinal study

Setting: 318 fractured females (mean age 66 years) of two Dutch Fracture and Osteoporosis clinics

Methods: fear of falling, depressive symptoms and clinical risk factors were measured at baseline using questionnaires. After 12 months, subjects were asked whether or not they suffered from a subsequent fracture or fell. Adjusted odds ratios were calculated to investigate the contribution of the risk factors to subsequent fracture risk.

Results: 7% suffered from a subsequent fracture. Lower fear of falling, lower bone density and an increasing number of falls significantly contributed to subsequent fracture risk (p<0.05). Depressive symptoms did not.

Conclusions: Low fear of falling significantly affected subsequent fracture risk in females, which may be explained by the association between fear of falling, age and physical activity. In addition to clinical risk factors, fear of falling and falls should be included to accurately estimate subsequent fracture risk.

INTRODUCTION

Osteoporotic fractures affect one in two females and one in five men older than 50 years, with subsequent mortality, morbidity and decreased quality of life[1,2]. In Europe, osteoporotic fractures account for more Disability Adjusted Life Years lost than common cancers, with the exception of lung cancer[2]. Fracture risk is majorly increased if a prior fracture occurred after the age of 50 years. About 40-60% of fractured elderly will suffer a subsequent fracture within 10 years[3], especially in the first year after the event[3,4]. The risk for a hip or vertebral fracture is doubled in subjects with a prior fracture compared to those without[5]. The European guidance of osteoporosis has recommended to treat all postmenopausal fractured females without bone densitometry[6].

So far, most studies have been conducted on biological and life style risk factor of fractures. In addition to Bone Mineral Density (BMD), age, sex and a prior fracture, other independent risk factors have been defined such as low Body Mass Index (BMI), a parental history of hip fracture, current smoking, systemic use of glucocorticosteroids, rheumatoid arthritis, and excessive alcohol use[6]. Center et al. studied subsequent fracture risk and showed that BMD, age and smoking were significant predictors in women and BMD, physical activity and calcium intake in men[3].

In addition to clinical risk factors, research has been conducted on psychological factors in relation to fractures. High fear of falling increases the risk for falls[7], and has been shown to significantly increase the risk for fracture-causing falls[8]. Depressive symptoms may also increase fracture risk. In addition to biological explanations for this association (e.g. hyperactivity of the hypothalamic pituitary-adrenal axis and hypercortisolaemia), it has been suggested that poor health behaviour,

(limited physical functioning, nutritional deficiencies, excessive alcohol use and smoking) and psychotropic medication use may negatively affect bone strength and/ or increase the risk of falling and fractures[9].

Research on fear of falling in relation to fractures is limited. Few longitudinal studies on depression and fracture risk have been conducted. By our knowledge, no research has been conducted on psychological risk factors for subsequent fractures. Therefore, we aim to investigate the role of fear of falling and depressive symptoms in subsequent fracture risk in elderly women, after 12 months follow-up.

METHOD

Participants

In the period between October 2006 and July 2008, all eligible patients of the fracture and osteoporotic (F&O) outpatient clinics of two hospitals in the South of the Netherlands were invited to participate in a prospective cohort study on the effects and processes of osteoporosis and subsequent fractures, called the Eindhoven Subsequent Fracture and Osteoporosis Reduction-project (ESFOR-p). Inclusion criteria were: (1) age 50 years or over, (2) a recent fragility fracture (resulting from a fall of standing height or less), (3) sufficient knowledge of the Dutch language and (4) sufficient cognitive abilities. The Medical Ethical Committee of the Maxima Medical Centre approved this study. Of the 1339 patients who visited the clinics, 534 signed informed consent (96 man and 438 females (mean age 65.5, SD=9.7)). There were no significant differences in mean age and BMD between the research population and the overall population of the F&O clinics (data not shown).

In the current study only female Caucasian subjects were included (n=438). Next, only females who had been followed up for a period of 12 months were included (n=318). Due to missing data, 25 females were excluded, resulting in a research population of 293 subjects. Their characteristics are presented in Table 1. There were no significant differences in baseline characteristics between included and excluded subjects (data not shown).

Measurements

Baseline characteristics and risk factors

According to the European Guidance, we defined the following clinical risk factors: femoral BMD (expressed in T scores; standard deviations (SD) of the healthy adult mean), age, BMI (kg/m^2), current smoking, alcohol intake (units/day), rheumatoid arthritis, parental history of a hip fracture and systemic use of glucocorticosteroids. In addition, physical activity, calcium intake and the use of anti-osteoporotic drugs were included. Information regarding DXA outcome, types of prior fractures and calcium intake were provided by the F&O clinics. Regarding vertebral fractures it was assumed that individual T-scores between adjacent vertebrae of the DXA outcome should be within 1 S.D. of each other. If not, additional lumbar spine X-rays were conducted to investigate (partially) compressed vertebra(e) or an artefact. In addition, F&O nurses screened the radiology history of each participant for X-rays of the thorax or spine. Patients characteristics and information about the clinical risk factors and physical activity (hours per week spend on daily physical activities such as walking, cycling, gardening etc.) were measured using purpose designed questionnaires. Low physical activity was defined as less than 4 hours of physical activity per week.

Table 1. Characteristics and clinical risk factors of 293 Caucasian fractured elderly women

		Mean	SD	N	%
Type of fracture					
Hip fracture				25	9
Vertebral fracture				12	4
Wrist fracture				87	30
Other fractures[a]				166	57
Multiple fractures[b]				3	1
DXA outcome					
Osteoporosis				130	44
Osteopenia				111	38
Normal BMD				52	18
Living situation					
Independently				184	63
Independently with help				104	36
Hospitalised				4	1
Biological and life style risk factors					
Age		65	8.3		
BMI	kg/m^2	26	4.4		
Alcohol intake	≥3 units per day			23	8
Current smoking				45	15
Rheumatoid arthritis				24	8
Systemic use corticosteroids				10	3
Parental history hip fracture				53	18
Low physical activity	<4 hours/week			62	21
Calcium intake	mg/day	890	277		
Anti-osteoporotic drugs				116	40

[a]hand, forearm, elbow, clavicle, ankle, foot. [b]1x hip and vertebral fracture; 1x vertebral and wrist fracture; 1x wrist and other fracture.

Depressive symptoms

To measure depressive symptoms, participants were asked to fill out the Edinburgh Depression Scale (EDS) at baseline, which was originally designed and validated as the Edinburgh Postnatal Depression Scale (EPDS) to assess postpartum depression[10]. After validation in non-childbearing female community samples and in men[11-13], the EPDS has been renamed the Edinburgh Depression Scale (EDS). In the Netherlands, the EDS has been validated in postnatal[14] and menopausal[15,16] and for internet use[17].

The EDS is a ten-item self report questionnaire over a period of seven days, with a total scores range from 0 to 30. More depressive symptoms are associated with higher scores. Generally, a cut-off score of 12/13 is recommended[10]. With Cronbach's alpha of at least 0.80, the EDS has a good internal consistency[10,11,13].

Fear of falling

To assess fear of falling, the Dutch version of the Activities specific Balance confidence (ABC) was used[18]. The ABC contains 16 items, describing activities of daily living that require bending, reaching, transferring or walking. Participants are asked to rate their confidence in these situations, within a range of 0% (no confidence) to 100% (full confidence). Higher scores thus reflect greater confidence and lower fear of falling. The overall score is derived by computing the sum of the items scores divided by 16. A score ≥80% indicates low fear of falling[19]. The ABC has strong internal-consistency (α = 0.95) [20,21] and has been validated in Dutch by van Heuvelen et al.[21].

Follow-up measurement

After a period of 12 months, patients were asked how often they fell and if they suffered from a new fracture.

Statistics

As fear of falling and depressive symptoms were not normally distributed, Spearman's rho coefficients (ρ) were calculated to investigate their association with the clinical risk factors. The systemic use of glucocorticosteroids was excluded from analyses as a variable because this was reported by only 3% of the population. If a significant correlation occurred, Mann-Whitney U Tests were performed for dichotomous variables and MANOVA for categorical variables to test for significant differences in the mean level of fear of falling or depressive symptoms between subgroups, based on the significant clinical risk factor. After verifying assumptions, adjusted odds ratios (OR) were calculated (95% confidence interval (CI)) to assess the contribution of fear of falling and depressive symptoms to subsequent fracture risk, after adjusting for the clinical risk factors. Analyses were performed using SPSS software (version 16.0).

RESULTS

After a follow-up period of 12 months, 90 subjects (31%) fell once or more during the follow-up period and 21 subjects (7%) suffered from a subsequent fracture: 1 hip fracture, 1 vertebral fracture, 3 wrist fractures, 4 fractures of the proximal humerus, 3 fractures of the humerus, and 9 other fractures (rib, too, feet, finger, hand, knee, leg). Of these, 12 suffered from osteoporosis, 8 had osteopenia and one had normal BMD. In

the overall population, the average score on the EDS was 6 (SD 5; range 0-23). Using a cut-off value of 12 points, 47 subjects (16%) suffered from depressive symptoms. The mean score on the ABC was 80% (SD 20: range: 6-100). We computed the tertiles of the ABC score (0-78; 78-93; 93-100) to investigate the percentage of fractured subjects in subgroups with highest, moderate and lowest fear of falling. As can bee seen in figure 1, the percentage of subjects with a subsequent fracture was highest in those who reported the lowest and highest fear of falling.

Figure 1. Percentage of subjects with a subsequent fracture in subgroups with the highest, moderate and lowest fear of falling.
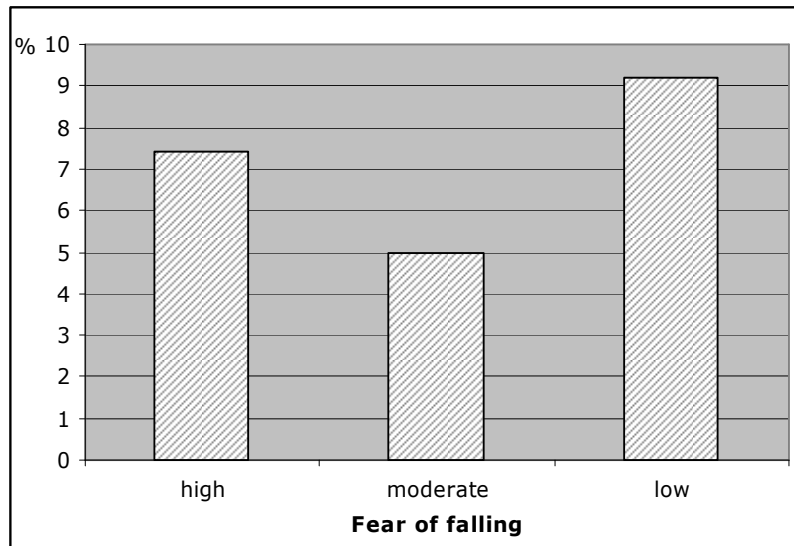
A higher level of fear of falling was significantly correlated ($p<0.05$) with higher depressive symptoms ($\rho=0.43$), higher age ($\rho=0.40$), higher BMI ($\rho=0.26$), suffering from rheumatoid arthritis ($\rho=0.17$), lower physical activity ($\rho=0.21$) and an increasing number of falls ($\rho=0.13$). Higher depressive symptoms were significantly associated with higher fear of

falling (ρ=0.43), higher age (ρ=0.12), higher BMI (ρ=0.13), current smoking (ρ=0.14), suffering from rheumatoid arthritis (ρ=0.15), lower physical activity (ρ=0.16) and an increasing number of falls (ρ=0.20). Additional analyses showed that the average level of fear of falling significantly differed between subjects with and without depressive symptoms ($p<0.001$) and between subjects with and without rheumatoid arthritis ($p<0.01$). Depressive symptoms significantly differed between smokers and non-smokers ($p<0.01$), subjects with and without rheumatoid arthritis ($p<0.01$) and subjects who did and did not fall ($p<0.05$). Moreover, significant differences in the average levels of fear of falling and depressive symptoms occurred between subjects of different ages (50-59; 60-69; 70-79; ≥80 years) and subjects who reported different levels of physical activity. Using a Bonferri adjusted alpha level of 0.025, fear of falling significantly increased with age ($F_{(3, 289)}$=15.5, $p<0.001$, partial eta squared = 0.14) and lower physical activity ($F_{(4, 288)}$=13.6, $p<0.001$, partial eta squared = 0.16). There were no significant differences in depressive symptoms between subgroups based on the level of physical activity or age. Additional analyses (Chi square tests) showed that the level of psychical activity significantly decreased with age ($p<0.05$).

Table 2 presents the adjusted OR's of fear of falling and depressive symptoms for subsequent fracture risk after controlling for clinical risk factors. As can be seen, lower fear of falling, lower BMD, and an increasing number of falls significantly contributed to subsequent fracture risk after 12 months ($p<0.05$).

Table 2. Adjusted Odds Ratios (OR) for subsequent fracture risk in 293 Caucasian elderly women

	Adjusted OR	95% CI
Lower fear of falling*	1.04	1.02 - 1.09
Higher depressive symptoms	0.98	0.89 - 1.10
Lower femoral BMD (T scores)*	0.39	0.18 - 0.83
Higher age	1.07	0.99 - 1.15
Higher BMI (kg/m^2)	1.06	0.92 - 1.22
Current smoking (yes/no)	1.91	0.49 - 7.50
Alcohol intake (units per day)	1.24	0.79 - 1.95
Parental history of hip fracture (yes/no)	1.25	0.40 - 3.87
Rheumatoid arthritis (yes/no)	1.98	0.35 - 11.22
Lower physical activity (<4 hours/week)	0.29	0.06 - 1.40
Higher number of falls*	1.63	1.22 - 2.17
Higher calcium intake (mg/day)	0.99	0.99 - 1.01
Use of anti-osteoporotic drugs (yes/no)	0.81	0.45 – 1.45

significant at p<0.05

DISCUSSION

We investigated the role of fear of falling and depressive symptoms in subsequent fracture risk in elderly women after a follow-up period of 12 months. Low fear of falling significantly increased subsequent fracture risk, independently of femoral BMD and falls. Depressive symptoms did not.

The one year prevalence of a subsequent fracture varies between 2% and 10%[22]. We found that 7% of the subjects suffered from a subsequent fracture, which is in accordance with the one year incidence reported by

Fear of falling and fracture risk | 139

van Helden et al. (7%)[23] and Johnell et al. (7%)[4]. Sixteen percent of the total sample suffered from depressive symptoms at baseline. In general, symptoms of depression occur in 8 to 16% of elderly[24]. Balance confidence was high on average (80%), representing a low level of fear of falling. Previous research in a Dutch community sample showed an average score of 77%[21]. These figures suggest that our study sample is comparable with other samples in literature regarding subsequent fractures, fear of falling and depressive symptoms.

We found that *lower* fear of falling increased subsequent fracture risk. In contrast, Luukinen et al.[8] reported that *frequent* fear of falling contributed to fracture-causing falls. As the mean age of research population of Luukinen et al.[8] was higher (76 years) than the mean age in our research population (66 years), it might be suggested that the relationship between fear of falling and fracture risk is affected by age. According to our results, fear of falling significantly differed between subgroups of different ages. In addition, this was also found for subgroups based on the level of physical activity. Therefore, physical activity might also play a role in the relationship between fear of falling and fracture risk. In general, low physical activity has been described as a risk factor for falls and fractures through musculoskeletal and neuromuscular pathways and a negative effect on bone density and bone quality[25]. However, opposite associations have been found in the most active and inactive subjects[26], implying a U-shaped relationship between physical activity and fracture risk. Based to figure 1, there are also indications for a U-shaped relation between fear of falling and fracture risk. However, as the level of physical activity did not significantly affect subsequent fracture risk in our study, it might be suggested that the type of physical activity plays a role. Perhaps, subjects with low fear of falling are more often involved in activities that

encompass high levels kinetic energy, which are known to increase fracture risk[27]. In addition, the relationship between physical activity and fracture risk may be different for subjects with different types of fractures. Most studies which reported that low physical activity increases fracture risk concerned hip fractures. Opposite findings on the relationship between physical activity and fracture risk have been reported from studies on non-hip fractures[26]. In our study, relatively young females were included of which few suffered from a hip fracture. On average, a low level of fear of falling and high levels of physical activity were reported. Relatively younger women with low fear of falling may be more physically active, especially regarding high kinetic activities, thereby being more prone to fracture risk situations.

In contrast with literature[28-30], our study provided no indications for depressive symptoms as a risk factor for subsequent fractures. This might be explained as Mussolino et al.[28] only investigated hip fracture risk and Whooley et al.[29] included an older sample (mean age 74 years). Sprangler et al.[30] found only a minimal association (p=0.05) between depressive symptoms and fragility fractures in women (mean age 64 years), which was limited to females not using antidepressants and which was not found for hip, spine and wrist fractures.

Another important finding of our study is that falls significantly affected fracture risk, which is in accordance with recent reports that falls are more important in determining fracture risk than low BMD[31]. It is striking that falls are not included as a risk factors for fractures in the European Guidance, nor in fracture risk calculation tools such as the FRAX®.

A strength of our study is that we included a relatively young and healthy sample. We found that 31% of these females fell at least once during the follow-up period and 7% suffered various types of subsequent fracture.

This implies that subsequent fracture prevention should not be limited to the oldest elderly, nor to hip fracture patients. Our study also comprises some limitations. First, only 40% of the patients of the original F&O clinics participated in our study. However, because our figures on the prevalence of subsequent fractures, fear of falling and depressive symptoms are comparable to data in literature, no bias seems to have occurred. Second, the follow-up period in our study is rather limited. However, other studies showed that the majority of subsequent fractures occurred within the first years after the prior fracture[3,4]. Third, the oldest elderly and hip fracture patients were underrepresented in our study. This is in accordance with previous reports on the same F&O outpatient clinics[32]. As a result, our sample was too small to perform separate analyses in subgroups based on age or type of fracture. Finally, we did not differentiate between different types of physical activity.

Our study favours a psycho-biological model for the estimation of subsequent fracture risk, which should comprise fear of falling, in addition to biological and life style risk factors. Moreover, falls should be included. There are indications that the effect of fear of falling on fracture risk differs with age and is affected by physical activity. Moreover, subsequent fracture prevention should not be limited to the oldest elderly. We found no indications that depressive symptoms affect subsequent fractures risk. There is urge for further research to investigate the contribution of fear of falling on the long term, as well as its relation with prior fractures, different types of physical activities and in groups of different ages. Furthermore, research should be conducted on the effects of cognitive-behavioural interventions in fracture risk reduction programmes, regarding fear of falling in subjects of different ages.

REFERENCES

1. Cummings SR, Melton III R. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2000; **359:**1761-1767.

2. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006; **17:**1726-1733.

3. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. *JAMA* 2007; **297:**387-394.

4. Johnell O, Kanis JA, Odén A, *et al.* Fracture risk following an osteoporotic fracture. *Osteoporos Int* 2004; **15:**175-179.

5. Klotzbuecher CM, Ross PD, Landsman PB, *et al.* Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res* 2000; **15:**721–739.

6. Kanis JA, Burlet N, Cooper C, *et al.* on behalf of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) European Guidance for diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2008; **19:**399-428.

7. Scheffer AC, Schuurmans MJ, van Dijk N, *et al.* Fear of falling: measurement strategy, prevalence, risk factors and consequences among older persons. *Age Ageing* 2008; **37:**19-24.

8. Luukinen H, Koski K, Laippala P, Kivelä SL. Factors predicting fractures during falling impacts among home-dwelling older adults. *J Am Geriatr Soc* 1997; **45:**1302-1309.

9. Menzuk B, Eaton W, Golden S. Depression and osteoporosis: epidemiology and potential mediating pathways. *Osteoporos Int* 2008; **19:**1-12.

10. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale (EPDS) in non-postnatal women. *Br J Psychiatry* 1987; **150:**782-786.

11. Matthey S, Barnett B, Kavanagh DJ, Howie P. Validation of the Edinburgh Postnatal Depression Scale for men. and comparison of item endorsement with their partners. *J Affect Disord* 2001; **64:**175-184.

12. Cox JL, Chapman G, Murray D, Jones P. Validation of the Edinburgh Postnatal Depression Scale in non-postnatal women. *J Affect Disord* 1996; **39:**185-189.

13. Murray L, Carothers AD. The validation of the Edinburgh Post-natal Depression Scale on a community sample. *Br J Psychiatry* 1990; **157:**288-290.

14. Pop VJ, Komproe IH, van Son MJ. Characteristics of the Edinburgh Post Natal Depression Scale in the Netherlands. *J Affect Disord* 1992; **26:**105-110.

15. Nyklíček I, Scherders MJ, Pop VJ. Multiple assessment of depressive symptoms as an index of depression in population-based samples. *J Psychiatr Res* 2004; **128:** 111-116.

16. Becht MC, van Erp CF, Teeuwisse TM, *et al.* Measuring depression in women around menopausal age: towards a validation of the Edinburgh Depression Scale. *J Affect Disord* 2001; **63:**209-213.

17. Spek V, Nyklícek I, Cuijpers P, Pop V. Internet administration of the Edinburgh Depression Scale. *J Affect Disord* 2008; **106:**301-305.

18. Powel LE, Meyers AM. The activities-specific balance confidence (ABC) scale. *J Gerontol* 1995; **50:**M28-M34.

19. Myers AM, Fletcher PC, Myers AH, Sherk W. Discriminative and evaluative properties of the Activities-specific and Balance Confidence (ABC) Scale. *J Geront A Biol Sci Med Sci* 1998; **53:**M287-94.

20. Filiatrault J, Gauvin L, Fournier M, *et al.* Evidence of the psychometric qualities of a simplified version of the Activities-specific Balance Confidence scale for community-dwelling seniors. *Arch Phys Med Rehabil* 2007; **88:**664-672.

21. van Heuvelen MJ, Hochstenbach J, de Greef MH, *et al.* Is the Activities-specific Balance Confidence Scale suitable for Dutch older persons living in the community? *Tijdschr Gerontol Geriatr* 2005; **36:**146-154.

22. Egan M, Jaglal S, Byrne K, *et al.* Factors associated with a second hip fracture: a systematic review. *Clin Rehabil* 2008; **22:** 272-82.

23. van Helden S, Cals J, Kessels F, *et al.* Risk of new clinical fractures within 2 years following a fracture. *Osteoporos Int* 2006; **17:**348-354.

24. Cole MG, Dendukuri N. Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *Am J Psychiatry* 2003; **160:**1147-1156.

25. Moayyeri A. The association between physical activity and osteoporotic fractures: a review of the evidence and implications for future research. *Ann Epidemiol* 2008; **18:**827-835.

26. Joakimsen RM, Fønnebø V, Magnus JH, *et al.* The Tromsø Study: physical activity and the incidence of fractures in a middle-aged population. *J Bone Miner Res* 1998; **13:**1149-1157.

27. Luukinen H, Herala M, Koski K, *et al.* Fracture risk associated with a fall according to type of fall among the elderly. *Osteoporos Int* 2000; **11:**631-634.

28. Mussolino ME, Jonas B, Looker A. Depression and bone mineral density in young adults: results from NHANES III. *Psychosom Med* 2004; **66:**533-537.

29. Whooley M, Kip K, Cauley J, *et al.* Depression, falls, and risk of fracture in older women. Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 1999; **159:**484-490.

30. Spangler L, Scholes D, Brunner RL, *et al.* Depressive symptoms. bone loss. and fractures in postmenopausal women. *J Gen Intern Med* 2008; **23:**567-574.

31. Järvinen TL, Sievänen H, Khan KM, *et al.* Shifting the focus in fracture prevention from osteoporosis to falls. *BMJ* 2008; **336:**124-126.

32. Blonk MC, Erdtsieck RJ, Wernekinck MG, Schoon EJ. The fracture and osteoporosis clinic: 1-year results and 3-month compliance. *Bone* 2007; **40:**1643-1649.

Chapter 8

General discussion and summary
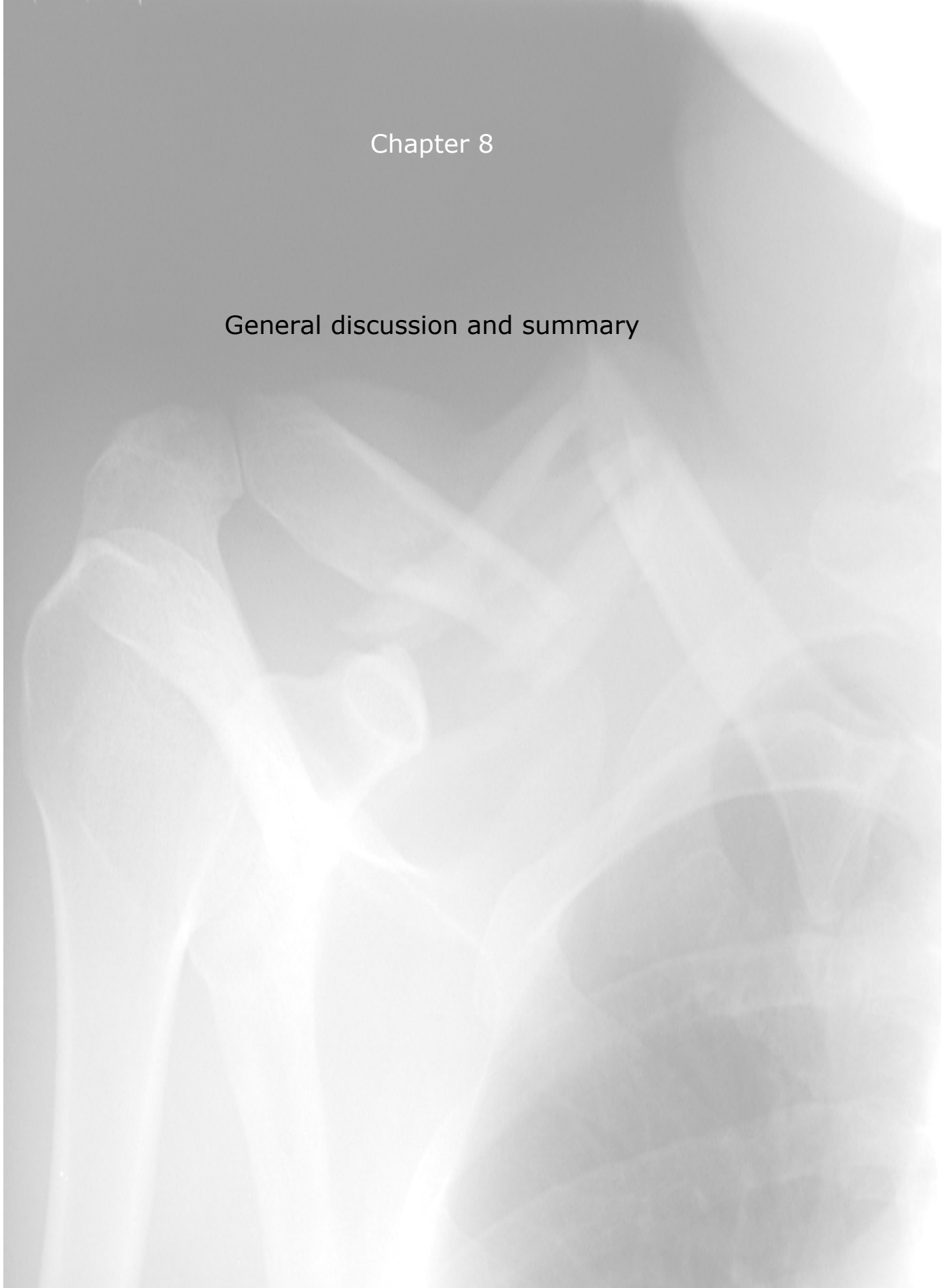
MAIN FINDINGS

The aim of this thesis was to study the current use of risk factors for primary and secondary fracture prevention in general practice and F&O clinics in the Netherlands, and the additional value of psychological factors for subsequent fracture risk estimation.

Primary fracture prevention has been described in the current guidelines of the Dutch College of General Practitioners by means of case finding[1]. This method comprises eight risk factors with weighted scores, to identify patients at risk for osteoporosis. In this thesis we investigated the validity of this case-finding method. Despite appropriate specificity (86%) and NPV (87%), we found that the sensitivity and PPV were low: 20% and 19%, respectively. We therefore conclude that the case-finding method is of limited value to identify patients at risk for osteoporosis. In practice, the use of the current case-finding method implies that about four patients with osteoporosis will be missed for every patient that is found. Compared to other international case finding instruments, the Dutch method showed the poorest outcomes. An important explanation for the low validity of the Dutch case-finding method is the use of the relative risk of risk factors for hip and vertebral *fractures* to detect patients at high risk for *osteoporosis*.

Additional analyses in women showed that the clinical performance of the Dutch case-finding method improved if the cut-off score decreased, with a sensitivity up to 88% if a cut-off score of one was used instead of four points. Although the PPV remained low, the majority of female osteoporotic patients would be referred for DXA measurement and would thus receive proper diagnosis and treatment. However, the specificity was moderate and screening would occur in females over the age of 60 or 65 years. Although it has been shown that the treatment of women over the

age of 65 years with at least one risk factor is cost-effective and although the US Guidelines have recommended screening from the age of 65[1,2], screening for osteoporosis is generally not recommended[2]. In addition, the question rises if a case finding strategy aimed at osteoporosis is still appropriate, regarding the shifting focus towards fracture prevention. As will be discussed below, further research on these issues is necessary.

Furthermore, we evaluated the current intervention strategy of two Dutch F&O clinics which is mainly based on bone densitometry. We found that the current intervention policy is accurate towards females with osteoporosis, however for not those without. Treatment of all fractured women without bone densitometry may be justified based on the average fracture probability and cost-effectiveness. However, this policy may be questioned from risk-benefit and ethical point of view. As the estimation of fracture probability integrates BMD and clinical risk factors, the incorporation of fracture risk estimation may improve the current strategy of Dutch F&O clinics for fracture prevention. Clinicians should profess the incorporation of BMD to estimate fracture risk.

As the focus is shifting from osteoporosis towards fracture prevention strategies, risk factors for fractures are becoming increasingly important to identify subjects at high risk. In addition to biological and life style risk factors, there are indications that psychological factors may play a role. Various studies have been conducted on depression, osteoporosis and fractures. Previous reviews described contradictory results, to be partially explained by substantial differences in research designs and the definitions of depression and parameters of osteoporosis that have been used. Therefore, we studied the literature on depression and osteoporosis and fractures, while making a distinction between (i) depressive symptoms and the syndrome depression, and (ii) cross-sectional and

longitudinal studies. The majority of the studies which have been performed are cross-sectional. Based on the results of these studies, it can be concluded that depressive syndrome and symptoms are associated with decreased BMD. Moreover, cross-sectional studies showed that depressive syndrome is related with deviant bone turnover. However, the clinical implication for osteoporosis remains unclear, because the majority of the studies described low BMD without defining osteoporosis in terms of a T score ≤-2.5 SD. From longitudinal research it can be concluded that depressive syndrome and symptoms are risk factors for fractures, independently of BMD and falls. Hence, research on depression is important, especially regarding fractured elderly with low BMD.

To overcome the time consuming character and costs of psychiatric interviews to diagnose depressive syndrome, assessment of depressive symptoms is often used as a proxy in research. The Edinburgh Depression Scale (EDS) is a highly accepted and user-friendly questionnaire in research of depressive symptoms. Because it has never been validated in elderly, we investigated the reliability and validity of the EDS in a sample of older fractured women. We showed that the EDS is a reliable and valid questionnaire to assess depressive symptoms in older fractured women with low BMD. However, a lower cut-off score (nine instead of 12) is recommended. Based on the high prevalence of major depression (12%) and depressive symptoms (30%; using 'nine' as a cut-off) and the knowledge that undiagnosed depression might interfere with appropriate revalidation, we concluded that the assessment of depressive symptoms in fractured elderly with low BMD is important.

In addition to depression, there are also indications that fear of falling may play a role in fracture risk. Therefore, we investigated depressive symptoms and fear of falling as risk factors for subsequent fractures in

older women after a follow-up period of 12 months. Based on our results we concluded that lower levels of fear of falling are a significant psychological risk factor for subsequent fracture risk in older women, independently of BMD. The relationship between fear of falling and fracture risk may be affected by physical activity and age. Moreover, we concluded that falls should be included as a risk factor for accurate fracture risk estimation.

IMPLICATIONS FOR PRACTICE

Our study (FRACPREZOB-II) is part of a large osteoporosis project (FRACPREZOB), which comprised case-finding in more than 21,500 subjects. Based on the low validity of the case-finding method we concluded that within this project, the majority of patients with osteoporosis have been missed. We therefore recommend that the Dutch College of General Practitioners revises her case-finding method, taking into account fractures as an outcome parameter instead of osteoporosis. In addition, we recommend that a revised case-finding method should be validated before implementation in General Practice.

Secondary fracture prevention by means of Dutch F&O clinics is mainly based on bone densitometry. We concluded that this policy is not accurate towards patients without osteoporosis, which implies revision of the current guidelines of the Dutch Institute for Health Care Improvement. As in primary prevention, more attention should go out to the integration of BMD and risk factors. Therefore it might be suggested to incorporate the estimation of fracture probability in the management of fractured women. The decision to include bone densitometry should be professed by the clinician.

152

In accordance with the integrated approach to estimate fracture risk, intervention should address other risk factors besides BMD. As behavioural risk factors for fractures are modifiable, more attention should go out to cognitive-behavioural interventions that affect lifestyle habits (e.g. smoking, alcohol use, vitamin D and calcium intake, body weight, physical activity and fall risk assessment) and psychological risk factors (fear of falling). Especially since little is known about the effects of anti-osteoporotic drug treatment for fracture risk reduction in patients without osteoporosis. Standardized assessment of psychological and lifestyle aspects is becoming increasingly common in other chronic medical diseases such as diabetes and cancer. This approach might also be helpful in fracture risk prevention.

The findings presented in this thesis imply an increasing appeal to health care regarding fracture prevention, compared to the current situation. For example, in the FRACPREZOB project it was shown that only a minority (10%) of subjects (mean age 63 years) was referred for DXA. In contrast, Kanis et al. showed that, using the FRAX® method, 19% of women aged between 60 and 65 years were eligible for bone densitometry[3]. In addition, more women will meet intervention thresholds based on fracture probability than intervention thresholds that are solely based on BMD. Furthermore, interventions aimed at risk factors other than BMD (fall risk assessment and life style advice such as diet, exercise, smoking, and compliance with treatment) may result in an enlarged workload.

In the introduction section, the growing incidence and burden of chronic medical disease due to ageing was described. As a result, the organisation and financial structure of chronic health care in the Netherlands is changing, with an increasing appeal on primary care. By means of

multidisciplinary programmes, patients are treated in primary care as long as possible. Only if special care is needed hospital care is applied, which is characterised by disease specific management and treatment. If hospital care becomes routine, it should be considered to shift (parts of) that care towards primary care. With regard to osteoporosis and fracture risk management, primary prevention is currently conducted in primary care. However, secondary prevention is mainly provided in hospital care by means of F&O clinics. It can be questioned whether the assessment of risk profiles and lifestyle advice requires specialised or routine care, particularly as the monitoring of behavioural changes (routine care) is important to succeed. General practitioners and specialised nurses may play an important role here. Hence, more effort should go out to accurately set tasks, cooperation and organisation between primary and secondary care to come to a multidisciplinary fracture risk reduction programme. Furthermore, from our population and literature it was shown that hip fracture patients were underrepresented in the F&O clinics. It might be concluded that the patients of the F&O clinics currently mainly refer to mobile persons. F&O clinics might play a role in providing more attention to the identification of elderly (hip) fracture patients who are in hospitalised care.

RECOMMENDATIONS FOR FURTHER RESEARCH

We recommended that the Dutch College of General Practitioners should revise her case finding method. We suggested that more attention should go out to fracture risk estimation above osteoporosis. There is urgent need for research to validate the use of fracture risk probabilities (by means of the FRAX® or another method) in the Dutch population: in the general population as well as in fractured subjects. Intervention

154

thresholds based on fracture risk should be defined and cost-effectiveness should be investigated. Moreover, it is important to acknowledge that little is known about the effects of bisphosphonate therapy for fracture risk reduction in subjects without osteoporosis. Research showed that subjects with normal BMD did not benefit from alendronate therapy[4]. Moreover, research on the effect of calcium-intake in a community-based sample of elderly showed the compliance is problematic in preventive health practice[5]: 43% of the included subjects took less than 80% of their assigned medication. This issue should be further investigated. Furthermore, as fracture probability is based on other risk factors besides BMD, accurate therapy should also address these (behavioural and psychological) aspects. Attention should go out to the systematic assessment of psychological and behavioural risk factors in fractured subjects and the contribution of fear of falling to subsequent fracture risk on the long term. Moreover, the role of fear of falling in prior fracture risk should be investigated as well as the effects of cognitive-behavioural therapy for fracture risk reduction.

STRENGHTS AND LIMITATIONS OF THE STUDIES

In this thesis two projects have been described, FRACPREZOB and ESFOR-p, which strengths and limitations should be acknowledged with regard to the presented results. In the FRACPREZOB-II project we included the sample of a general practice. Several limitations in this project were that the sample comprised only one General Practice which was in a rural area and included only Caucasian patients. Moreover, relatively young subjects participated and men were under-represented. Therefore, the results of this project cannot be generalized to the Dutch population. A strength was the high response rate (67%), which suggests no recall bias.

Several limitations of the ESFOR-project should also be mentioned. First, only 40% of the patients of the original F&O clinics participated in our study. Despite the low response rate, our population accurately reflected the population that visited the F&O clinics in the same period. There were no significant differences in mean age and incidence of osteoporosis, osteopenia and normal BMD between our population and the overall population. Furthermore, our study sample was comparable with previous reports of the same F&O clinics regarding age, DXA outcome and fracture type, as well as the under-representation of hip fracture patients[6]. Moreover, our sample was comparable with literature on psychological characteristics (fear of falling and depression) in elderly[7,8]. A strength of the study is that we showed that insight in the risk profile and fracture probability of a relatively young healthy population is important. As falls and subsequent fractures were frequently reported, fracture prevention should not be limited to the oldest elderly.

CONCLUSIONS

The current policy on primary and secondary fracture prevention should be revised, taking into account the shifting focus from osteoporosis towards fracture prevention as an outcome parameter. In addition, the estimation of fracture risk should be based on a bio-psychological model. More research is needed to investigate the definition, application and consequences of fracture risk estimation in the Dutch population.

REFERENCES

1. The National Osteoporosis Foundation (NOF) *Clinician's Guide to prevention and treatment of osteoporosis 2008.* Washington, DC, US: National Osteoporosis Foundation, 2008.
   http://www.nof.org/professionals/NOF_Clinicians_Guide.pdf

2. Kanis JA, Burlet N, Cooper C, *et al*. European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporosis Int* 2008; **19:**399-428.

3. Kanis JA, McCloskey E, Johansson H, *et al.* Case finding for the management of osteoporosis with FRAX® - assessment and intervention thresholds for the UK. *Osteoporos Int* 2008; **19:**1395-1408.

4. Cummings SR, Black DM, Thompson DE, *et al.* Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998; **280:**2077–2082.

5. Prince L, Devine A, Satvinder S, *et al.* Effects of calcium supplementation on clinical fracture and bone structure. *Arch Intern Med* **166:**869-875.

6. Blonk MC, Erdtsieck RJ, Wernekinck MG, Schoon EJ. The fracture and osteoporosis clinic: 1-year results and 3-month compliance. *Bone* 2007; **40:**1643-1649.

7. van Heuvelen MJ, Hochstenbach J, de Greef MH, *et al.* Is the Activities-specific Balance Confidence Scale suitable for Dutch

older persons living in the community? *Tijdschr Gerontol Geriatr* 2005; **36:**146-154.

8. Cole MG, Dendukuri N. Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *Am J Psychiatry* 2003; **160:**1147-1156.

SUMMARY

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural derangements, resulting in increased fracture risk. In 2005, about 640,000 women and 210,000 men suffered from osteoporosis in the Netherlands[1]. Fractures occur in about 83,000 people aged over 55 each year[2,3] and the current annual medical costs of osteoporotic fractures are estimated at € 500 million[3]. It is expected that by 2025 over 1 million persons will suffer from osteoporosis, with a financial burden over one billion euro's[3].

Low bone mass, increasing age and female sex are important risk factors for fractures. In addition, other risk factors have been identified that independently affect fracture risk, such as a prior fragility fracture, low body weight, long term use of high dose corticosteroids, a family history of a hip fracture, smoking and excessive alcohol use. Moreover, there are indications that psychological factors such as fear of falling and depression may play a role. This thesis aims to study (i) the current use of risk factors for primary and secondary fracture prevention in general practice and fracture (F&O) clinics in the Netherlands and (ii) the value of psychological factors for fracture risk estimation. Therfore, two health care projects on osteoporosis were conducted: the FRACture PREvention Zuid Oost-Brabant (FRACPREZOB) and the Eindhoven Subsequent Fracture and Osteoporosis Reduction Project (ESFOR-p).

As a part of the FRACPREZOB project we assessed the validity of the case-finding procedure as recommended by the guidelines of the Dutch College of General Practitioners. Therefore, the population of one general practice was screened for osteoporosis. Because the sensitivity and predictive value showed to be very low, we concluded that the case-finding method

is of limited value to identify patients at risk for osteoporosis. An important explanation is the use of risk factors for *fractures* to detect patients at high risk for *osteoporosis*. Additional analyses showed that the sensitivity of the Dutch case-finding method can be improved for females by using a lower the cut-off. However, with alternative usage, the specificity was moderate and screening would occur in females over 60 years.

In the ESFOR-project, all eligible patients of the fracture and osteoporotic (F&O) outpatient clinics of two hospitals in the South of the Netherlands were invited to participate in a prospective cohort study on the effects and processes of osteoporosis and subsequent fractures between the period October 2006 and July 2008. By estimating fracture risk in female patients, we evaluated the current intervention policy of the Dutch F&O clinics. The current policy appeared to be accurate towards females with osteoporosis, however not those without. We concluded that the current intervention policy should be revised and that fracture risk should be defined as the outcome parameter.

In this thesis we described a systematic literature review on the relationship between osteoporosis, fractures and depression. We found that depressive syndrome and symptoms are associated with decreased BMD and that depressive syndrome is related with deviations in bone turnover. Furthermore, depressive syndrome and symptoms are risk factors for fractures. Because depressive symptoms can be assessed as a proxy for depressive syndrome, we studied the psychometric aspects of the Edinburgh Depression Scale in fractured older women. The EDS showed to be a reliable and valid questionnaire if a lower cut-off was used: nine instead of the 12 points which are commonly recommended in literature. In addition we assessed depressive symptoms and fear of

160

falling as risk factors for subsequent fractures after a follow-up of 12 months. We found that lower fear of falling significantly increased subsequent fracture risk. Depressive symptoms were not associated with subsequent fracture risk. This relationship may be explained by the association between fear of falling, physical activity and age. In addition, falling showed to be an important risk factor for subsequent fractures.

Overall, we conclude from these studies that the use of risk factors in general practice and F&O clinics is aimed at predicting osteoporosis rather than primary and secondary fractures. Therefore, the current guidelines should be revised and should focus on fractures, taking into account bio-psychological risk factors, in addition to low BMD.

REFERENCES

1. Blokstra A, Verschuren WMM, Baan CA, *et al.* Vergrijzing en toekomst van ziektelast. Prognose chronische ziekteprevalentie 2005-2025. Rijksinstistiuut voor Volksgezondheid en Milieu, Bilthoven, 2007.

2. Kwaliteitsinstituut voor de gezondheidszorg CBO. Osteopose: tweede herziene richtlijn. Alphen a/d Rijn: Van Zuiden Communications, 2002.

3. http://cognosserver.prismant.nl/cognos7/cgi-bin/ppdscgi.cgi?DC =Q&E=/Prisma-Landelijke-LMR/Landelijke+LMR-informatie+-+ Diagnosen

SAMENVATTING

Osteoporose is een aandoening van het skelet die gekenmerkt wordt door een verminderde botmassa en botarchitectuur, waardoor de kans op een fractuur toeneemt. In 2005 hadden 640.000 vrouwen en 210.000 mannen in Nederland osteoporose[1]. Fracturen komen jaarlijks voor bij zo'n 83.000 mensen boven de 55 jaar[2,3]. De kosten daarvan zijn geraamd op 500 miljoen euro[3]. Het is te verwachten dat in 2025 meer dan 1 miljoen mensen osteoporose heeft en dat de kosten 1 miljard euro zullen overschrijden[3].

Een lage botmassa, hoge leeftijd en het vrouwelijk geslacht zijn belangrijke risicofactoren voor een fractuur. Daarnaast zijn andere, onafhankelijke risicofactoren geïdentificeerd zoals een eerdere fractuur, een laag lichaamsgewicht, langdurig gebruik van een hoge dosis corticosteroïden, een heupfractuur bij een naast familielid, roken en een hoog alcohol gebruik. Er zijn ook aanwijzingen dat psychologische factoren een rol spelen zoals valangst en depressie. Het doel van dit proefschrift is enerzijds om het gebruik van deze risicofactoren bij preventie van fracturen in de huisartsenpraktijk en fractuur poliklinieken in Nederland te bestuderen en anderzijds om de impact van psychologische risicofactoren voor fracturen te onderzoeken. Om dit te onderzoeken hebben we 2 zorgprojecten rondom osteoporose opgezet: FRACtuur PREventie Zuid Oost-Brabant (FRACPREZOB) en het Eindhovense Secundaire Fractuur and Osteoporose Reductie Project (ESFOR-p).

Als onderdeel van het FRACPREZOB-project hebben we de validiteit van de case-finding methode onderzocht zoals die is omschreven in de standaard van het Nederlandse Huisartsen Genootschap. Omdat de sensitiviteit en voorspellende waarde erg laag bleken concludeerden we dat de case-finding methode weinig waarde heeft voor het opsporen van

mensen met een verhoogd risico op osteoporose. Een mogelijke verklaring hiervoor is de toepassing van risicofactoren voor *fracturen* voor het opsporen van *osteoporose*. Verdere analyses toonden aan dat de sensitiviteit van de case-finding methode bij vrouwen verbeterde door een lagere afkapwaarde te gebruiken. Echter was de specificiteit matig en zouden vrouwen boven de 60 jaar gescreened worden.

In het ESFOR-project hebben we in de periode tussen oktober 2006 en juli 2008 alle beschikbare patiënten van de fractuur en osteoporose polikliniek van 2 ziekenhuizen in het zuiden van Nederland uitgenodigd om deel te nemen aan een prospectieve cohort studie over de effecten en processen van osteoporose en recidief fracturen. Door het risico op een nieuwe fractuur bij vrouwen te berekenen, hebben we het huidige behandelbeleid van de fractuur poliklinieken geëvalueerd. Hieruit bleek dat het huidige beleid accuraat is voor vrouwen met een fractuur en osteoporose maar niet voor vrouwen met een fractuur zonder osteoporose. De behandelstrategie zou ons inziens herzien moeten worden, waarbij fracturen als uitgangspunt zouden moeten worden genomen.

In dit proefschrift hebben we een systematisch literatuur onderzoek gedaan naar de samenhang tussen osteoporose, fracturen en depressie. Hieruit bleek dat depressieve symptomen en het syndroom depressie gerelateerd zijn aan verlaagde botmassa en dat depressieve symptomen gerelateerd zijn aan een afwijkend botmetabolisme. Daarnaast bleek dat depressieve symptomen en het syndroom depressie risicofactoren zijn voor fracturen. Omdat depressieve symptomen de belangrijkste voorspeller zijn voor een depressief syndroom, hebben we de psychometrische aspecten van de Edinburgh Depression Scale (EDS) in oudere vrouwen met een fractuur onderzocht. De EDS bleek een betrouwbare en valide vragenlijst te zijn als een lagere afkapwaarde werd

164

gebruikt: negen punten in plaats van de 12 punten die doorgaans in de literatuur worden aanbevolen. Daarnaast hebben we de rol van valangst en depressieve symptomen als risicofactoren voor een recidief fractuur na 12 maanden onderzocht. Een lage valangst bleek het fractuurrisico te vergroten. Depressieve symptomen hadden hierop geen invloed. De gevonden relatie kan mogelijk verklaard worden door de samenhang tussen valangst, fysieke activiteit en leeftijd. We concludeerden uit deze studie ook dat vallen een belangrijke risicofactor is voor een recidief fractuur.

In het algemeen kunnen we uit deze studies concluderen dat de risicofactoren die in de huisartsenpraktijk en de fractuur polikliek gebruikt worden vooral gericht zijn op het opsporen van mensen met een hoog risico op osteoporose in plaats van een hoog risico op fracturen. De huidige richtlijnen zouden ons inziens herzien moeten worden en meer gericht moeten zijn op fractuurrisico. Naast een lage botmassa zou aandacht uit moeten gaan naar de bio-psychologische risicofactoren die hierbij een rol spelen.

REFERENTIES

1. Blokstra A, Verschuren WMM, Baan CA, *et al.* Vergrijzing en toekomst van ziektelast. Prognose chronische ziekteprevalentie 2005-2025. Rijksinstistiuut voor Volksgezondheid en Milieu, Bilthoven, 2007.

2. Kwaliteitsinstituut voor de gezondheidszorg CBO. Osteopose: tweede herziene richtlijn. Alphen a/d Rijn: Van Zuiden Communications, 2002.

3. http://cognosserver.prismant.nl/cognos7/cgi-bin/ppdscgi.cgi?DC =Q&E=/Prisma-Landelijke-LMR/Landelijke+LMR-informatie+-+ Diagnosen

NHG standaard voor indicatie van botdichtheidmeting bij patiënten met osteoporose niet betrouwbaar

Noortje Verdijk[1], Ronald Erdtsieck[2], Arnold Romeijnders[3], Victor Pop[1]

1. the Centre Of Research for Psychology in Somatic diseases (CORPS), Medische Psychologie en Neuropsychologie, Universiteit van Tilburg
2. Maxima Medisch Centrum
3. Praktijkondersteuning Zuid-oost Brabant (PoZoB)

ABSTRACT

Objective: calculation of the sensitivity, specificity, positive and negative predictive value of the case-finding method of the Dutch College of General Practitioners for the identification of patients at risk for osteoporosis, who should be referred for DXA measurement. Additionally, the optimal cut-off value in women is evaluated.

Design of Study: cross-sectional.

Setting: 444 patients of a Dutch general practice were invited for DXA measurement and asked to complete a questionnaire regarding risk factors according to the Dutch case-finding method.

Methods: according to the Dutch case-finding method, a sum score was calculated for the questionnaire. In addition, DXA measurement was performed to investigate bone density. Sensitivity, specificity, positive and negative predictive value of the questionnaire for the identification of patients at risk for osteoporosis, based on the DXA outcome, were obtained for cut-off score 4 (95% Confidence Intervals). Additionally, these values were calculated for different cut-offs in women.

Results: Using the recommended cut-off (4 points), the sensitivity was 17% and PPV 14%. In women, the optimal cut-off value was '1', with a corresponding sensitivity of 79%.

Conclusion: the NHG case-finding method is unreliable to identify patients at risk for osteoporosis. The sensitivity of the Dutch case finding method in women largely increases using lower cut-offs ('1' instead of '4'). We suggest that the Dutch Organization for General Practitioners revises her guidelines regarding the selection of patients for bone densitometry. Further research is necessary to revise the current guidelines in women as well as men and to validate these before implementation in general practice.

INLEIDING

Naar schatting hadden in 2005 ruim 850.000 mensen in Nederland osteoporose[1]. Ten gevolge hiervan lopen jaarlijks meer dan 85.000 mensen boven de 55 jaar een fractuur op[2,3]. De kosten die hiermee gemoeid zijn worden geraamd op 500 miljoen euro en zullen naar verwachting boven het miljard uitstijgen in 2025[2]. Vanwege de toenemende incidentie is fractuurpreventie en dus tijdige diagnostiek van osteoporose van groot belang. Zeker gezien het feit dat het risico op een (nieuwe) fractuur met 50% afneemt door adequate en kosteneffectieve behandeling[4].

De diagnose van osteoporose is doorgaans gebaseerd op een botdichtheidmeting door Dual Energy X-Ray Absorptiometry (DEXA). Volgens de Europese en de World Health Organization (WHO) richtlijnen is case-finding van osteoporose kosteneffectiever dan DEXA-screening op populatieniveau[4-6]. Hoewel er internationaal verschillende case-finding methoden ontwikkeld zijn, bestaat hierover geen consensus[7-16].

In 2005 heeft het Nederlands Huisartsen Genootschap (NHG) een standaard voor huisartsen gepubliceerd voor de preventie, diagnostiek en therapie van osteoporose[17]. Hierin is een case-finding methode beschreven voor de indicatie van botdichtheidmeting bij patiënten met een verhoogd risico op osteoporose (zie Tabel 1). Echter, de validiteit van deze methode voor het opsporen van osteoporose is nooit bepaald. In een onlangs verschenen publicatie hebben wij de sensitiviteit, specificiteit, positief en negatief voorspellende waarde beschreven van deze case-finding methode voor de indicatie van botdichtheidmeting van patiënten met een verhoogd risico op osteoporose[18]. Vervolgens zijn aanvullende analyses toegepast om bij vrouwen de betrouwbaarheid van de case-

finding methode te evalueren voor verschillende afkapwaarden[19]. Dit artikel betreft een samenvatting van deze publicaties.

Tabel 1. NHG richtlijnen voor indicatie van botdichtheidmeting: DEXA meting geïndiceerd bij een somscore ≥4

Risicofactoren	score	geslacht
Doorgemaakte wervelfractuur	4	♂♀
Langdurig gebruik van hoge dosis corticosteroïden (>3 maanden; >7·5 mg/dag)	4	♂♀
Fractuur na 50ste levensjaar	4	♀
Leeftijd > 70 jaar	2	♀
Leeftijd > 60 jaar	1	♀
Heupfractuur 1e graads familielid	1	♀
Gewicht < 60 kg	1	♀
Ernstige immobiliteit	1	♀

METHODE

In het kader van een zorgproject zijn alle vrouwen vanaf 50 jaar (345) en mannen vanaf 65 jaar (99) van een Nederlandse huisartsenpraktijk uit een landelijk gebied in Zuid Oost Brabant uitgenodigd voor een DEXA meting. Tevens vulden zij een vragenlijst in waarin de risicofactoren van de NHG richtlijnen in vragende vorm beschreven waren. Patiënten die reeds gediagnosticeerd waren met osteoporose (n=12) en patiënten met een terminale aandoening zijn niet aangeschreven (n=8). Er respondeerden 234 vrouwen en 65 mannen (response rate 67%). Er

waren geen significante verschillen in geslacht, leeftijd, en sociaaleconomische status tussen mensen uit de huisartsenpraktijk die wel en niet deelnamen. Dit artikel betreft uitsluitend patiënten die een DEXA hebben laten maken én die de vragenlijst hebben ingevuld (N=290; 226 vrouwen en 64 mannen). Alle deelnemers waren van Caucasisch ras. In Tabel 2 staan de overige karakteristieken van deze groep beschreven.

Tabel 2. Karakteristieken van de onderzoekspopulatie: gemiddelde leeftijd, prevalentie van risicofactoren en DEXA resultaten van 290 patiënten

Karakteristieken	gemiddelde (SD)	% totaal (N=290)	% ♀ (n=226)	% ♂ (n=64)
leeftijd	63 (9)			
vrouwen		78		
Risicofactoren NHG richtlijn				
Doorgemaakte wervelfractuur		1	1	3
Langdurig gebruik hoge dosis corticosteroïden		6	6	5
Fractuur na 50ste		9	10	5
Leeftijd > 70 jaar		22	14	52
Leeftijd > 60 jaar		38	35	48
Heupfractuur 1e graads Familielid		14	12	20
Gewicht < 60 kg		15	18	5
Ernstige immobiliteit		10	8	14
Risicoscore ≥ 4		15	17	8
DEXA uitslag				
Osteoporose		12	11	17
Osteopenie		51	47	64
Gezonde botdichtheid		37	43	19

Botdichtheid van de heup en lumbale wervelkolom (LWK) werd gemeten met behulp van DEXA (Hologic QDR 4500W, versie 12.4). Botdichtheid werd uitgedrukt in T scores (standaard deviaties (SD) ten opzichte van de gezonde jonge populatie) en Z scores (SD ten opzichte van de leeftijd en geslacht gerelateerde populatie) op basis van de National Health and Nutrition Examination Survey database voor de heup en Hologic database voor de LWK. Volgens de WHO richtlijnen werd botdichtheid gediagnosticeerd als normaal (T score >-1.0 SD), osteopenie (T score ≤-1.0 SD en >-2.5 SD) of osteoporose (T score ≤-2.5 SD). Conform de Nederlandse richtlijnen werd bij mensen vanaf 70 jaar een Z score ≤-1.0 aangehouden om een afwijkende botdichtheid te diagnosticeren. Osteopenie werd in deze leeftijdsgroep niet gedefinieerd.

Conform de NHG case-finding methode werd een somscore berekend voor de vragenlijst. Vervolgens berekenden wij de sensitiviteit, specificiteit, positief voorspellende waarde (PPV) en negatief voorspellende waarde (NPV) van de vragenlijst voor het opsporen van osteoporose (95% Confidence Interval (CI)). Bovendien berekenden wij in aanvullende analyses deze waarden voor vrouwen bij gebruik van andere afkappunten. Dit kon niet bij mannen omdat zij volgens de case-finding methode slechts 3 scores kunnen behalen (0, 4 of 8) omdat slechts enkele risicofactoren voor mannen zijn onderzocht. Statistische analyses werden uitgevoerd met SPSS software (versie 16.0).

RESULTATEN

In tabel 3 zijn de resultaten van de DEXA meting en vragenlijst samengevat. Op basis van de DEXA resultaten had 12% (35/290) van de patiënten osteoporose, 51% (147/290) osteopenie en 37% (108/290) een

normale botdichtheid. Vijftien procent (43/290) scoorde tenminste 4 punten op de vragenlijst. Bij patiënten met osteoporose was dat 17% (6/35).

Tabel 3. Risicoscore volgens de NHG case-finding methode voor indicatie van botdichtheidmeting en resultaten van DEXA meting van 290 patiënten

	osteoporose	geen osteoporose	N
totale populatie			
risicoscore ≥4	6	37	43
risicoscore <4	29	218	247
N	35	255	290
Vrouwen			
risicoscore ≥4	5	33	38
risicoscore <4	19	169	188
N	24	202	226
Mannen			
risicoscore ≥4	1	4	5
risicoscore <4	10	49	59
N	11	53	64

In tabel 4 staan de sensitiviteit, specificiteit, PPV en NPV beschreven van de NHG case-finding methode voor de indicatie van botdichtheid meting bij een afkapwaarde van 4 punten. In de totale populatie was de sensitiviteit 17%, de specificiteit 86%, de PPV 14% en de NPV 88%. De resultaten van de aanvullende analyses staan eveneens beschreven in tabel 4.

Tabel 4. Sensitiviteit (sens), specificiteit (spec), positief voorspellende waarde, (PPV), en negatief voorspellende waarde (NPV) van de NHG case-finding methode voor de indicatie van botdichtheidmeting

Afkapwaarde	geslacht	sens % (95% CI)	spec % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
4	♂♀	17 (5-30)	86 (81-90)	14 (4-24)	88 (79-98)
	♂	9 (-8-26)	92 (85-100)	20 (-15-55)	83 (50-116)
	♀	21 (5-37)	84 (79-89)	13 (2-24)	90 (80-100)
1*	♀	83 (68-98)	33 (27-40)	13 (8-18)	94 (91-98)
2	♀	50 (30-70)	61 (54-68)	13 (6-20)	91 (85-97)
3	♀	29 (11-47)	78 (73-84)	14 (4-23)	90 (82-98)
* leeftijdsgrens 65 jaar:		79	42	14	94

Een afkapwaarde van 1 punt gaf de hoogste betrouwbaarheid van de case-finding methode voor het opsporen van vrouwen met osteoporose: een sensitiviteit van 83%, een specificiteit van 33%, een PPV van 13% en een NPV van 94%. Bij een afkapwaarde van '1' vervalt de toegevoegde waarde van de gewogen scores. Echter leidt dit tot screening bij mensen vanaf 60 jaar. Omdat de Europese richtlijnen op basis van kosten-effectiviteit DEXA meting aanbevelen bij vrouwen vanaf 65 jaar met tenminste 1 risicofactor[4], herhaalden wij de analyse met 1 risicopunt voor een leeftijd vanaf 65 jaar in plaats 1 punt voor 60-70 jaar en 2 punten >70 jaar. Dit leverde een hogere specificiteit (42%) op. De sensitiviteit (79%), PPV (14%) en NPV (94%) bleven nagenoeg gelijk.

174

DISCUSSIE

Dit artikel informeert over de betrouwbaarheid van de NHG case-finding methode voor de indicatie van botdichtheidmeting bij patiënten met een verhoogd risico op osteoporose. Hoewel bij een afkapwaarde van 4 punten de specificiteit (85%) en NPV (88%) goed waren, waren de sensitiviteit (17%) en PPV (14%) laag. Vervolgens is de optimale afkapwaarde bij vrouwen geëvalueerd. Dit bleek een score van 1 te zijn, waarbij de sensitiviteit toenam tot 83%. De specificiteit daalde tot 33% en de PPV bleef nagenoeg gelijk (13%). Indien 65 jaar als risicofactor werd gebruikt in plaats van 60 jaar, bleven de sensitiviteit en PPV ongeveer gelijk en nam de specificiteit toe (42%).

De PPV van de NHG case-finding methode is laag voor alle afkapwaarden. Dit betekent dat de kans klein is dat iemand met een risicoscore hoger dan de afkapwaarde daadwerkelijk osteoporose heeft. Instrumenten met een lage PPV kunnen bruikbaar zijn in de dagelijkse eerstelijns praktijk, mits de sensitiviteit hoog is. Echter, bij een afkapwaarde van 4 is de sensitiviteit van de NHG case-finding methode voor de indicatie van botdichtheid meting laag. Deze methode is dus niet betrouwbaar voor het opsporen van patiënten met osteoporose. Volgens onze resultaten zou dit in de praktijk betekenen dat voor elke patiënt die gediagnosticeerd wordt met osteoporose, men vijf patiënten met osteoporose mist. De lage betrouwbaarheid van de case-finding methode kan op verschillende manieren verklaard worden. In de eerste plaats kunnen de resultaten beïnvloed zijn door de lage prevalentie van osteoporose in de onderzoekspopulatie. De lage prevalentie kan het gevolg zijn van de relatief jonge leeftijd van de populatie, het gebruik van Z-scores bij patiënten vanaf 70 jaar, de exclusie van patiënten die reeds met

osteoporose gediagnosticeerd waren en het feit dat alleen Caucasische patiënten aan het project deelnamen. Echter, een betrouwbare vragenlijst zal ook in een populatie met een lage prevalentie minimaal redelijke uitkomsten moeten geven. Een andere belangrijke verklaring is dat de case-finding methode van de NHG richtlijn gebaseerd is op suggesties voor case-finding zoals omschreven in de CBO richtlijnen[3]. De gewogen scores zijn gebaseerd op literatuuronderzoek, zonder dat hier (regressie)analyses aan ten grondslag liggen. Bovendien beschrijven de CBO richtlijnen case-finding in termen van <u>fractuur</u>risico. In tegenstelling hiermee gaat in de NHG standaard de aandacht uit naar de diagnostiek en het beleid van patiënten met risicofactoren voor <u>osteoporose:</u> één van de kernboodschappen van de standaard is dat men een botdichtheidmeting alleen dient aan te vragen bij mensen met een verhoogde kans op <u>osteoporose</u>. Tenslotte is een mogelijke verklaring voor lage betrouwbaarheid de operationalisatie van de risicofactoren. Zo kan de relevantie van het navragen van bestaande wervelfracturen betwist worden, wetende dat ongeveer 2/3 van de wervelfracturen niet herkend wordt[20]. De vraag over ernstige immobiliteit wordt in de NHG richtlijnen niet verder gekwantificeerd. Beide items zijn bovendien niet in internationale case-finding methoden opgenomen[7-16]. Het is tevens opmerkelijk dat aan leeftijd relatief weinig gewicht toegekend wordt in vergelijking met andere internationale case-finding methoden.

Uit aanvullende analyses bleek dat de sensitiviteit van de case-finding methode bij vrouwen stijgt tot 83% door een afkapwaarde van 1 punt te gebruiken. Ondanks de matige specificiteit (33%) en lage PPV (13%), neemt hierdoor de bruikbaarheid voor de klinische praktijk toe. Op basis van literatuur over kosteneffectiviteit zou gekozen kunnen worden om de risicofactor leeftijd te verhogen van 60 naar 65 jaar. De sensitiviteit daalt

iets (79%), maar de specificiteit neemt toe tot 42%. Hoewel de lage PPV en matige specificiteit impliceren dat met een afkapwaarde van '1' een aanzienlijk deel van vrouwen zonder osteoporose in aanmerking komt voor een DEXA, neemt de relevantie voor de dagelijkse praktijk bij een hogere sensitiviteit toe: slechts 1 vrouw met osteoporose wordt gemist voor iedere 4 vrouwen bij wie men osteoporose vaststelt. Hoewel het gebruik van andere afkapwaarden de case-finding methode verre van optimaliseert (aangepast gebruik zou leiden tot screening vanaf een bepaalde risicoleeftijd), kunnen we wel concluderen dat de methode na aanpassing betere resultaten oplevert voor het opsporen van osteoporose. De waarde van onze bevindingen is van klinisch belang omdat de NHG standaard voor osteoporose op grote schaal wordt toegepast in Nederland voor het opsporen van patiënten met osteoporose. Dit artikel is tot stand gekomen als onderdeel van een zorgproject rondom osteoporose, dat met behulp van de zorgverzekeraars in de regio Zuid Oost Brabant is uitgevoerd in 2006 en 2007. In dit project hebben huisartsen case-finding toegepast op hun praktijkpopulatie volgens de NHG richtlijnen, waarbij ruim 21.500 patiënten zijn aangeschreven. Op basis van de resultaten van dit artikel kan men concluderen dat binnen het project veel patiënten met osteoporose niet ontdekt zijn en dus niet de behandeling hebben ontvangen die zij behoeven.

Bij de interpretatie van de resultaten van dit artikel moeten enige beperkingen worden genoemd. Hoewel de respons voldoende was, is de populatie van slechts één huisartsenpraktijk onderzocht. Deze huisartsenpraktijk was gelegen in een landelijk gebied en uitsluitend blanke mensen hebben deelgenomen aan het project. Bovendien was de gemiddelde leeftijd relatief laag. Dit kan de lage prevalentie van osteoporose in onze populatie verklaren. Daarnaast hebben aan dit project

hebben vooral vrouwen hebben deelgenomen. De beschreven resultaten kunnen daarom niet zonder meer gegeneraliseerd worden naar de algemene Nederlandse populatie. Een andere beperking is dat door de opbouw van de NHG richtlijnen het optimale afkappunt bij mannen niet kon worden bepaald. Tenslotte kan het gebruik van de NHG case-finding methode voor de indicatie van botdichtheidmeting op populatieniveau betwist worden. Echter, de betrouwbaarheid op populatieniveau en individueel niveau zijn gelijk: de kans dat een individuele patiënt met osteoporose ten onrechte geen botdichtheidmeting krijgt blijft even groot. Bovendien dient men zich te realiseren dat de (preventieve) zorg voor chronische ziekten zoals osteoporose in de eerstelijn steeds meer geïnstitutionaliseerd is in grote zorggroepen. Binnen deze zorggroepen wordt voor efficiënte preventie met behulp van praktijkverpleegkundigen op protocollaire wijze gebruik gemaakt van landelijke richtlijnen.

Op basis van onze bevindingen is het aan te bevelen dat de NHG haar standaard herziet wat betreft de indicatie voor botdichtheidmeting. Het is hierbij van groot belang het doel van case-finding duidelijk te definiëren en het toenemend grootschalig toepassen van richtlijnen door praktijkondersteuners in zorggroepen in acht te nemen. Aanvullend onderzoek is nodig om een herziene case-finding methode te valideren alvorens te implementeren in de praktijk, ook voor mannen. Hierbij dient ook aandacht uit te gaan naar de huidige discussie in de literatuur over het opsporen van patiënten met een hoog fractuurrisico in plaats van het opsporen van patiënten met een verhoogd risico op osteoporose[4].

REFERENTIES

1. Blokstra A, Verschuren WMM, Baan CA, *et al.* Vergrijzing en toekomst van ziektelast. Prognose chronische ziekteprevalentie 2005-2025. Rijksinstistiuut voor Volksgezondheid en Milieu, Bilthoven, 2007.

2. http://cognosserver.prismant.nl/cognos7/cgi-bin/ppdscgi.cgi?DC =Q&E=/Prisma-Landelijke-LMR/Landelijke+LMR-informatie+-+ Diagnosen

3. Kwaliteitsinstituut voor de gezondheidszorg CBO. Tweede herziene richtlijn osteoporose. Alphen aan den Rijn: Van Zuiden Communications; 2002. p. 1-156.

4. Kanis JA, Burlet N, Cooper C, *et al*.; European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2008;**19:**399-428.

5. Genant HK, Cooper C, Poor G, *et al*. Interim report and recommendations of the World Health Organization Task-Force for Osteoporosis. *Osteoporos Int* 1999;**10:**259-264.

6. Kanis JA, Johnell O. Requirements for DXA for the management of osteoporosis in Europe. *Osteoporos Int* 2005;**16:**229-238

7. Cadarette SM, Jaglal SB, Murray TM, *et al*. Evaluation of decision rules for referring women for bone densitometry by dual-energy x-ray absorptiometry. *JAMA* 2001;**286:**57-63.

8. Salaffi F, Silveri F, Stancati A, Grassi W. Development and validation of the osteoporosis prescreening risk assessment (OPERA) tool to facilitate identification of women likely to have low bone density. *Clin Rheumatol* 2005;**24:**203-211.

9. Cadarette SM, Jaglal SB, Kreiger N, *et al*. Development and validation of the Osteoporosis Risk Assessment Instrument to facilitate selection of women for bone densitometry. *CMAJ* 2000;**162:**1289-1294.

10. Sedrine WB, Chevallier T, Zegels B, *et al*. Development and assessment of the Osteoporosis Index of Risk (OSIRIS) to facilitate selection of women for bone densitometry. *Gynecol Endocrinol* 2002;**16:**245-250.

11. Reginster JY, Ben Sedrine W, Viethel P, *et al*. Validation of OSIRIS, a prescreening tool for the identification of women with an increased risk of osteoporosis. *Gynecol Endocrinol* 2004;**18:**3-8.

12. Richy F, Gourlay M, Ross PD, *et al*. Validation and comparative evaluation of the osteoporosis self-assessment tool (OST) in a Caucasian population from Belgium. *QJM* 2004;**97:**39-46.

13. Adler RA, Tran MT, Petkov VI. Performance of the Osteoporosis Self-assessment Screening Tool for osteoporosis in American men. *Mayo Clin Proc* 2003;**78:**723-727.

14. Koh LK, Sedrine WB, Torralba TP, *et al.*; Osteoporosis Self-Assessment Tool for Asians (OSTA) Research Group. A simple tool to identify asian women at increased risk of osteoporosis. *Osteoporos Int* 2001;**12:**699-705.

15. Sedrine BW, Devogelaer JP, Kaufman JM, *et al*. Evaluation of the simple calculated osteoporosis risk estimation (SCORE) in a sample of white women from Belgium. *Bone* 2001;**29:**374-380.

16. Michaëlsson K, Bergström R, Mallmin, H *et al*. Screening for osteopenia and osteoporosis: selection by body composition. *Osteoporos Int* 1996;**6:**120-126.

17. Elders PJ, Leusink GL, Graafmans WC, *et al*. NHG standaard osteoporose. *Huisarts Wet* 2005; **48:**559-570.

18. Verdijk NA, Romeijnders AC, Ruskus JJ, *et al*. Validation of the Dutch guidelines for dual X-ray absorptiometry measurement. *Br J Gen Pract* 2009;**59:**256-260.

19. Verdijk NA, Leusink G, Erdtsieck R, Pop VJ. Improving the sensitivity of the Dutch guidelines for case finding in osteoporosis. *Br J Gen Pract* 2009;**59:**370-371.

20. Kanis JA, McCloskey EV. Epidemiology of vertebral osteoporosis. *Bone* 1992;**13:**S1-S10.

ABOUT THE AUTHOR

Noortje Verdijk was born on december 28th, 1981 in 's-Hertogenbosch. She completed her pre-university education at R.C. Gymnasium Beekvliet in Sint-Michielsgestel in 2000. From 2000 to 2005 she studied psychology at Tilburg University, with a specialisation in clinical health psychology. Subsequently she started her PhD project on osteoporosis at the Coordination Centre of Nurse Practitioners for South East Netherlands (PoZoB). From 2008, she combined her research activities with project management in health care at POZOB. From 2009, Noortje continued her research activities at Tilburg University.

Noortje Verdijk is geboren op 28 december 1981 in 's-Hertogenbosch. Zij voltooide haar VWO aan R.C. Gymnasium Beekvliet te Sint-Michielsgestel. Van 2000 tot 2005 studeerde ze psychologie aan de Universiteit van Tilburg, met een specialisatie in de klinische gezondheidspsychologie. Na haar afstuderen startte ze met haar promotieonderzoek naar osteoporose bij Praktijkondersteuning Zuidoost Brabant (PoZoB). Vanaf 2008 combineerde ze haar onderzoeksactiviteiten met projectmanagement in de gezondheidszorg bij PoZoB. Vanaf 2009 zette Noortje haar onderzoeksactiviteiten voort bij de Universiteit van Tilburg.