Hip fracture prevention by screening and intervention of elderly women in Primary Health Care

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Abstract

Background – One in four Swedish women suffers a hip fracture (HF)**.** In order to identify high-risk women we developed clinical 4-item scores as the FRAMO (Fracture and Mortality) Index, evaluated heel bone mineral density (BMD) and undertook interventions to improve mobility, reduce falls and HF.

Methods - In pilot study 1998, a questionnaire regarding HF risk factors was sent to100 elderly women, with follow-up in 2001.

Based on questionnaire 2001 sent to 1498 women aged ≥70, participants were analyzed with FRAMO Index (Risk Model I) for HF, fragility fracture (FF) and mortality in 2002–2003.

A questionnaire regarding HF risk was 2003 returned by 285/435 women in the intervention population and heel BMD was assessed by portable dual X-ray laser absorptiometry (DXL), and correlated with 2-year incident HF and FF. Heel BMD was compared to hip BMD.

In the controlled cohort intervention study, 296 (I=103, C=193) women were at high risk for HF (in Risk Model II). House calls were made to 61 % in intervention group, initiating exercising and home hazard reduction. After BMD determination pharmacological treatment was considered for 80 %. We evaluated mobility outcomes from questionnaires 2001 and 2004 and incident fractures in 2004–2005.

Results - The 1998 questionnaire was answered by 92%; 34% had needs for fracture prevention. The 2001 questionnaire was returned by 83% (n=1248). Four items – age ≥80, weight <60kg, prior fragility fracture and using arms to rise from sitting - were combined in FRAMO Index. The 2-year HF risk was 0.8% risk for 63% with scores 0–1, and 5.4% (OR 7.5; 95%CI 3.0–18.4) for remaining 37% women with scores 2–4, having a 23.7% mortality risk.

During 2004–2005, 7 HFs and 14 FFs occurred among the 285 women in intervention group, 60% of whom had heel osteoporosis (≤ -2.5 SD). The revalidated FRAMO Index showed HF OR 5.9 and FF OR 4.4. Heel BMD showed HF OR 2.7 and FF OR 2.3 for each SD decrease. Combining FRAMO Index + prior fragility fracture + low heel BMD yielded an annual HF risk of 7.8% for 11% and 0.4% for 89%.

In the intervention group, we found less women with inability to rise (OR 0.21) and less falls (OR 0.46) in 2004, in women with initially impaired mobility. Home exercise was

more common in intervention group (RR 2.1). Women with impaired rising ability who home exercised improved (p=0.03). Three interventions seemed related to improvement in rising ability on multivariate analysis; current home exercise, calcium-vitamin D_3 treatment and previous group exercise (p=0.04–0.06). Two HFs occurred in the intervention group vs 11 in controls (OR 0.33 and p=0.23).
Conclusion – Study questionnaires were feasible in PHC. The FRAMO Index yielded good fracture and mortality prediction. Heel BMD showed increased HF and FF risk. Heel osteoporosis prevalence was high. Hip osteoporosis corresponded to a heel DXL level of around -3.3 SD. Clinical risk factors combined with very low heel BMD defined a small high risk group for HF, NNT=13. Intervention group subjects with impaired mobility and high HF risk improved their mobility more than controls, one year after major multi-factorial intervention. Home exercise, group exercise and calcium- vitamin D treatment seemed related to improved rising ability. This risk assessment and intervention program with 1–2 years duration, appears useful in population-based HF prevention.

Key words: Hip Fracture, Fractures, Mortality, Women, Aged, Risk Factors, Risk Assessment, Accidental Falls, Questionnaires, Accident prevention, House Calls, Exercise Therapy, Drug Therapy, Bone Density, BMD, Absorptiometry, Intervention Studies, Primary Health Care, Sweden.

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This thesis is based on the following Papers (Studies), referred to in the text by their Roman numerals

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II. Albertsson DM, Mellstrom D, Petersson C, Eggertsen R. Validation of a 4-item score predicting hip fracture and mortality risk among elderly women. Ann Fam Med. 2007;5:48-56. (http://www.annfammed.org/cgi/reprint/5/1/48).

III. Albertsson D, Petersson C, Mellstrom D, Grahn B, Eggertsen R. Improved ability to rise and less falls among women aged over 70 at high hip fracture risk – results from an intervention study. 2007, in manuscript.

IV. Albertsson D, Mellström D, Petersson C, Thulesius H, Eggertsen R. Hip and fragility fracture prediction in elderly women: A 4-item risk score and heel BMD DXL assessment study. 2007, in manuscript.

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CONTENTS

Abbreviations

BMD = bone mineral density
BMI = body mass index (the body weight divided by squared body height)
BUA = broadband ultrasound attenuation
CI = confidence interval
DXA = Dual X-ray absorptiometry
DXL = dual X-ray laser absorptiometry
EPIDOS study = European Patent Information and Document Service Fracture Study
FF = fragility fracture/s
FRAMO Index = Fracture and Mortality Index (Risk Model I)
GP = general practitioner
HF = hip fracture/s
HR = hazard ratio
HRT = hormone replacement therapy
ICD-10 = International Classification of Diseases, 10th Revision
MOF study = Melton Osteoporotic Fracture study
NNT = number needed to treat
OR = odds ratio
PHC = Primary Health Care
PTH = parathyroid hormone
QCT = quantitative computed tomography
QUS = quantitative or broadband ultrasound
R&D-unit = Research and Development unit
RCT = randomized controlled trial
ROC curves = receiver operating characteristic curves
RR = relative risk
SD = standard deviations
SERM = selective estrogen receptor modulators
SOF = Study of Osteoporotic Fractures
SOS = speed of sound
SPA = single photon absorptiometry
SPSS = Statistical Package for the Social Sciences; SPSS Inc, Chicago, Ill
SSRI = selective serotonin re-uptake inhibitors
T-score value = express BMD in SDs, compared to the mean value of a young, healthy, adult reference population
$\text{T-score}_{\text{Low}}$ = lowest T-score value of either side after bilateral measurement
WHI study = Woman's Health Initiative study
WHO = World Health Organization
vitamin D_3 = cholecalciferol

Background

The skeleton is essential for human life, it is light enough to facilitate rapid movement, yet strong enough to bear the weight of the body and to move it in the upright position. The skeleton is a dynamic organ, rebuilt continuously,[1] partly due to daily load and stress.[2]

There is less daily physical activity than previously among people in modern society. During the 20th century fracture incidence increased worldwide,[3, 4] especially in urban areas.[5, 6] Recently, the increase in hip fracture (HF) rates among women has tended to slow down in some regions, but it still remains high.[7] This marked increase in fracture risk high-lightens both the possibility and the importance of lowering the incidence. Advanced age is a strong predictor for falls and fractures[8, 9] related to weaker bone and impaired balance and muscle strength, especially among women and related to physical inactivity.[5, 10-12]

Nowadays, every fourth Swedish woman suffers a HF after the age of 50[13]often leading to pain and impaired ability; mortality is 20% after one year.[14]

Prevention approach

Disease preventing is a challenge for which primary health care (PHC) should be a suitable arena. The elderly population often has established and rather frequent contact, as well as designed caregivers, with the PHC system. This could encourage a dialogue, based on the individual's concerns, within the wide field of biopsychosocial issues,[15] including prioritizing among several concurrent diseases. An extensive preventive agenda focusing on biomedical issues may divert the dialogue away from important social issues related to the patient's health.[16]

Simple effective health-improving lifestyle interventions, such as daily outdoors walks out-doors and smoking cessation can often be recommended for treating and preventing several common diseases among the elderly, such as cardiovascular disease, diabetes mellitus, depression, chronic obstructive pulmonary disease, osteoporosis and HF. Encouraging efficient self-treatment for prevention, emphasizes more active and self reliant patients´ attitudes toward their own health, compared to extensive medication based on weak evidence and leaning to limited benefits effects among elderly. More intensive initiatives aimed at improving health among elderly individuals who are currently free of symptoms require time-consuming discussions about benefits and harm.[16]

Fall accident attitudes

Falls and fractures are common among elderly women, especially women at high risk of HF. During my own work as a general practitioner (GP) I have found different explanation patterns and planning after an accident, both among the patients and, occasionally, among the caregivers.
Some patients take active and appropriate steps to avoid recurrence after their accidents. Others present attitudes of denial based on selective loss of memory for that occasion, or simply avoiding the subject. They may claim that it will not happen again and state it was extremely "bad luck", that the fall was unpredictable, without any identifiable causal factors, or that such accidents are unavoidable. These women often have a fear of repeated falls,[17] followed by less physical activity leading to further deterioration in mobility often combined with a more restricted social life.
By involving elderly women in a fracture prevention program, participants are made aware of both their mobility resources and their shortcomings. An effective and feasible intervention program can meet several needs for mobility improvement, although participants have varying preferences or abilities to cope with and accept the actual capacity of their ageing bodies.[18] In caring for this aged group, with physical or mental (often memory) impairments, the clinician have to repeat or adjust advice and occasionally involve relatives or other caregivers.

Study goals and assumptions

When planning the study the following goals and assumptions were essential:

- To involve a total population representative for a PHC district.
- To identify women at high HF risk in clinical practice.
- The HF risk is multi-factorial and fracture prediction is improved by combining selected clinical variables.
- As fracture prevention is usually more efficient for women at high absolute risk, the preventive resources were directed to them.
- Several feasible non-randomized intervention alternatives were offered, with sufficient time to enable dialogue and individual choice. The interventions were performed by ordinary PHC or community staff, emphasizing both reduction in shortcomings (risk factors) and possible improvement in individual mobility resources (protective factors). All of these factors may increase compliance and effects of a preventive program.
- Exercise is a major factor for mobility improvement and fracture prevention. Various exercise alternatives were developed and offered to participants.

Introduction

History

Early knowledge and treatment of fractures
HF were described as early as in the 1630s, as was the fact that the bone size was related to body weight and physical activity.[19] During the 19th century, bone fragility, the different fracture types and their relation to age and sex were described,[19] and it was established in the 1960s that the majority of HF occurred among women, due to fragility after low energy trauma, and that HF incidence doubled for every five year of age.[20] At that time, the three-month mortality after a HF caused by a moderate trauma was around 20%[21] The results of HF surgery in the 1950s were uncertain; mortality related to surgery was equal in some studies and lowered in others[21] compared to a conservative approach.

Clinical risk factor evaluation
Fracture prediction based on clinical risk factors has been evaluated more extensively since the1990s.[9, 22-24] The bone mineral density (BMD) level alone is less predictive although additional BMD assessment in women with clinical risk factors improves fracture prediction.[22, 25] Work is ongoing to draw up international guidelines for long-term prediction of absolute fracture risk,[26] for treatment based on clinical risk factors for different regions and to clarify the value of additional BMD assessment.[27]

Bone mineral density
The first international World Health Organization (WHO) report concerning assessment of fracture risk was published in 1994, defining osteoporosis in women as BMD ≥2.5 standard deviations (SD) below the mean of the young adult reference range.[28, 29] Osteoporosis has been assessed in larger international pharmacological studies with Dual X-ray Absorptiometry (DXA) technique applied to the hip and spine, evaluating fracture prediction and treatment effects on BMD and fracture incidence.[30, 31] Application of other BMD assessment techniques at peripheral sites usually yielded less accurate fracture prediction.[24, 31, 32]

Lifestyle interventions
During the last 10 years a reduction in falls and fall-related injuries has been seen in connection with several, mainly mobility-related, interventions. Single or multiple intervention strategies include walking, exercise, home hazard reduction and physical health examination directed to risk groups or applied in population-based intervention programs.[33, 34] Less HF have been seen among moderately physically activity postmenopausal women compared to those with low physical activity level,[12] and in

residential care hip protectors use seems to reduce HF risk[35] An elevated HF risk has been found among cigarette smokers.[36]

Pharmacological treatment

During the 1990s studies on calcium and vitamin D treatment showed HF and non-vertebral fracture reduction among the elderly.[37, 38] As a consequence the prescription of these substances to postmenopausal women increased. Recent studies indicate that the major fracture-preventive effect of calcium and vitamin D is confined to women aged over 80, at least among women in residential care.[39]

Bisphosfonate treatment has been extensively studied in post menopausal women, showing fracture-preventive effect, especially in elderly women with previous fractures and low BMD.[40, 41] Treatment effects, as absolute fracture risk reduction increased by age, have been studied up to age 85.[42]

Hormone replacement therapy (HRT) is frequently used by post menopausal women, for its fracture-preventive effect, among other reasons. This effect was confirmed in the Women´s Health Initiative (WHI) study[43] but the negative side effects exceeded the benefits. Hence, HRT has been discarded as a long-term fracture-preventive strategy.

Recent treatment alternative are selective estrogen receptor modulators (SERM) that prevent vertebral fractures,[44] parathyroid hormone (PTH) for severe osteoporosis or after repeated fractures[45] and orthopedic bone cement stabilization for advanced vertebral compressions[46]

Bone metabolism

Normal bone formation and bone structure

The skeleton must both be light and have sufficient strength to adapt to a mobile daily life. Ten percent of the total skeleton is remodeled annually,[1] partly due to load and stress.[2] It is embedded and stabilized by the softer adipose, cartilage and muscle tissues, and serves as a reservoir for mineral salts and calcium.

The skeleton consists of cortical and trabecular bone. The cortical bone outlines the bone surface, surrounding the trabecular bone. Cortical bone constitutes 80% of the skeleton and is mostly found in the shafts of tubular bone.[19] The blood supply comes from the periosteal and intracortical vessels.

Trabecular bone is found in the middle of bones, in the vertebrae, at the end of long bones, in the pelvis and in other flat bones. About 20% of the skeleton is trabecular. Trabecular bone is remodeled on the surface of the trabeculae. Incomplete trabeculae are very common in osteoporosis.[19] Trabecular bone has a larger surface area with the highest turnover; this type of bone can thus alter its bone mass more rapidly.

Bone tissue and remodeling
There are several bone cell types engaged in bone metabolism, mainly osteoblasts, osteoclasts and osteocytes. Osteoblasts orginate from stromal precursors of bone marrow. They are bone forming cells that synthesize bone matrix and enhance bone mineralization. Bone matrix is composed of 90% collagen; the remaining substance consists of protein chains specific for the skeleton, including locally active growth factors.[1] Phosphate and calcium are incorporated as salts into the organic matrix, which transforms into calciumhydroxyapatite in the mineral phase.[19]
Osteoblasts incorporated in the bone are called osteocytes. They develop cytoplasmic processes that connect other osteocytes and the osteoblast lining cells on the skeleton surface into a network.[2] The osteocytes probably sense bone deformation, thereby signaling the need for adaptive remodeling of bone size, shape, and distribution to accommodate prevailing loads.[2]
The remodeling process starts with the osteoclast-mediated resorption of the mineralized bone. The osteocyte orginates from a haematopoietic stem cell and developed into a sort of leucocyte with many nuclei and a ruffled border, which comes into direct contact with bone and the resorption area. It dissolves bone mineral by lowering pH and digesting the bone matrix by releasing proteolytic enzymes, creating a resorption lacuna at that skeletal site. However, it is unclear how an osteoclast chooses a specific site for remodeling, when to process will be terminated and which changes in the skeleton induce or promote remodeling.[1] The osteoblasts appear in the resoption lacunae after the osteoclasts.[2] Bone formation is equal to osteoclastic bone resorption under normal conditions. Normally there is ongoing remodeling at about 1-2 million single sites; bone resorption lasts about one month and the rebuilding phase lasts three months.[1]
Furthermore, the osteoblasts and their precursors are necessary for the differentiation and activation of the osteoclastic cells, stimulated by activation of the osteoblast receptors for PTH and 1,25$(OH)_2$-vitamin D (vitamin D_3).[1]

Age- and treatment-related postmenopausal bone remodeling Postmenopausal osteoporosis with low BMD (≤ -2.5 SD) and less complete trabecula network there is an increased risk of fragility fracture (FF).[1] The BMD loss accelerates around and after menopause due to a lowered oestrogen level, mostly affecting the trabecular bone.[1] This leads to a dramatically increased number of remodeling sites by inducing more osteoclastic activity, combined with insufficient resorption lacuna repair by the osteoblasts.
There is also an age-related BMD decline in both genders, due both to more bone resorption and less bone formation. This bone resorption increase is related to hypogonadism, calcium loss with vitamin D deficiency and secondary hyperparathyroidism.[1] After the age of 65 the bone mass decrease is equal in both genders, affecting both the cortical and trabecular bone.[1] The additional age-related

BMD decline with less cortical bone and thinner trabeculae, gradually increases the fracture risk.
The bone metabolism effects of several pharmacological treatments have recently been clarified. Bisphosfonates are bound to the skeletal tissue, inducing osteoclastal apoptosis.[47] The osteoclast inhibition decreases the bone resorption and fracture reduction has been shown among high-risk groups.
Oestrogen deficiency after menopause is clearly related to lowered BMD, mainly via increased bone resorption in trabecular bone. HRT preserves BMD and reduces the fracture incidence, although this type of long-term fracture prevention is currently avoided due to serious side effects. An alternative treatment with selective oestrogen receptor modulators (SERM) has been shown to prevent vertebral fracture, with less side effects.[44]
PTH given as an intermittent daily injection, leads to increased osteoblastic anabolic activity with marked bone formation and fracture reduction in elderly risk groups.[48] On the other hand, continuous PTH administration leads to the reverse effect, an increase in osteoclast activity and bone resorption, an effect more expected since hyperparathyroidism is a known cause of osteoporosis.
Strontium is bound to the skeletal hydroxiapatite, replaceing calcium, exerting an anti-resorptive effect[49] Fewer fractures have been seen in trials of this substance on postmenopausal risk groups.
Calcium and vitamin D mechanisms of fracture prevention have been discussed; lowered PTH level, followed by less bone resorption, and vitamin D-induced muscle and balance improvement, reducing fall accidents, are possibilities. In more recent analyses, fracture reduction seems to be concentrated to elderly women. When specific fracture-preventive drugs are prescribed, calcium and vitamin D should be added.

Fracture incidence, prevalence and consequences

Hip fracture

Between the 1950s and the 1980s there was an increase in HF incidence, irrespective of age and gender [50, 51] and BMD decreased in the urban Swedish population, having a more sedentary life-style.[3, 52] The higher fracture prevalence in urban area could be explained by having a less physically active life-style compared to rural areas.[53]
At present, HF account for 26% (18 000) of the 70 000 annual FF in Sweden.[7, 54] The lifetime risk of HF is estimated at 23% for Swedish women over age 50[13] with the first fracture occurring at the mean age of 81 and increasing risk at higher ages. Five to ten percent will suffer bilateral HF.[6, 55] Many women suffer pain and decreased mobility after their HF and 20% of these women will die within one year.[14] Preventing a single HF in a person surviving the first year has been calculated to reduce society’s costs by SEK 150 000 ($ 19 000).[56]

Other fragility fractures

Vertebral fractures increase from the age of 65 and account for 21% (15 000) of FF. They usually cause sudden vertebral pain that often decreases within three months. Multiple vertebral fractures may cause longstanding pain, kyphosis, decreased height and impaired mobility. Increase mortality is also seen after vertebral fracture.[57]
Of all FF, proximal humerus fractures account for 14% (10 000) and radius fractures for 36% (25 000) annually, both leading to fewer complications than HF. Radius fracture increases as early as from the age of 45. Pelvic, rib and proximal tibial fractures are other fragility-related fractures.

Risk factors for fracture

Fracture mechanisms

The fracture risk is dependent on several mechanisms:
The fall risk: A fall usually precedes a FF.[8] Falls among the elderly have often multi-factorial, caused by a combination of imbalance (due to impaired mobility, diseases or sedatives)[58, 59] and inadequate adaptation to home hazards, see Figure 1.[60]
Trauma type: The trauma contributing to a FF is usually a fall from standing at ground level. HF are usually preceded by a fall sideways.[61, 62]
Energy absorbtion: Fall energy is absorbed both by the skeleton and the adipose tissue, embedding the skeleton. Adipose tissue on the hips or the use of hip pads prevents HF.[62, 63] An adequate muscular defense reaction toa fall can also reduce fall velocity and its effect on a specific skeleton site.
Bone strength: The bone strenght is dependent on skeletal BMD,[9] but also on the quality, geometry,[2, 64] and size of the proximal femur.[65, 66] These factors are largely determined by genetics.[67]

Risk factor interactions

Fracture risk is usually multi-factorial (see Figure 1). Women contracting HF usually have several coexisting risk factors, as in the Cumming study 1995, see Figure 2.[22]
Age, impaired mobility, previous fracture and BMD are some well-known risk factors, each adding some additional fracture risk independent of the others.[22, 25, 68] Risk factors can be modifiable or not; intervention may modify risk factors and possibly the fracture risk.

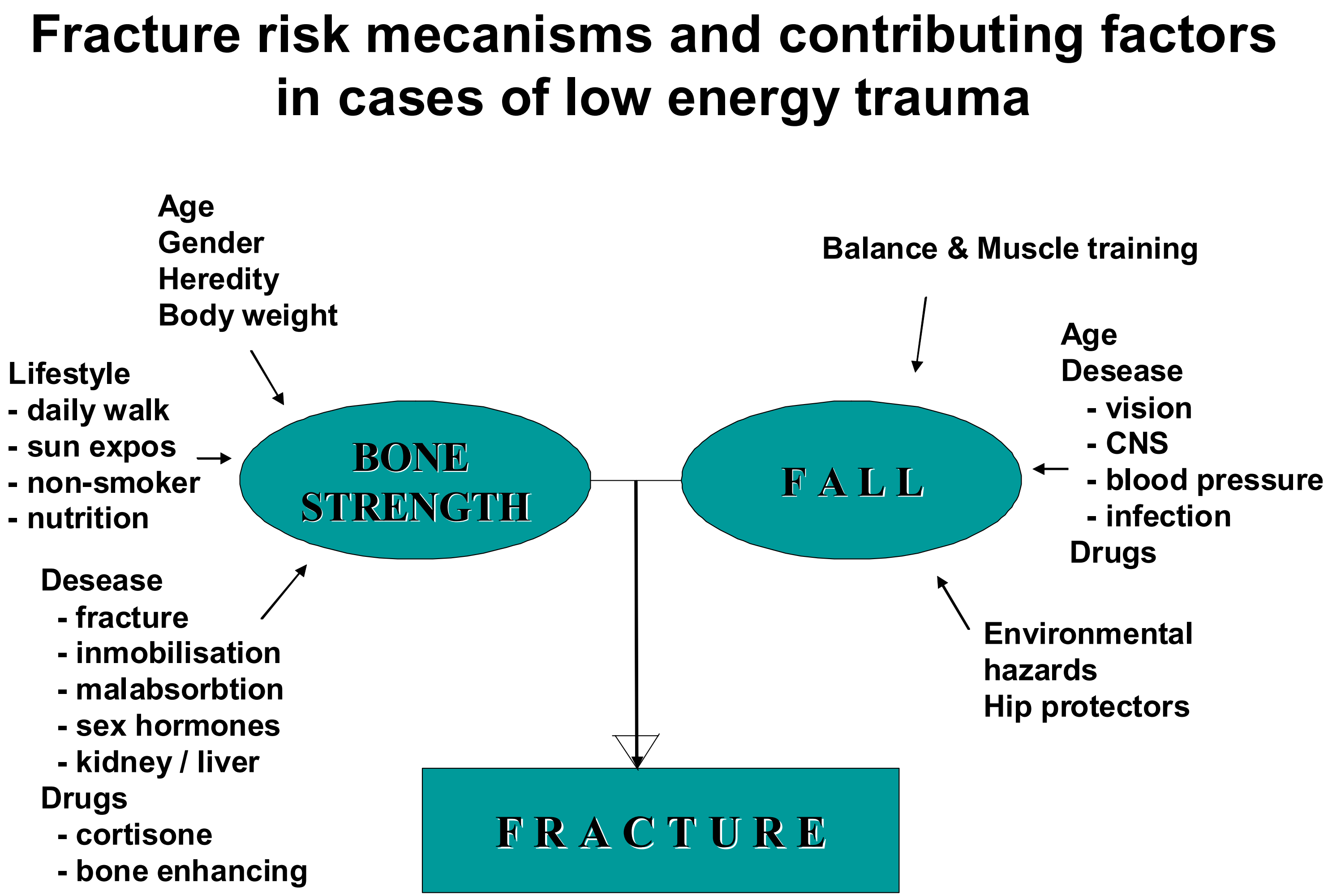

Figure 1: The multi-factorial fracture risk, mainly affecting bone strength and falling.

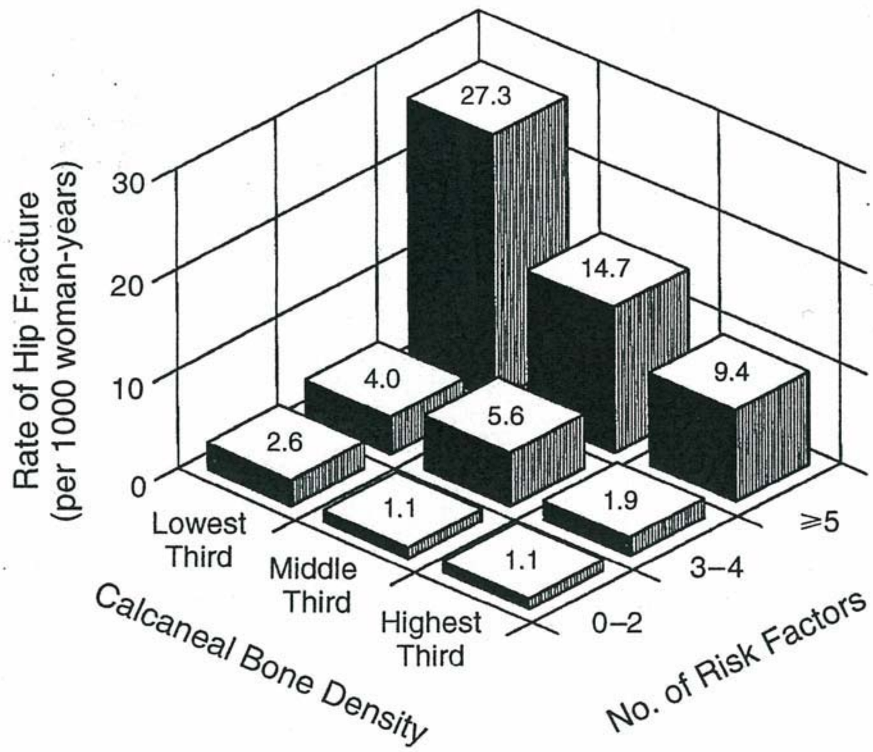

Figure 2. Annual Risk of Hip Fracture According to the Number of Risk Factors and the Age-Specific Calcaneal Bone Density.

The risk factors (from Table 2) are as follows: age ≥80; maternal history of hip fracture; any fracture (except hip fracture) since the age of 50; fair, poor, or very poor health; previous hyperthyroidism; anticonvulsant therapy; current long-acting benzodiazepine therapy; current weight less than at the age of 25; height at the age of 25 ≥168 cm; caffeine intake more than the equivalent of two cups of coffee per day; on feet ≤4 hours a day; no walking for exercise; inability to rise from chair without using arms; lowest quartile (standard deviation >2.44) of depth perception; lowest quartile (≤0.70 unit) of contrast sensitivity; and pulse rate >80 per minute.

Risk factors - non-modifiable

Age

Advanced age is an important risk factor for FF.[9, 69] After age 80 women's HF risk increases by nearly 60% every year.[27]Another study showed that the HF rates in both sexes nearly doubled every five-years period between ages 70 and 90.[70] Bone is mineralized during childhood, reaching maximum stability by adulthood with a higher BMD among men. Thereafter, BMD declines with age, a decline that accelerates among postmenopausal women.[71] Before the age of 50, the prevalence of osteoporosis is only a few percent in Swedish women but it increases to more than 30% after age 70.[71] Nonetheless, the HF risk increased six-fold in women aged 80 who had the same BMD level as women aged 50.[69]

Race, gender and heredity

Fracture risk is highest in the Scandinavian countries illustrated by a life-time HF risk of 28.5% in Swedish women, compared to a 1% risk in Turkish women aged 50 and up.[72]

Women's fracture risk is around three-fold higher than men's.[73] Women's HF incidence was found to be twice as high as men's but men reached that higher incidence when they were five years older. [9,70] Men have a higher mortality rate than women after a HF, being doubled within one-year after the fracture.[74] Osteoporosis is more prevalent in women than in men, partly due to women's lower body mass, smaller bone size, postmenopausal BMD decrease and longer average life span.

A history of HF in parents increased the HF risk, mostly regardless of BMD.[75] Around 14% of Swedish postmenopausal women have heredity for HF.[27]

Previous fragility fracture

Women who had suffered a fragility fracture had a doubled risk of a future fracture, compared to controls.[76, 77] This risk increase for recurrent FF was only dependent on BMD to a minor extent.[23] Women who contracted a vertebral fracture had a four-folded risk of recurrent vertebral fracture, compared to women without prior fracture; the risk was even higher for women with multiple vertebral fractures.[27, 77]

Among women contracting a HF, radiographic lowered vertebrae (-3 SD with quantitative morphometry) was 2.6-folded, compared to population-based urban cohorts,[78] in which lowered vertebrae was found in 39% at age 70-79 and in 63% at age 80-89.[79]

Risk factors - modifiable

Weight and other related body measures

The skeleton becomes thinner and more fragile with decreasing load. Low body weight, weight loss after age 25 and low Body Mass Index (BMI, defined as the body weight divided by the squared body height) are clearly related to an increased fracture risk.[22, 25, 80, 81] The HF risk increase was confined to women with low weight (<57 kg) or BMI.[25, 82] Low weight and BMI are related to low BMD,[82, 83] and the minimal adipose padding around the hips could partly explain the high HF risk among these slim women.

Body height >163 cm increased the risk of HF and FF, except vertebral fracture.[80]

Height reduction ≥3 cm since age 25 increased the spine fracture risk five-fold, compared with individuals with unaltered height.[80] There are two explanations for the increased fracture risk in tall individuals. Falling from the erect position means that the hips are higher above the floor than in shorter individuals and tall individuals are more likely to have an increased hip-axis length.[66] Substantial geographical differences in femoral neck geometry and BMD have been found, possibly contributing to the large variations in HF risk across Europe.[66]

Falling and impaired mobility

Most fractures, and over 90% of HF, are preceded by a falls.[8] One third of elderly community residents and 60% of nursing home residents fall each year.[8] Around 4% acquired a fracture annually after a fall in a population aged over 70.[84] Women with an increased fall rate fracture their hips more often.[85] Impaired ability to rise from a chair, low gait speed and other mobility impairments are related to increased HF risk.[22, 25, 86, 87]

The tendency to fall often increase together with acute airway or urinary tract infections. Cerebrovascular ischemia and Parkinson's are rather common diseases related to impaired mobility. Cerebrovascular incidents impair both mobility and mental abilities but these deficits often improve within six months after the incident. Stroke patients have been shown to have a higher fracture risk-around three times that of the general population-and 84% of the fractures were caused by a fall.[88] Most fractures were HF (59%) and occurred on the paretic side;[88] that side usually acquires a lower BMD after the stroke. Parkinson's disease causes mobility impairment due to rigidity, tremor and mobility onset disturbances. These patients have an increased fracture risk,[89] due to their tendency to fall and lower BMD.[90] Their rigidity, long reaction time and slowness in initiating movement contribute to their high falling tendency and probably worsen the fracture impact of a fall.

Lifestyle

Physical activity: Daily physical activity is natural in a historical perspective and improves general health as it reduces the risk of other common diseases, such as coronary heart disease, diabetes mellitus, depression and obesity. Regular loading on the skeleton adapts the bone according to the degree of load. It has been shown that exercise increased young people's bone mass[91-93] to a level that was maintained after five years though continued regular physical activity. In another study, exercise-induced BMD benefits were reduced after retirement from sports,[94] although the old athletes had fewer fractures than matched controls.[95] Postmenopausal women with low physical activity, low muscle function or previous falls suffered osteoporotic fractures more often, independent of their BMD.[68]
Exercise has been shown to increase muscle strength at very high ages (around 87).[10] Women regularly performing a moderate exercise program had better muscle strength and gait and sustained fewer fractures, compared to urban controls.[96] Active exercise

has been shown to be strongly related to less HF in both sexes.[70]
Sunlight exposure: Low sunlight exposure has been related to increased HF risk in European women[81] and geographical latitude, which affects sunlight exposure, seems to contribute to global HF risk variations.[97] The Swedish Drug Therapy Handbook**.**[98] recommends spending 15 minutes outdoors every day during the summer half-year in order to stimulate endogenous vitamin D production.
Nutrition: A healthy diet is important for general wellbeing and appropriate weight. In addition to sunlight-induced production, vitamin D is found in fatty fish and in some enriched fat and dairy products.[99] A low self-reported nutritional calcium intake, e.g. less than one glass of milk daily, was not related to increased HF risk, although a slightly increased FF risk was seen over age 80.[100]
Tobacco: Smoking was related to lower postmenopausal BMD and increased HF risk,[36, 101] especially at high age, and there was a dose-dependent effect on the HF risk.[102]
Female smokers are usually thinner and undergo menopause earlier which probably contributes to their fracture risk. Smoking cessation probably reduces the fracture risk but not to the level of never-smokers.[36, 102]
Alcohol: A high alcohol intake increases osteoporosis, falling accidents and fracture risk. A daily consumption of >2 units of alcohol, increased the HF risk 1.7 times, independently of BMD, when studied in both women and men.[71, 103]

Medication side effects

Pharmacological treatment is an indicator of concurrent diseases which may themselves increase falling tendency or fracture risk. Poly-pharmacological interactions or side effects have not been extensively studied, especially among the more susceptible elderly who are prone to fractures and who often use several medications. This emphasizes the need to consider non-pharmacological treatment alternatives.
Oral glucocorticoid treatment frequently causes negative side effects on the skeleton, with loss of BMD related to the cumulative dose and increased fracture risk related to the daily dose.[104] The fracture risk increases rapidly (within 3 to 6 months) and decreases after stopping therapy. Therefore, when more than 5 mg prednisolon is administrated daily, early preventive measures for corticosteroid-induced osteoporosis are recommended.[104] Thiazides have been shown to reduce fractures in both men and women; HF are reduced with long-term treatment exceeding five years.[105]
Medication side effects that increase the tendency to fall are usually mediated by impaired vision, mobility or consciousness. Overdosage of antihypertensive drugs, causing blood pressure drops, or stronger analgesics with sedating side effects may cause falls. Anxiolytics, sedatives, antidepressants and neuroleptics are related to falling and HF and selective serotonin re-uptake inhibitors (SSRI) are associated with a higher fracture risk than tricyclic antidepressant agents.[106]
Falling reduction has been seen after discontinuation of psychotropic drugs.[107] In these elderly it is important to re-evaluate medication, especially after changes in health.

Low BMD

Osteoporosis, defined as low bone mineral density (BMD), is one of several risk factors that increases the fracture risk. Osteoporosis is diagnosed based on DXA measurement at the hip and spine, or at the hip alone, expressed as a T-score ≤ -2.5 SD below the mean peak value of a young adult reference population.[28] Fracture is the only clinical manifestation of osteoporosis. Pharmacological treatment should thus be based on the absolute fracture risk rather than on the osteoporosis itself. Age is especially predictive for hip fracture but prior fracture also has high prediction when combined with low BMD.[27] The HF incidence rate for osteoporotic women aged ≥80 years was 20 per 1000 women-years, more than two-folded greater than the women in the same age without osteoporosis.[108] For the younger women aged 75–79 being osteoporotic the corresponding incidence rate was 12.5, with a four-folded risk compared to non-osteoporotic women. There are biochemical markers, that has been used for fracture prediction together with BMD,[109] but they have not been developed for clinical use.

BMD measuring and related techniques

Conventional X-ray

Conventional vertebral X-ray often reveals asymptomatic vertebral fractures, frequently combined with low BMD. The skeletal density in conventional X-ray images is not reliable for assessing the BMD level. Specific BMD-enhancing therapies prevent recurrent vertebral fractures in postmenopausal women with spinal fractures.[110]
In radiogrammetry the cortical thickness of metacarpal bones is measured with conventional X-ray and digital picture evaluation. Cortical thickness is related to BMD, although this technique requires further evaluation before being applied in the clinical setting.[111]

SPA

Single photon absorptiometry (SPA), based on a gamma-ray radionucleotide source and a scintillation detector, was the earlier method of BMD measurement.[19] The photons were absorbed differently by bone minerals, soft tissue and surrounding water. The technique could be used only where the soft tissue was constant, at peripheral locations such as the forearm or calcaneal bone.

DXA and DXL

DXA is the current reference method for BMD assessment and is well-established in clinical routine. BMD in the proximal femur and lumbar spine have been correlated to fracture risk and treatment effects, especially among post menopausal women. HF prediction with optimal DXA technique shows a 2.6-fold increased risk per SD decrease.[24, 31] DXA-technique is also used for measuring BMD in the distal forearm and

heel. The heel-measuring device is simpler and cheaper. Since the heel has high trabecular bone content, assessment here may also reveal early changes in bone metabolism.[111] DXA technique uses two energy beams from X-ray generators. This method has high precision and calculates areal BMD (g/cm^2).[112]
In the dual X-ray laser absorptiometry (DXL) technique[113] additional laser is combined with the two X-ray energies to determine the different absorptions of bone mineral, lean soft tissues and adipose tissues,[114] in order to measure bone mineral content without the influence of adipose tissue. BMD has only been evaluated retrospectively for prior fractures.[115]

QCT
Ouantitative computed tomography (QCT) is used in peripheral sites and in the spine. It can measure the volumetric skeletal density as well as the micro-architecture. This method leads to a higher radiation exposure and higher costs, compared to DXA.[112]

Ultrasound
Quantitative ultrasound or broadband ultrasound (QUS) is measured in the heel. A sound wave at different frequencies (broadband) is transmitted through the heel bone. The speed of sound (SOS) is the time required and the profile of sound passing through the heel is called the broadband ultrasound attenuation (BUA). The SOS and BUA are calculated, resulting in a variable called stiffness, as an indirect measure of BMD. Heel QUS seems to have good HF risk prediction studied prospectively[116] and has been compared to DXA technique.[117]

Risk factor models for hip fracture

There is a need for improved clinical fracture prediction and risk group identification, in order to detect individuals who may benefits from fracture prevention at different levels, such as lifestyle advice, mobility training, home hazard reduction and, basic or specific pharmacological treatment.
HF risk is multi-factorial. There are several studies that show better HF prediction by evaluating selected clinical risk factors (alone or in combination), compared to BMD assessment alone.[9, 22, 23] In case of women with clinical risk factors who also have low BMD fracture prediction is additionally improved.[22, 25] Pharmacological intervention trials in clinically defined high risk-groups usually result in higher treatments gains.[40, 42, 118]

Clinical risk models usually comprise age, prior fracture, any mobility-related factor and heredity, each predicting fracture independently of the BMD level.[22, 25, 86] Low weight and BMI predict both HF and low BMD.[25, 119] Therefore, by adding BMD assessment to fracture risk models, weight or BMI become less fracture-predictive.[82, 83]

There are several clinical risk factor models for HF prediction in elderly women, often combined with BMD. A summary of well-known risk models described below is also presented in Table VII (page 54) in the Discussion section, in addition to our own risk model described in the Results section.
In the 1995 Cummings study, the 16 clinical risk factors, mentioned in Figure 2 above, were analyzed with heel SPA and four-year HF incidence rate was found ranging from 1.1 among women with no more than two risk factors and normal BMD, to 27 per 1000 women-years in those with ≥5 items and BMD at the lowest third for their age. Several of the measured items were modifiable.
In the 1996 European Patent Information and Document Service (EPIDOS) fracture study 1996, a four-item score consisting of fall-related factors (slower gait speed, difficulty in heel-to-toe- walk, visual acuity and small calf circumference) predicts the two-year HF risk.[86] After BMD adjustment, the three first items remained significant. The highest HF risk was defined as both high fall-risk status and low BMD, corresponding to a HF incidence rate of 29 per 1000 women-years, compared to 11 for women with either high fall-risk status or low BMD. Only five HF per 1000 women-years occurred in women classified as at low risk, both concerning fall-risk and BMD.
The FRACTURE Index developed in 2001 in the Study of Osteoporotic Fractures (SOF) uses the BMD T-score and six clinical risk factors (age, prior fracture, maternal HF, weight <57 kg, smoking status and use of arms to rise from a chair) to predict hip, vertebral or non-vertebral fracture within five years.[25] The clinical index can be used with or without BMD.
In the 2002 Melton Osteoporotic fracture (MOF) study, six clinical risk factors (low weight, kyphosis, poor trunk manoeuvres, poor circulation in the foot, short-term use of steroids and epilepsy) predicted HF within three years in a total population of women; the study had a 70% participation rate. Calcaneal BUA did not independently predict HF.

Fall and fracture prevention

The impact of regular physical activity on falls and fracture risk has been shown or indicated in an increasing number of studies. However, opinions differ among researchers concerning its fracture-preventive effects and on how to implement the appropriate preventive activities in society. Fracture preventive benefits of pharmacological treatments have been more widely studied and evaluated among elderly women.
Below, some studies related to bone and muscle strength improvement and fall and fracture prevention will be mentioned. On the cellular level in skeleton, bone-strengthening adaptive mechanisms in response to physical stimulation are pointed out.[2] Bone mineralization improves after modestly increased prepubertal physical training[91,]

[93] with the additional benefit of muscular activation. Muscle strength has been doubled by training, and maintained by weekly exercise, even among individuals aged around 90 in residential care.[120]

Lifestyle factors

Maintaining a physically active lifestyle is essential not only for mobility and lowering the fracture risk,[96] but it also prevents and improves cardiovascular and diabetic disorders and improves mental health. Other main fracture-preventive lifestyle habits include a balanced diet and sufficient sunlight exposure for vitamin D formation, as well as avoiding tobacco and alcohol abuse.[36, 71, 100-103, 121]

In population studies, a lower HF risk was found in both sexes performing more than one hour of daily exercise, compared to less than ½ hour.[70] Furthermore, women performing moderate-intensity long-term physical activity, such as walking 4 hours per week, had a 41% lower HF risk, compared to walking less than one hour.[12] Fracture risk decreased linearly with increasing level of activity among those women who did not take postmenopausal HRT. Spending more time standing also lowered the risk.

Specific physical training

Among the elderly, less falls have been seen after more intense training periods. A Cochrane review of randomized controlled trials (RCT) investigating the of muscle and balance retraining, individually prescribed at home, on fall prevention showed a relative risk (RR) of 0.80 (95% confidence interval (CI) 0.66-0.98).[33]

In a RCT studying a home-based exercise program, falls and fall-related injuries were reduced during two years in women aged 80 and up.[11] The program was individually prescribed by a physiotherapist at the beginning of the study and included muscle strength and balance retraining at increasing levels, to be carried out during ½ hour at least 3 times weekly and walking 3 times a week. Subjects were telephoned regularly to help maintain their motivation.[122]

Equivalent fall reduction was observed in another study of the combination of three interventions; group exercise followed by home exercise, home hazard management and vision improvement.[123] Community residents aged 70-84 were randomized to participation in this study. Exercise alone led to fall reduction, although less efficiently than the combination of all three interventions. Physical training consisted of a one-hour weekly exercise class for 15 weeks, supplemented by daily home-based exercises designed individually by a physiotherapist.

A 40% one-year fall rate reduction was seen after a group and home exercise program among subjects (mean age 75) attending general practice clinics in an Australian RCT.[124] Participants were considered to be at increased risk of falling, and thus selected, by simple tests of lower limb weakness, poor balance and slow reaction time. Exercise was offered as weekly group training in a community setting during one year (median attendance 23 times) and home exercise sessions based on the group training content that were performed at least weekly by most subjects. The exercise groups were also informed about practical strategies for avoiding falls.

In another exercise RCT,[125] including individuals with mild deficits in strength or balance at age 68-85 years exercising subjects reported 18% fewer falls, compared to controls, during the first 12-month follow-up. The exercise consisted of supervised physical training for one hour, 3 times weekly during six months, followed by self-supervised training.

Reduction of falls related to home hazards and medications

Professionally prescribed home hazard reduction led to a reduction in falls in elderly people with a history of falling (odds ratio (OR) 0.66, 95%CI 0.54-0.81), according to a Cochrane review.[33, 60] Withdrawal of unnecessary psychotropic medication also reduced the tendency to fall (Hazard Ratio (HR) 0.34, 95%CI 0.16-0.74).[33, 107]

Multidisciplinary and multi-factorial interventions

A Cochrane review of combined interventions focusing on fall prevention, including multidisciplinary, multi-factorial, screening intervention programs in the community, reported a RR of 0.73 (95%CI 0.63-0.85) among an unselected elderly population, a RR of 0.86 (95%CI 0.76-0.98) among elderly individuals with fall-related risk factors and a RR of 0.60 (0.50–0.73) in residential care facilities.[33]

In a 1999 RCT of individuals aged over 65 seeking medical care after a fall,[126] the one-year fall reduction was 61% after an intervention consisting of detailed medical and occupational therapy assessments, including home hazard reduction and, if indicated, referral for further medical treatment.

Five coordinated studies of community-wide, multi-strategy initiatives were analyzed by Cochrane. In these studies fall-related injuries among the elderly were lowered by 6–33%.[34] Despite not being RCTs and not all showing significant reductions, the consistency of reported reductions in fall-related injuries in connection with all of these programs supports the idea that the population-based approach to the prevention of fall-related injury is effective.[34]

Hip protectors

HF can be prevented by hip protector use among elderly people in institutional care.[35] Both fall and HF reduction were seen after a multi-factorial prevention program in residential care, including provision of free hip protectors.[127] One problem is the poor compliance of wearing protectors and compliance has been studied, by giving nursing staff a single education in hip protector use.[128] They then educated the residents in who also got provision of free protectors. Wearing protectors at falling improved, from 15% among controls compared to 68% in intervention group.

A Cochrane review[129] on pooled data, from randomized cluster studies, described HF reduction (RR=0.77) in residential care. No significant difference (RR=0.86) was found in an analysis based exclusively on individually randomized pooled studies, concluding uncertain effectiveness of hip protector use in institutional settings and that there was a need for further studies with sufficient power and ways of improving hip protector acceptance and adherence. For community residents hip protector use was ineffective.

Calcium and/or vitamin D

A fall reduction of 22% related to the use of vitamin D was seen among elderly individuals in a meta-analysis.[130] The effects were most pronounced for women using active vitamin D. 800 IU of vitamin D_3 seemed to have the same effect in both genders. Fall reduction has also been verified among individuals in residential care, getting vitamin D.[131]

The fracture-preventive effects of calcium and around 800 IU of Vitamin D have been shown in previous studies, for both HF[37] and non vertebral fractures.[38] Recent meta-analyses indicate that the fracture-preventive effect of calcium and vitamin D is limited to women age over 80, or at least to those in residential care.[39] Recent studies that questioned the effect of calcium and vitamin D treatment on secondary fracture prevention[132,133] have excluded risk groups, had many dropouts or had insufficient power (non-significant HF prevention: OR 0.73 in Pourthouse study).

The fracture–preventive effect of Vitamin D alone has also been questioned. Primary preventive vitamin D_3 treatment (100 000 IU orally every 4 months), during a five-years period among community residents aged over 65 led to fracture reduction.[134]

The side effects of calcium and vitamin D_3 are usually mild, although there is a slightly raised risk of kidney stones.[135] The risk of hypercalcaemia seemed to be low with moderate doses of vitamin D_3 (as cholecalciferol) and was previously overestimated.[39, 136]

Bisphosfonates

The vertebral fracture incidence was reduced (usually halved) by bisphosfonate treatment of postmenopausal women with prior spine fracture and/or osteoporosis (BMD ≤ -2.5 SD according to the WHO definition).[137] The number needed to treat (NNT) for a repeat vertebral fracture was very low in women with multiple vertebral fractures.[40] Most bisphosfonate studies have included calcium and vitamin D treatment. Preventive calcium and vitamin D treatment has been recommended for women on cortisone treatment, adding bisphosfonates for more than three months when prednisolone intake is over 5 mg and BMD levels below -1– -2 SD.[67] In studies with bisphosfonate treatment to postmenopausal women with prior spine fracture or osteoporosis, vertebral fracture reduction was shown, with an early and marked fracture reduction, as early as during the first treatment year.[110, 138] After seven years of ongoing bisfosphonate treatment there was no indication of any loss in fracture-preventive efficacy, although the study was conducted without controls.[139] Women who added bisphosfonate treatment during the last 2 years achieved similar vertebral fracture

reduction as those on seven-year treatment.
HF reduction (around 50%) or prevention of clinical fractures was also shown among these postmenopausal women with osteoporosis and/or prior vertebral fracture.[110, 140]
The individual fracture-preventive gains increased with age up to around 80 among osteoporotic women, or among women with multiple vertebral fractures compared to single.[40, 42]
During a five-year period after discontinuation of a five-year bisphosfonate treatment, the incidence of non-vertebral fractures was comparable to those on continuous treatment (RR=1.0),[141] but for incident clinical vertebral fractures they were less frequent (RR=0.45) with ongoing 10-year treatment.
The risk of oesophagitis, a serious side-effect, can be reduced by a thorough anamnesis, patient information and medication intake instructions.

Other specific bone-strengthening drugs and vertebral fracture surgery
SERMs have only been shown to prevent vertebral fracture and are a second-choice treatment. The risk of venous thrombosis is equal to that of HRT and a thorough history is thus important.
PTH given as an intermittent daily injection, leads to increased osteoblastic anabolic activity with marked bone formation and fracture reduction,[48] especially of vertebral fractures. It is a second choice treatment, being expensive, for cases of severe osteoporosis or recurrent fracture despite bisphosfonate treatment; treatment should be revaluated after 18 month. Side effects are mild.
Strontium has led to fracture reduction in postmenopausal women with osteoporosis or prevalent vertebral fractures.[49] Potential vascular and neurological side-effects require further elucidation.
Kyphoplasty or vertebroplasty are surgical procedures that have been undergone by women with advanced vertebral fractures leading to severe body deformity or neurological deficits, for pain relief, bone stabilisation and improvement of body posture. There are related severe complications and new methods are being developed.[46]

Aims

General aims

- To identify a risk group for hip fracture by evaluating clinical factors collected from questionnaire screening.
- To improve hip fracture prediction in a high-risk group by combining clinical factors and heel BMD, assessed by portable DXL technique.
- To evaluate the implementation of a feasible multi-factorial intervention program for impaired mobility and hip fracture risk, in a high-risk group in PHC.

Specific aims

Study I: Identify elderly women at high risk of future hip fracture, using several clinical risk factors collected from questionnaire.
Evaluate ability to recall the major risk factors after three years.
Describe needs for possible fracture prevention.

Study II: Develop and validate a practical tool for hip fracture risk assessment and evaluate the prediction of fragility fracture and total mortality, in PHC settings.

Study III: Evaluate, in a high-risk group for hip fracture among elderly women, effects of multi-factorial intervention on mobility during 2.5 years and on fracture incidence during a 2-year follow up.

Study IV: Evaluate the 2-year hip and fragility fracture risk, in an elderly female population participating in a fracture prevention program, predicted by clinical 4-item risk scores and/or by bilateral heel BMD assessed by DXL.
Describe heel osteoporosis prevalence, assessed by DXL among elderly women in PHC. Compare DXL-asessed BMD in heel to reference values in hip.

Materials and Methods

Study populations

Studies I-IV
In May 1998, in the pilot Study I, a 46-item questionnaire about HF risk including brief advice, was sent to 100 randomly chosen women aged 70 and up in the Vislanda PHC district recruited from the National Swedish Population Register. That questionnaire

was returned by 92% (92/100) women and 84% of the respondents (77/92) also answered the following questionnaire in Nov 2001.

The main studies started in Nov 2001. In Study II, we send a 22-item fracture risk questionnaire and brief advice to 1498 women aged ≥70 living in three rural PHC districts in southern Sweden. We selected the entire female population in the Vislanda district (501 women) as the intervention group and a similar number of age-matched women from each of two other municipalities, Tingsryd and Emmaboda, as controls. Altogether 83% (1248/1498) women, who were still alive in 2002, participated by responding that questionnaire, see Figure 3.
Of these 1248 women, 473 in the intervention group (n=161) and controls (n=312) were classified at high-risk of HF, according to Risk Model II (described below).
In Study III, 296 (n=103 intervention, n=193 control) out of 365 women (81%) participated. They had all been classified as at high risk of HF, based on their responses to the 2001 questionnaire and they returned an additional questionnaire in May 2004, see Figure 3.
Study IV, in 2003 (illustrated in Figure 4), involved 285 (73% of 390) participants in the intervention group who returned a questionnaire and underwent heel BMD assessment. They were evaluated for HF and FF risk during 2004─2005. Fourteen per cent (41/285) of these women also underwent BMD assessment of the hip and spine. Twenty-six per cent (74/285) of the participants in Study IV were also evaluated in Study III, which was undertaken at the same time.

Study design

Study I

The 1998 pilot questionnaire returned by 92 women contained 46 questions pertaining to risk and protective factors for falls and fracture.
The covering letter was combined with brief advice on fracture prevention and signed by district physicians and nurses. The questions were simply worded with multiple choice alternatives, with the exceptions of the medication question. Relatives or home nursing staffs were allowed to assist the participants in answering. Non-responders were reminded twice.
Questions were chosen partly from the Cummings study,[22] in which risk factors such as age, maternal history of HF, weight loss (or low current weight), height, history of fracture after age 50, falls during the last year, rising from the sitting position (as a test) and perception of health were validated prospectively with regression analysis against HF in a white US population. Additional topics, such as height at age 25, walking capacity, menopause, smoking, cortisone medication and diseases related to falling or

osteoporosis, were collected from the Scandinavian Scandos study,[76, 80] and current medication, time spent outdoors, home situation and contacts with the health care system were also reported. Dietary calcium intake was estimated from usual milk, yoghurt and cheese consumption.
After returning the questionnaire all participants received a leaflet with fall- and fracture-preventive advice. Some participants with special needs were offered a house call from a district nurse as well as some written advice.
The shorter questionnaire in 2001 was used as a follow-up for the 77 women who had filled out both forms.
A simplified risk estimation for HF was based on Cummings study,[22] in which advanced age, weight loss since age 25, falling during the preceding year and prior fracture after age 50 were all significant risk factors. These four risk factors were dichotomized, weight loss was replaced with low current weight and prior fracture was replaced by prior fragility fracture of the radius, humerus, hip or vertebrae.

Study II

Questionnaire data and follow-up

The baseline questionnaire sent to all 1498 women in Nov 2001, included a shorter, simply worded 22-item questionnaire focused on risk factors for fracture. The intervention group in Vislanda received 15 additional questions. The questionnaire was returned by 1248 women aged 70 and up.
We attempted to involve a total population representative of the PHC district, aiming at high study participation, and used the same layout and instructions as in the questionnaire in 1998 (see Study I). The 22-item form was restricted to questions concerning age, weight, height, physical activity, falling during the last year, ability to rise five times from a chair without using the arms (recommended self-test), previous fracture and maternal HF heredity, diet, smoking, medication, children, perception of health, vision and living conditions. The additional questions to the Vislanda women dealt with previous vertebral fractures diagnosed by X-ray, other diseases, specific medications and about their interest in follow-up
The five questions used in our two risk models concerning age, weight, previous fragility fracture, impaired ability to rise, and falling during the last year resembled questions used for fracture risk evaluation in previous studies.[22, 25, 76]
In cases with reported fracture of uncertain location, we used the PHC system's radiology data bank to specify the location.

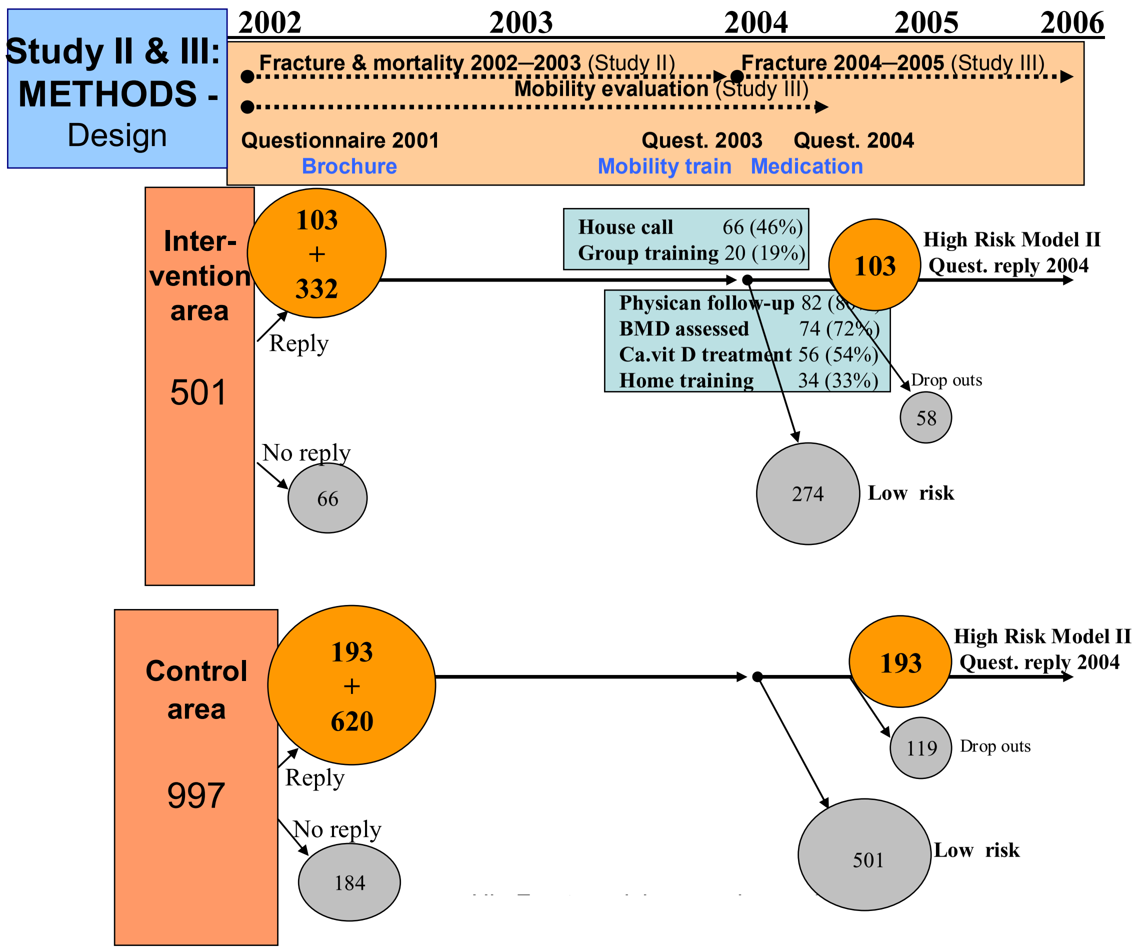

Figure 3: Design in Study II: Clinical Risk Models evaluated on hip, fragility fracture and mortality during 2002–2003 for1248 women. Design in study III: Mobility evaluation (for falls and ability to rise from sitting position) between Nov 2001 to May 2004 and hip and fragility fracture registration 2004–2005 for 103 women in intervention area high risk classified (in Risk model II) compared to 193 women in control area. Percentage on intervention estimated on all 103 participants.

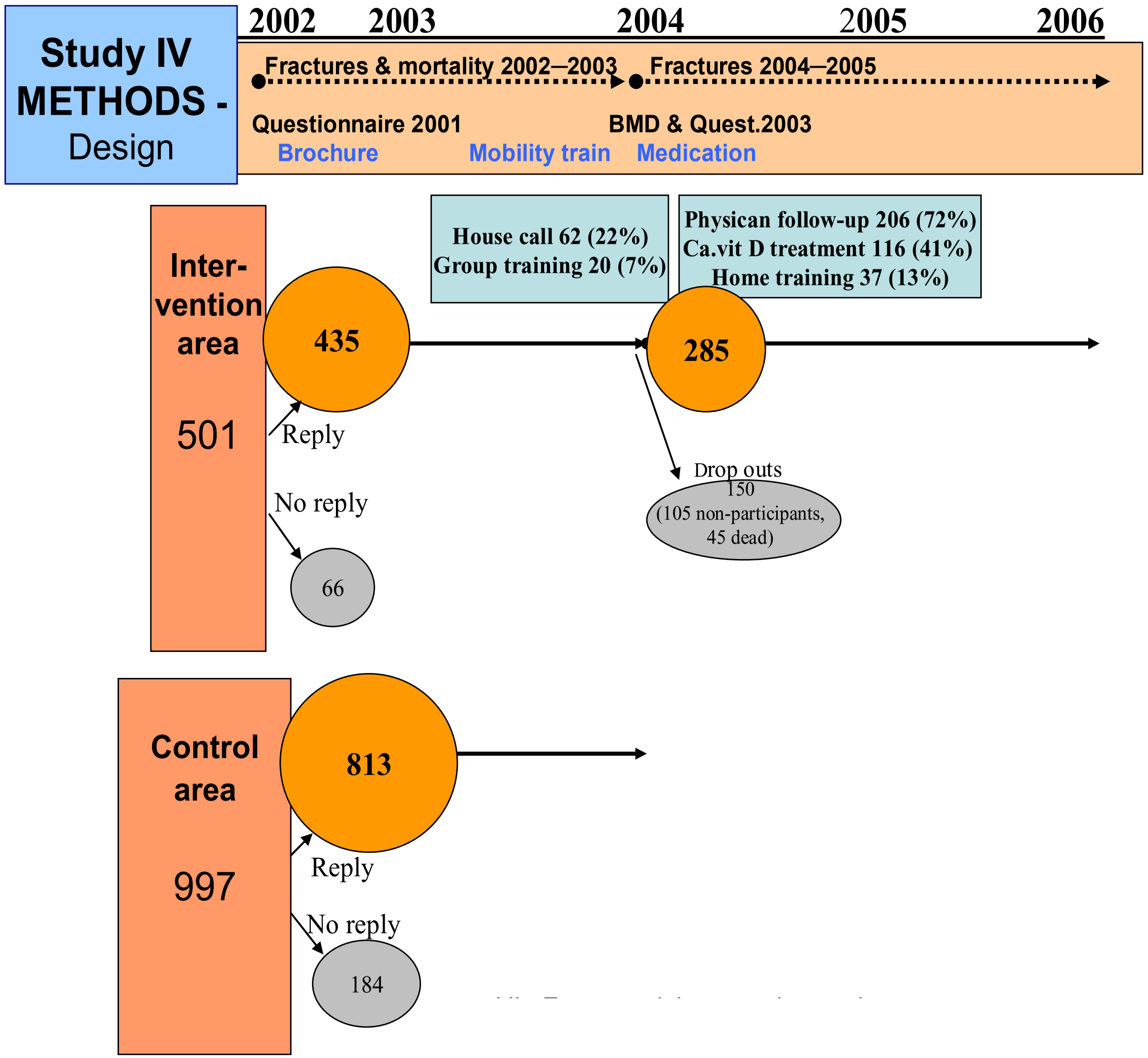

Figure 4: Design in Study IV: Hip and fragility fracture registration (2004–2005) for 285 women in intervention area, evaluating clinical risk factor models and heel BMD measured during late 2003. Percentage of intervention types calculated on all 285 participants.

Risk models development and ascertainment of fracture and mortality 2002–2003

We intended to develop a practical and reliable population-based risk factor model for HF risk screening in PHC. By developing a simple risk model it could be possible to assess even without any form. The items included in such a risk model should be known as both major and prevalent risk factors for HF in women and should be easy for aged women (or their relatives/caregivers) to report. The risk model items should cover three different aspects; i.e. aging, skeletal weakness and mobility impairment. All items should be converted to binary values, with Yes/No alternatives, with a predefined cutoff for the number of risk factors identifying the group at risk.

At first we developed a HF risk model with seven independent weighted items (age, weight, prior fragility fracture, falling during the last year, height, cortisone medication and smoking) calculated by logistic regression model from retrospective data from the Scandos study (personal communication, D. Mellstrom, 1999) of 14643 women aged 74-82 years. According to the framework described above, we chose the four most predictive of these seven items - age ≥80, weight <60 kg, prior fragility fracture and falling during the last year - and convert them into binary variables,[142] thus creating Risk Model II.

The Risk Model I – FRAMO Index (see Table 1) was similar to Risk Model II but instead of the item “fall during last year”, we used the mobility item “requires arms to rise five times from sitting position”,[22, 25] as a self-assessed test. “Fall during the last year” seemed susceptible to random variation and to memory impairment, verified in Study I by low three-year reliability at 45%.

The two risk assessment models were defined before outcome data collection. In both models, we compared women with at least 2 of 4 risk factors with women with 0 or 1 risk factor. Each model was tested as a predictor of future HF, FF and total mortality during a 2-year period, both in the whole population and in subpopulations.

We defined new FF as fractures occurring in the hip, wrist, proximal humerus, pubic bone, ischial bone or vertebrae during 2002-2003.

Vertebral fractures were classified as new if the X-ray report confirmed vertebral compression in women who had localized pain. We identified all incident fractures using diagnosis registers from the departments of orthopedics and geriatrics and from radiology reports. We used the corresponding ICD-10 (International Classification of Diseases, 10th Revision) diagnostic codes for the Vislanda and Tingsryd populations. Outpatient care registers were incomplete for the Emmaboda population; therefore, we only documented HF in this population.

We ascertained mortality from the National Swedish Population Register.

Table I: Questions Used to Assess the 4 Risk Factors in Risk Model I (FRAMO Index)

	Question Points
1. **What is your present age?**	
□ ≥80 y	1
□ 70-79 y	0
2**. What is your current weight?**	
□ <60 kg	1
□ ≥60 kg	0
3. **Can you rise 5 times from a chair without using your arms? (Try if you want.)**	
□ No, I must use my arms to rise	1
□ Yes	0
4. **Have you broken any bones after the age of 40 y? If so, which bone? Have your vertebrae been x-rayed?***	
□ Fracture of wrist/lower arm, upper arm, hip, or vertebrae, or vertebral compression seen on radiograph	1
□ No fracture, or fracture in some other location	0

* Specific question about vertebral radiographs posed only to women in the Vislanda population.

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Study III

Questionnaires 2001 and 2004

In Study III, all 296 participants had answered the 22-item baseline questionnaire in 2001 (see Study II, above). All participants, both in the intervention and control groups, were classified as being at high risk of HF, according to Risk Model II. The 103 women in the intervention group were asked some additional questions (see Study II, above), including if they were interested in specific follow-up. In May 2004, all 296 women also answered a 20-item follow-up questionnaire containing similar questions concerning their mobility and fracture risk.

In Study III, the major mobility outcomes were change in falls during last year and impaired ability to rise from sitting position, between 2001 and 2004. Initially, all 296 participants (103 in the intervention group and 193 controls) were analyzed in 2001 and 2004. In further analysis comparing mobility changes between the study groups and different study periods, we analyzed only the 91% (268/296) who answered all questions regarding any falls during the last year and the ability to rise, both in 2001 and 2004. Of these 268 participants, 90 belonged to intervention group and 178 were controls.

Mobility methods, training and fracture prevention in the intervention area

Intervention methods were developed during the pre-study period in 1999-2001. We wrote a brochure with fall- and fracture-preventive advice including instructions for home exercise and home hazard reduction. Eight women tested group exercise led by a physiotherapist, combined with home exercise, leading to a reduction in falls during the following year.[142] A nurse made house calls to seven women, identified by the 1998 questionnaire as being at high HF risk. These house calls were conducted according to a manual.

The intervention in Study III was initiated in 2002 by sending a brochure with fall and fracture preventive advice to all 103 participants in the intervention area. The major intervention began during 2003─2004, as described in Figure 3, and was restricted to women at high HF risk.

A non-randomised intervention design was used in order to achieve high intervention compliance and perform a study that resembled and would be applicable to normal PHC conditions. House calls were received by 64 % (66/103) in 2003─2004; they were usually repeated twice during one year. Advices was given concerning lifestyle (daily walks, spending time outdoors, calcium intake and smoking cessation), fall prevention for a safer home environment (using shoes indoors, avoiding carpets and loose electric cords, using rubber mats and handles in the bathroom, improvement of illumination, avoiding climbing on chairs or ladders and using anti-slip guards outdoors). Reported falls were evaluated individually to prevent recurrent falls. Home and group exercise in the community or lead by a physiotherapist was recommended. Hip protectors were demonstrated and distributed at low cost to women who had fallen during the last year and had had prior hip fracture or spinal fracture.

The home exercise program was practiced, under the nurse's guidance, at each house call. Stepwise increased intensity was recommended and a written training manual, meant to be fastened to the refrigerator, was distributed (see Table II).

Table II: Home training of balance and muscle strength

Loading is gradually increased and one exercise session will take about 10 minutes. Home exercise is recommended at least five times a week during two months, followed by at least twice a week.

Stand in a corner facing outward, with the back up of a chair in front of you

a) Stand with both feet together and if possible try to close your eyes for a minute.
b) As above, but stand on a foam rubber cushion
c) Try to stand on one leg with open eyes for half a minute. Then switch to the other leg.

Hold onto the back of the chair

a) Stand on your toes five times. After one week you may increaseby five times to 10-15-20 times, according to your capacity.
b) Do deep knee bends 5-10-15-20 times. After one week you may increase by five times to 10-15-20 times, according to capacity.
c) Try to do the exercises without holding onto the chair.

During 2003, after the first house call, 19 % (20/103) of the Vislanda women participated in physiotherapist-led group exercise, including training of functional balance, leg muscle strength and relaxation. These women performed group exercise at altogether 3‒15 occasions, once a week within two months periods, free of charge. Daily walks and further physical home exercise were recommended and advice was given, based on the falling history and need for a safer home environment.
Mobility, balance and leg muscle strength were tested by a nurse and a physiotherapist on three occasions during one year. The ability to rise five times from the sitting position without the use of one's arms was observed during the third house call and compared to the self-reported ability to rise in the questionnaire response four months later.
In late 2003, 72 % (74/103) of the women in the intervention group answered a questionnaire on fracture risk and heel BMD was measured (described in detail in Study IV).[115] If the lowest BMD T-score in either heel was ≤ -3.5 SD subjects were offered DXA assessment.[24, 114] All women subsequently received the results regarding fracture risk and advice, at least by mail. Contact with a physician, by phone or in person, was offered to the 80 % (82/103) to whom the nurse had previously made house calls and/or who had BMD measurements indicating increased fracture risk (see Study IV).

Fracture and mortality registration 2002–2003

Incident HF and FF in the intervention group were compared with the control group (a total of 296 women) in 2004‒2005. We identified all incident fractures via diagnostic registers from departments of orthopedics and geriatrics and from radiology reports, using the diagnostic codes from ICD-10 codes for new FF occurring in the hip, wrist, proximal humerus, pubic bone, ischial bone and vertebrae. Mortality data was collected from the National Swedish Population Register.

Study IV

Questionnaire 2003

All 285 participants from intervention area had previously answered the baseline questionnaire in 2001 (see Study II). After assessment of heel BMD in late 2003, a 15-item questionnaire about fracture risk was answered by the 285 surviving women who were then included in Study IV. In 2003 we used the same questions as in the 2001 questionnaire (see Study II) with the exception of medication, diet, subjective health and vision. Risk Model I (the FRAMO Index) and Risk Model II were then applied to the current clinical risk factors in 2003. The 2-year HF and FF risk of these 285 women, involved in the fracture preventive program, were evaluated in 2004‒2005 (the risk model constructions are described in Study II and the interventions in Study III).

BMD assessments

Heel BMD was assessed in 285 of the 390 women invited to do so by mail in late 2003. Bilateral calcaneal BMD was measured with a portable DXL Calscan device,[113] at homes for the elderly and the PHC centre in the intervention area. The two assistant nurses who measured the heel BMD and the physician in charge obtained measuring technique instructions and training from the manufactures (Demetech) and the device was tested before conducting the assessments. The DXL technique uses X-ray energies in combination with laser to determine calcaneal BMD (see "DXA and DXL" in Introduction). We used the DXL Calscan Workstation version 1.2 software programme calculating T-scores for heel BMD from Women-Europe-1001 reference population data.[115]

After BMD assessment, all 285 participants were given information concerning their fracture risk as well as fracture-preventive advice (see "Interventions"). Thirty consecutively chosen women and subjects with the lowest T-score in either heel ≤ -3.5 SD were recommended additional hip and spine DXA assessment. These assessments were performed at the Department of Internal Medicine at Ljungby Hospital, measuring total hip and femoral neck BMD on both sides and lumbar spine BMD at L2–L4, using a Lunar DPX-Alpha #8225 device. T-scores were then calculated, based on reference populations.

Since low BMD increases the fracture risk and DXL assessments are technically easy to perform without any known physical side effects, we analysed our heel BMD data based on the lowest T-score on either side (T-score$_{Low}$). The mean T-score was hereby lowered by 0.2 SD, compared to assessment exclusively on the left side. We found a substantially lower BMD in the right heel in 13% (36/280) of all women, with a T-score difference of ≥0.5 SD between sides.

BMD in different anatomical locations

A total of 41 subjects underwent additional DXA assessment of both hip and/or lumbar spine, 11 women due to heel T-score$_{Low}$ ≤ -3.5 SD and 30 women who were chosen consecutively. Their mean heel T-score$_{Low}$ was -3.1 SD, compared to -2.3 SD in the hip (femoral neck) ($p < 0.001$). The correlation for T-score$_{Low}$ in paired samples was 0.73 between the heel and hip, but lower (0.56) between the heel and lumbar spine.

For several reasons we chose hip BMD (femoral neck) as the reference measure site with which to compare heel BMD. HF is the most common serious fracture type.[13, 14] BMD assessment in the hip is the most predictive site for HF risk assessment, yielding a good prediction for other fracture types as well.[24, 31] Also, the heel BMD correlated better to the hip BMD than at spine (see above) and lumbar spodylosis frequently interferes with lumbar BMD assessment, especially among the elderly.

In our study, mean heel T-score$_{Low}$ were lower (0.7 SD) than T-scores at hip. This difference resembled that found in another study.[143]

Interventions

The interventions are also described in Study III (see Figure 3). In Study IV, during 2002 (see Figure 4), all 285 participants received a brochure with fall- and fracture-preventive advice. Twenty-two percent (62/285) of women classified as high-risk according to Risk Model II accepted house calls from a nurse, initiated around February 2003 and repeated after one year. Advice was given about lifestyle, fall prevention for a safer home environment and hip protectors. Instructions were provided concerning a home exercise program and 13% (37/285) women reported ongoing home exercise every week in 2004. During 2003 group exercise was carried out, led by a physiotherapist, by 7% (20/285) of these women.
After the BMD assessment and questionnaire reply in 2003, all 285 participants received information and fracture-preventive advice by mail. Around December 2003, 206 women were contacted by a physician who considered pharmacological treatment in cases of high age, prior fragility fracture and low BMD. For women with previous fragility fracture, calcium and vitamin D were considered if the heel $\text{T-score}_{\text{Low}}$ was ≤ -2.0 SD and bisfosphonates treatment was considered if the T-score was ≤ -3.0 – -3.5 SD. For women without previous fragility fracture, the treatment thresholds were one SD lower. High HF risk according to Risk Model II consolidated the treatment indication. When this major intervention was completed in May 2004, 41% (116/285) reported calcium and Vitamin D treatment and 13% (36/285) were taking bisphosfonates.

Fracture and mortality registration during 2004–2005

We identified all incident fractures among these 285 women in the intervention area via diagnostic registers from departments of orthopedics geriatrics and from radiology reports, using the ICD-10 codes for new FF occurring in the hip, wrist, proximal humerus, pubic bone, ischial bone, and vertebrae. Mortality data was collected from the National Swedish Population Register.

Drop-outs

Ninety-two percent (92/100) of the Vislanda women participated in the pilot questionnaire Study I at 1998. The 8% non-participants were 2.8 years older, a non-significant difference (p=0.26).

In the population–based Study II, 83% (1248/1498), mean age 79, returned the questionnaire. One woman who returned the form died before 2002 and was therefore excluded from the analysis. All 1248 women were analysed by the predefined risk models for main outcomes; if there were missing values they were recoded to the low-risk value. The 17% non-respondents (250/1498) were a significant 3.4 years older than the respondents.

In Study III, 296 of 365 surviving women in May 2004 (81%) returned the follow-up questionnaire; mean age was 82. Twenty-two percent (108/473) of all women classified as at high risk of HF after the 2001 questionnaire died before inclusion in the May 2004 study. The 19% (69/365) women who were alive in May 2004, and who did not respond to that questionnaire, were a significant 1.6 years older, less able to rise from sitting, more often lived alone and were taking medication more often in 2001, compared to the participants.

In the population–based Study IV, 285 of 390 (73%) surviving women, mean age 79, returned the questionnaire in 2003 and underwent BMD assessment. Fracture risk was re-evaluated during 2004–2005 in the intervention population only. Bilateral heel BMD assessment was performed on all 285 women except three, who were measured unilaterally. Ten percent of the women (45/435) in the intervention area died before the evaluation period in 2004–2005, including two women who had undergone BMD assessment. The 27% living non-participants (105/390) who did not participate in Study IV were four years older, less able to rise from sitting and more often lived in homes for the elderly in 2001, compared to the participants.

Statistical analysis

This study presents both relative and absolute risks for HF, absolute risks also reflect the magnitude of event incidence in specific risk groups. This risk is considered to be multi-factorial.[22] Using several independent predictors for risk estimation may realistically be assumed to yield more reliable, in the sense of less variable, estimates with higher sensitivity and/or specificity, compared to single factor risk evaluation.

Study I
RR with 95% CI were used to measure the association between binary outcomes and single potential risk factors. Significance levels were calculated by Fisher's exact test, and a two-sided $P < 0.05$ was considered to be a significant association. The SPSS (Statistical Package for the Social Sciences;
SPSS Inc, Chicago, Ill) version 10.0 for Windows and Epi Info 6.0 (Centers for Disease Control and Prevention, Atlanta, Ga) software were used.

Studies II-IV

When analyzing the un-adjusted association between two binary variables we used Fisher's exact tests whenever possible; otherwise the χ^2 test was used. Two-sided P <0.05 was considered to be significant.

Logistic regression models were used with binary outcomes versus continuous or binary risk factors and reported as ORs with 95% CI, both crude and adjusted. The Hosmer and Lemeshow test, as reported for the logistic regression model, was used to validate the appropriateness of the model for data with low cell frequencies in the predictors or few outcome events.

When risk factors were used in the predefined FRAMO Index and Risk Model II, cases with missing values were allocated to the low fracture risk group. This will avoid overestimating the fracture risk, while permitting us to retain all participants when evaluating the effect of remaining risk factors.

In Study II, Cox regression models were used to evaluate the effect on HF risk of single or multivariate factors when the time interval until the first fracture was taken into consideration. Those results are reported as Hazard Ratios (HR) with 95%CI. Cumulative survival curves (Kaplan-Meier curves) were compared by the Breslow test. The areas under the receiver operating characteristic (ROC) curves were calculated for the risk models as binary or as predicted probabilities, as one measure of risk model discrimination.

The t-test was used for symmetrically distributed continuous data and the Mann-Whitney U-test was used for asymmetrically distributed continuous data and for ordinal categorical data. Individual changes in mobility (unadjusted) between 2001 and 2004 were analysed with Wilcoxon signed ranks test.

In Study III difference between studied areas with respect to effects of interventions were analysed with multiple logistic regression for the whole study population and also stratified into mobility subgroups. These results were adjusted for age and mobility at baseline and for all additional variables with at least 2% prevalence difference between study areas in 2001. Associations between changes in mobility and single or multiple types of intervention were analysed by the logistic regression model. Differences in the incidence of fractures between the study areas were analysed with Fisher's Exact test. The software used were SPSS 13.0 and Epi Info 6.0.

Ethical considerations

HF preceded by falls are common accidents among elderly women. They are related to high morbidity, mortality, and high costs for society. By preventing HF, individual suffering and public expenditure can be reduced. Several fracture prevention methods are known but insufficiently developed for use in ordinary PHC.

In our studies, we developed both simple screening tools to identify a high-risk group for HF and feasible tools for fall and fracture prevention in ordinary PHC. We focused on high-risk groups for HF who could be expected to benefit more from intervention. In addition to evaluation and reduction of the individual HF risk, we also encouraged possible improvement of individual mobility resources and preferences. We emphasized feasible interventions, known to improve general health and/or without serious side-effects, such as daily walking, mobility training, home hazard reduction and calcium- vitamin D_3 treatment. For drugs with potentially serious side-effects, such as bisphosfonates, the treatment indications were stricter than generally recommended.[98] The X-ray radiation in connection with BMD assessments was minimal (less than the background radiation normally acquired during a week) and without any known side effects.

All individuals participated voluntarily, by returning questionnaires. It was made clear that participation was voluntary, confidential and could be terminated at any time. The participant answered a specific question concerning whether she wanted any subsequent individual contact with a nurse/physician for possible follow-up interventions such as exercise or medication. At the house calls the nurse's report was signed by the participant.

The Regional Ethics Committee at the University of Lund approved the study (LU 406-00, LI 00-218). The DXL and DXA screening was approved by the local radiation protection committee at Växjö Hospital in 2003.

Results

Study I

The response rate was 92% for the pilot 46-item questionnaire concerning HF risk, distributed to 100 women aged 70–95 in 1998. Ninety percent of these women answered the main 40 questions. Thirty percent belonged to the high-risk group in Risk Model II, reporting 2–4 major risk factors for HF (age ≥80, body weight <60 kg, falling during the last year and previous fragility fracture). Ninety-three percent of these women re-reported 2–4 of these items in the follow-up study three years later. One fourth reported a previous fragility fracture, confirmed in 94% (17 of 18 women) three years later. Only 22% of the women with previous fragility fracture had any pharmacological treatment for osteoporosis, primarily calcium substitution, in 1998. Possibilities for fracture prevention were seen in 34%; i.e. fall prevention and training for women at high HF risk (in Risk Model II), pharmacological treatment after prior fragility fracture or in cases of current cortisone medication, hip protector use in cases of falling tendency and prior serious/repeated fragility fracture or further investigation for signs indicating undiagnosed vertebral fractures.
Conclusion: The self-assessed questionnaire was a useful tool to identify risk groups for fracture in PHC, and participation was high. One third of the subjects were candidates for specific fall- and fracture-preventive efforts. We found good recall ability for prior fragility fracture or for having been at high risk of HF (according to Risk Model II) in the follow-up study three years later. A shorter questionnaire might be more useful for screening or for use in routine medical consultation.

Study II

In this rural-population-based study, 1248 women (83%) aged 70-100 participated by returning a simply worded questionnaire about HF risk. One third reported prior fragility fracture and one third had fallen during the last 12 months (see Table III). Ten percent lived in residential care. The majority (63%) had 0–1 risk factor (age ≥80, weight <60kg, previous fragility fracture and requiring arms to rise from the sitting position), classified as low-risk according to the FRAMO Index, and had a 2-year HF risk of 0.8% and a mortality risk of 3.2%.
In contrast, women with 2–4 risk factors had a 2-year HF risk of 5.4% (OR 7.5; 95%CI 3.0–18.4) and a mortality risk of 23.7% (OR 9.5; 95%CI, 6.0–14.9), see Figure 5 and 6. These differences remained significant after adjustment for age as a continuous variable. The 2-year FF risk was also elevated with OR 6.7 (95%CI 3.2–14.3), compared to the low-risk group. 81% of all HF occurred in the high-risk group (sensitivity) and the specificity was 64%. Each of the four FRAMO Index risk factors

Table III: Distribution and response frequency for 19 possible risk factors in questionnaire answered by 1248 women aged over 70 in 2001.

Characteristic	All 1248 subjects		
	Response rate	Risk group	
	%	N *or* mean value*	% †
Continuous risk factors			
Age (years)	100	78.8 ± 6.5	
Weight (kg)	97.2	67.3 ± 11.8	
Height (cm)	97.1	161 ± 6.1	
Dairy calcium intake (mg/day)	96.7	628 ± 292	
Five predefined risk factors			
Age (years)			
70–74	100	377	30.2
75–79	100	382	30.6
80–84	100	236	18.9
85–89	100	156	12.5
90–100	100	97	7.8
Weight under 60 kg	97.2	302	24.9
Prior fragility fracture after age 40 §,‖	96.6	398	33.0
Uses arms when rising five times from chair	96.9	362	29.9
Falls during last 12 months	95.4	397	33.3
Other possible risk factors			
Any type of fracture after age of 40 ‖	97.0	486	40.2
Cortisone medication more than three months	92.7	149	12.9
Has not given birth	99.1	164	13.2
Living in residential care (vs community)	98.5	123	10.0
Height over 167 cm	97.1	183	15.1
Dairy calcium intake under 500 mg/day.	96.7	377	31.2
Impaired vision, self-reported (vs good vision)	98.2	356	29.0
History of maternal hip fracture	88.7	123	11.1
Subjective health poor (vs excellent or fair)	98.0	120	9.8
Current smoking	98.6	53	4.3
Daily coffee intake 2 cups or more (vs 0-1 cup)	98.7	1040	84.3
Menopausal age less than 45 years	85.8	128	11.9
No daily medication ¶	98.4	152	12.4
Any parent of non-Nordic origin (vs Nordic) ¶	98.2	23	1.9

* Mean value as arithmetic mean ± SD.
† Estimated percentage for valid participants.
§ Prior fragility fracture located in hip, lower arm, upper arm or vertebrae after age 40.
|| Only the Vislanda subpopulation was asked the additional question about vertebral x-ray.
¶ This subgroup had lower fracture risk in previous studies.

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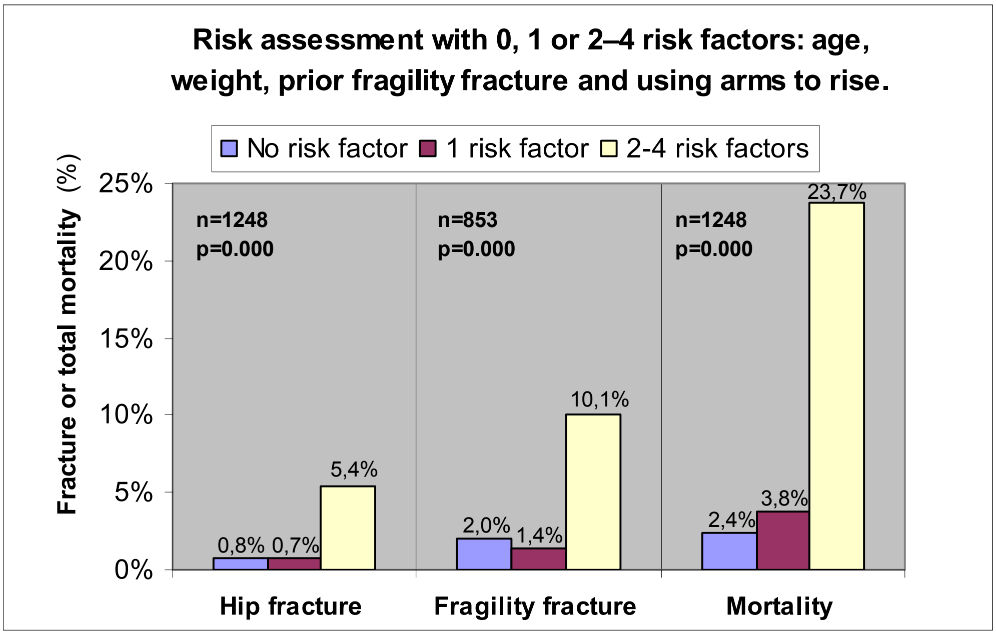

Figure 5: Two-year cumulative incidence of hip fracture, fragility fracture and total mortality, divided into tertiles with 0, 1 or 2–4 risk factors
(with 30, 34, and 37% participants in these three risk groups, respectively).
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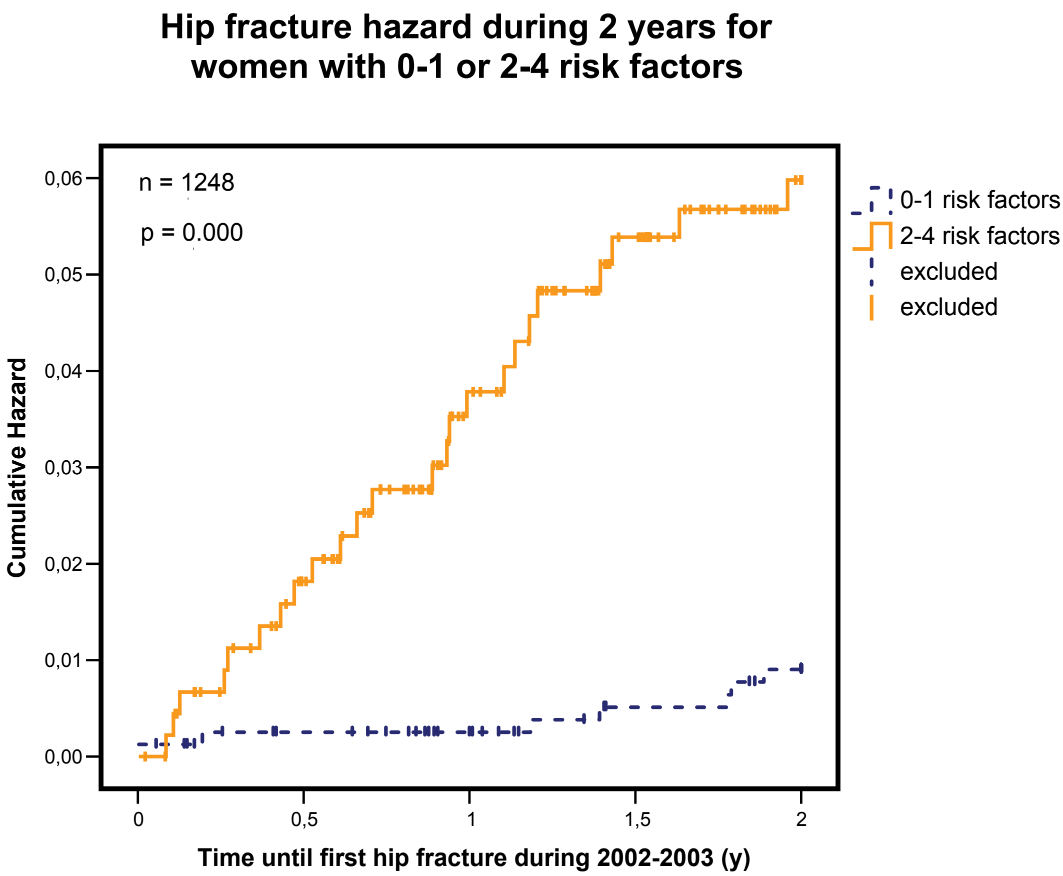

Figure 6: FRAMO Index two-year cumulative hazard for hip fracture
(Kaplan-Meier curve, participants excluded after death or first hip fracture).
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Table IV: Two-year hip fracture risk for clinical risk factors among 1248 women aged 70-100 in 2001, Fisher's test and Cox regression analysis.

Measurement	All 1248 subjects								
	Response rate	Hip fracture (n = 31)		No hip fracture (n = 1217)		P-exact †	Univariate ‡ HR (CI $_{95\%}$)	Multivariate ‡ 4 risk factors HR (CI $_{95\%}$)	Multivariate ‡,§ 11 risk factors HR (CI $_{95\%}$)
	n	n	(%)*	n	(%)*				
Five predefined risk factors									
Age 80-100	1248	19	(61)	470	(39)	0.014††	2.7 (1.3-5.6)††	2.2 (0.99-4.7)	2.0 (0.9-4.7)
Weight under 60 kg	1214	15	(48)	287	(24)	0.005††	3.1 (1.5-6.2)††	2.4 (1.2-5.0)††	2.6 (1.2-5.8)††
Prior fragility fracture after age 40 ‖,¶	1205	17	(55)	381	(32)	0.012††	2.5 (1.3-5.2)††	2.3 (1.1-4.7)††	2.6 (1.2-5.6)††
Uses arms when rising five times from chair	1210	14	(47)	348	(30)	0.067	2.3 (1.1-4.7)††	1.7 (0.8-3.6)	1.5 (0.6-3.7)
Falls during last 12 months	1192	12	(41)	385	(33)	0.42	1.5 (0.7-3.1)		1.0 (0.4-2.3)
Other possible risk factors									
Any type of fracture after age 40 ¶	1210	19	(61)	468	(40)	0.024††	2.4 (1.7-5.0)††		
Cortisone medication more than three months	1158	7	(26)	142	(13)	0.071	2.4 (1.0-5.6)††		2.6 (1.1-6.3)††
Has not given birth	1238	8	(26)	156	(13)	0.054	2.4 (1.1-5.4)††		2.4 (1.0-5.6)
Living in residential care (vs community)	1231	7	(23)	116	(10)	0.029††	3.3 (1.4-7.8)††		1.8 (0.6-5.0)
Height over 167 (cm)	1213	5	(17)	178	(15)	0.80	1.1 (0.4-2.9)		1.2 (0.4-3.5)
Dairy calcium dairy intake under 500 mg/day.	1208	9	(31)	368	(31)	1.00	1.0 (0.5-2.2)		1.0 (0.4-2.2)
Impaired vision, self-reported (vs good vision)	1226	8	(26)	348	(29)	0.84	0.9 (0.4-2.0)		0.5 (0.2-1.3)
History of maternal hip fracture	1108	4	(15)	119	(11)	0.52			
Subjective health poor (vs excellent or fair)	1224	1	(3)	119	(10)	0.36			
Current smoking	1231	0	(0)	53	(4)	0.64			
Daily coffee intake 2 cups or over (vs 0-1 cup)	1233	28	(93)	1010	(84)	0.21			
Menopausal age less than 45	1072	4	(18)	124	(12)	0.32			
No daily medication **	1229	2	(6)	150	(12)	0.42			
Any parent of non-Nordic origin (vs Nordic) **	1226	2	(7)	21	(2)	0.10			

* Estimated percentage on the valid participants.

† Exact P-value as Fisher's exact test, two-sided.

yielded a HF OR around 2 (see Table IV). The mortality risk clearly increased with the number of risk factors.

The proportion of women reporting previous vertebral fractures was higher at 10% in the group specifically questioned about vertebral X-ray, compared to 4.3%, of those not asked the question.

Conclusion: The four binary FRAMO Index questions were easy to answer for elderly women in PHC. A FRAMO Index score of 0–1 is associated with a very low 2-year HF risk (0.8%) among the majority (63%) of elderly women in primary care. The remaining 37% of the women had 2–4 risk factors and a 2-year HF risk of 5.4%. Mortality clearly increased with the number of risk factors. A specific question concerning vertebral X-ray improved reporting of previous vertebral fracture, important to reveal. The FRAMO Index, validated in this study, could be a practical fracture and mortality risk assessment tool for clinicians during routine consultations, and is easily applied even without a written questionnaire.

Study III

The 296 women (83% of 365 surviving women), all at high risk of HF according to Risk Model II, returned the follow-up questionnaire in May 2004. At baseline in 2001, the group's mean age was 82. The majority (61%) had fallen during the past year, 64% had sustained previous fragility fracture and one third had to use their arms to rise five times from the sitting position.

The number of women reporting any falls during the last year in the questionnaires was reduced by 22% (absolute risk) in the intervention group and by 12 % in controls between 2001 and 2004. The ability to rise from sitting only deteriorated in controls (see Figure 7).

In the intervention group, we found less women with impaired ability to rise (OR 0.21; 95%CI 0.06-0.82) and less women having fallen (OR 0.46; 95%CI 0.24-0.90), compared to controls; these findings were restricted to women reporting impaired mobility when the study started in 2001 and were significant after age adjustment in the logistic regression model.

In the intervention area, home exercise increased 2-fold compared to the control area. In the whole study population, current home exercise in 2004 was related to a better ability to rise at same time ($p<0.001$).

In the intervention area, 61% (63/103) received repeated fracture-preventive house calls. These women increased their home exercise between the first and third house calls ($p<0.001$). Univariate analysis for the change in their ability to rise, adjusted for baseline mobility, revealed a trend toward improvement for three intervention types; home exercise, calcium- vitamin D treatment in 2004 and group exercise in 2003; the respective p-values range between 0.08-0.11. Women performing home exercise

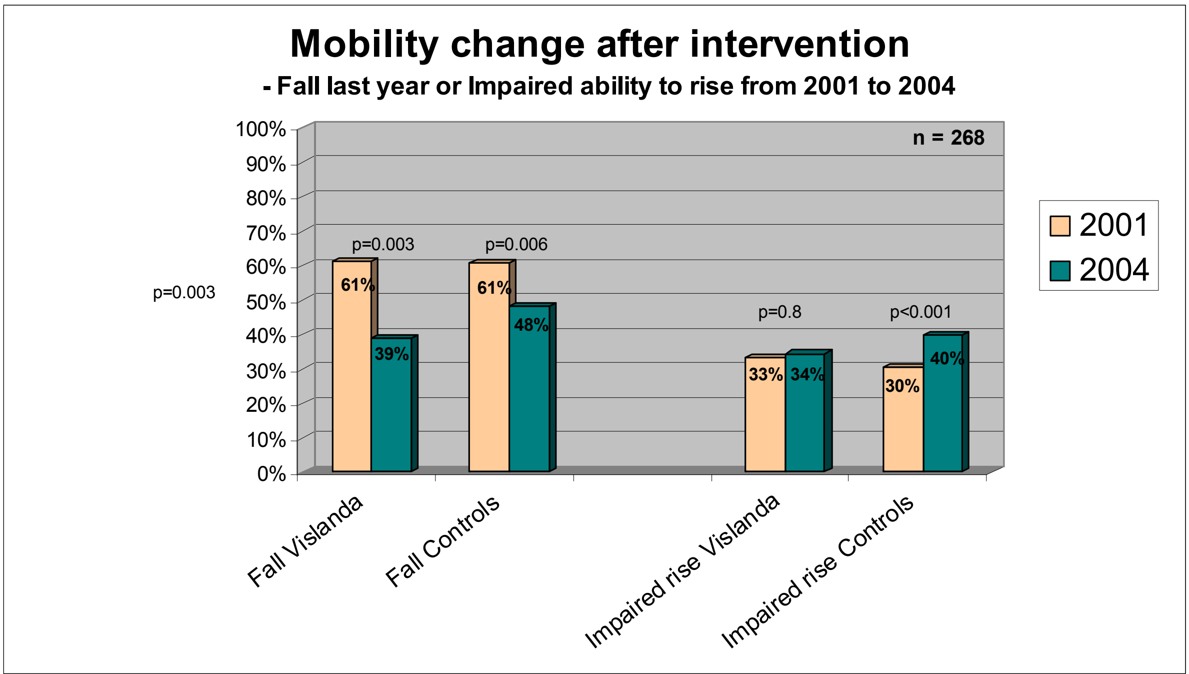

Figure 7: 2.5-year mobility change in "falling during last year" and "impaired ability to rise" from 2001 to 2004, for intervention population or controls.

currently in 2004 who had impaired rising ability in 2001 showed significant improvement (p=0.03). As illustrated in Table V**,** multi-variate analysis of these three intervention types **(**including interaction terms and adjusted for baseline mobility) yields p-values close to significance (0.04-0.06). Improvement in rising ability related to home exercise was restricted to subjects with impaired baseline mobility.

Table V: Rise up ability at 2004 depending on baseline mobility or on different interventions in intervention group (n=90),* at one-year house call follow-up or at physician follow-up.

Type of intervention	Intervened n of 90 (%)*	OR - univariate Impaired rise 2004 (CI $_{95\%}$)†	p	OR - multivariate Impaired rise 2004 (CI 95%)†	p
Home exercise (each week)	32 (36)	0.3 (0.09-1.1)	0.08	NA	NA
Impaired ability to rise 2001	7	0.1 (0.01-0.8)	0.03 ‡	0.1 (0.02-1.1)	0.06
Non-Impaired ability to rise 2001	25	0.7 (0.15-3.1)	0.62	NA	NA
Group exercise at 2003, physiotherapist led	17 (19)	0.2 (0.02-1.5)	0.10	0.1 (0.01-0.93)	0.04 ‡
Impaired ability to rise 2001	3	NA §	NA §	NA	NA
Non-Impaired ability to rise 2001	14	0.5 (0.05-5.0)	0.57	NA	NA
Calcium & vitamin D treatment may 2004	48 (53)	0.4 (0.1-1.2)	0.11	0.3 (0.09-1.0)	0.05
Impaired ability to rise 2001	16	0.2 (0.03-1.5)	0.12	NA	NA
Non-Impaired ability to rise 2001	32	0.6 (0.1-2.4)	0.44	NA	NA

* Number or % participators with actual intervention out of 90 analysed. Participants with no/unknown intervention classified as not intervened.
† Multivariate logistic regression of variables home exercise, group exercise, calcium & vitamin D and and their interactions, adjusted for baseline ability to rise at 2001, using stepwise backward removal when p > 0.1. All varibles had p<0.20 in univariate analyze as adjusted for age and baseline mobility. Age had no influence on the size of treatment effects for these three intervention types. To save power the presented analysis was not age-adjusted.
‡ p < 0.05.
§ Odds ratio not analysed [NA] when cellvalue at 0.

There was a slight, but significant, reduction in home environmental hazards between the house calls (p <0.01) in the intervention area. The risk of a fall was OR 0.48, a non-significant (p=0.24) difference, for women reducing home hazards between house calls, compared to women with unaltered hazards.
Pharmacological treatment was considered for 80% (82/103) after the house calls and BMD assessment. In 2004 54% were taking calcium and vitamin D treatment and 22% were taking bisphosfonates in the intervention area.
Two HFs occurred in the intervention group, vs 11 in controls (OR 0.33; p=0.23) but no difference was found for FF.
In addition to the objective mobility improvements in the intervention area, these women also reported more improved subjective health since the last year than controls, in 2004 (p <0.01).
Conclusion: The number of women falling or with impaired ability to rise was more than halved in the intervention area, compared to controls. This applies to subjects at high risk of HF and with impaired mobility at the study start.
Significantly fewer women fell in both study areas, despite the participants being 2.5 years older. In intervention area, the improved ability to rise seemed to be related to three intervention types; current home exercise and calcium- vitamin D treatment and previous group exercise. Home hazards were somewhat reduced. A HF reduction was an expected consequence of the study interventions, although the OR (0.33) was non-significant. The 2004 intervention population reported improved subjective health since the last year, compared to controls.

Study IV

In this prospective population-based study, seven HFs and 14 FFs occurred among the 285 women, aged 72-98, participating in a fracture prevention program. Sixty percent of the subjects had heel BMD at osteoporosis levels (T-score ≤ -2.5 SD) with portable DXL technique, shown in Figure 8.

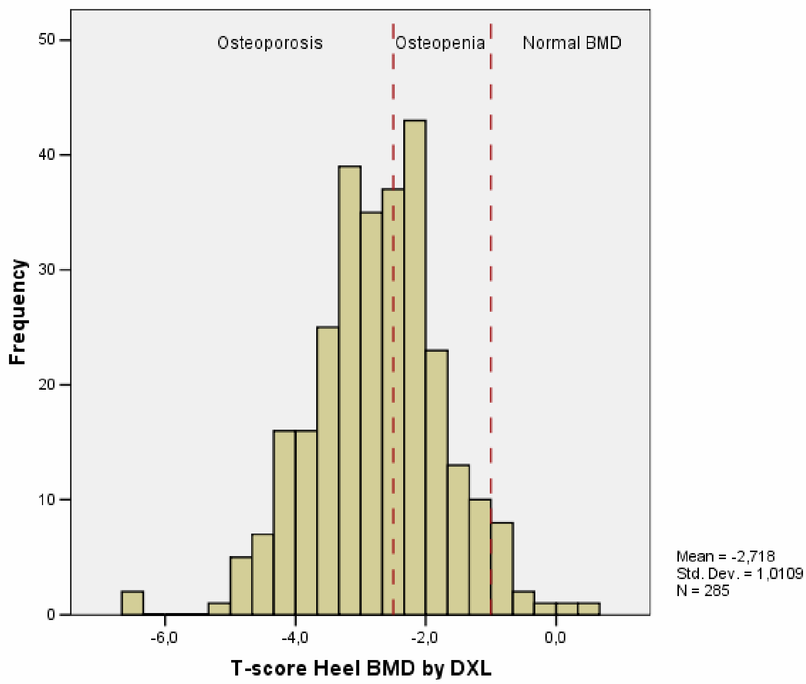

Figure 8: Population-based heel BMD T-score, assessed with DXL in 285 women, mean age 79.

We revalidated the clinical 4-item FRAMO Index (Risk Model I) by combining the risk factors age, low weight, prior fragility fracture and impaired rising ability. This yielded an OR for HF of 5.9 (95%CI: 1.1-31) and an OR for FF of 4.4 (95%CI: 1.4-14). The annual HF risk in the high- risk group was 2.8%, compared to 0.5% for the majority of women (69%) at low HF risk. The age-related HF and FF risks were doubled for every 5 year increase in age. Heel BMD, assessed by DXL, was associated with a HF OR of 2.7 (95%CI: 1.4-5.3) and a FF OR of 2.3 (95%CI: 1.4-3.9) per SD decrease. The 60% of women with osteoporosis (≤ -2.5 SD) had no significant difference in HF risk, compared to those with higher BMD (p=0.25).

We found a very high annual absolute HF risk (7.8%) among 11% of all women, by combining the FRAMO Index, prior fragility fracture and heel BMD T-score ≤ -3.5 SD. The HF risk was very low (0.4%) in the remaining 89% (Table VI). The corresponding FF risk was 9.4% annually for the 11% in the high-risk group, and 1.6% in the remaining low-risk group (Table VI).

In the case of the 41 women that also underwent DXA assessment, the osteoporosis value at the hip corresponded to a heel T-score around -3.3 SD, outside the scatter plot reference line.

Conclusion: The prevalence of osteoporosis, measured by portable heel DXL technique, was high. The clinical 4-item FRAMO Index was revalidated as a HF and FF risk assessment tool. Each SD decrease in heel BMD was associated with a more than doubled fracture risk. Very low heel BMD (≤ -3.5 SD) was related to increased HF and FF risk. HF prediction was improved by a combination of the FRAMO Index + a prior fragility fracture + BMD T-score ≤ -3.5 SD, predicting most HF in a small (11%) high-risk group. The remaining 89% women had a very low HF risk.

Table VI: Individual annual absolute risk of HF and FF, based on FRAMO Index, prior fragility fracture or heel BMD (T-score$_{Low}$) alone, or in combination (n=285).

		HF 2004-2005			FF 2004-2005		
Risk factor combinations	Women at high risk (% of 285)	High risk (%)	Low risk (%)	p *	High risk (%)	Low risk (%)	p *
FRAMO Index	88 (31)	2.8	0.5	0.03 *	5.1	1.3	0.01 *
Prior fragility fracture	94 (33)	2.7	0.5	0.04 *	3.7	1.6	0.13
Heel T-score ≤-2.5 SD	172 (60)	1.7	0.4	0.25	3.5	0.9	0.05
Heel T-score ≤-2.5 SD + FRAMO Index	74 (26)	3.4	0.5	0.01 *	5.4	1.4	0.01 *
Heel T-score ≤-2.5 SD + prior fragility fracture	70 (25)	3.6	0.5	0.01 *	5.0	1.6	0.05 *
Heel T-score ≤ -3.5 SD + FRAMO Index	42 (15)	6.0	0.4	0.001 *	8.3	1.4	0.001 *
Heel T-score ≤ -3.5 SD + prior fragility fracture	35 (12)	7.1	0.4	<0.001 *	8.6	1.6	0.003 *
Heel BMD$_{Low}$ ≤ -3.5 SD + prior fragility fracture + FRAMO Index	32 (11)	7.8	0.4	<0.001*	9.4	1.6	0.002*

* Exact P-value as Fisher´s two-sided test for binary variables, $p < 0.05$ as a significant difference.

General discussion

Main findings and other studies

Population base and study participation

Questionnaires were returned by 73-92% of the participants in these population-based fracture prevention studies of women aged 70-100 in community and residential care. The response rate to the baseline questionnaire in late 2001 was 87% in the intervention area, conditions closely resembling an intervention screening situation. The high questionnaire response rate could also be explained by the motivational effect of the fracture-preventive information presented in the covering letter signed by the GPs and nurses. The fact that the questionnaire consisted of simply worded, multiple-choice questions, that relatives or caregivers were permitted to assist in replying, and that two reminders were send may be other explanations.
At the beginning of the main study in 2001, these 1248 participants had a mean age of 79. Around one third had fallen during the last year**,** had impaired ability to rise or had sustained a prior fragility fracture, respectively. The vertebral fracture prevalence (10%) was more reliably reported from the intervention area, by the adding of a specific question about vertebral X-ray, compared to a prevalence of 4.3% when only a short question regarding known vertebral fracture was asked. During the intervention in 2004, the women at higher HF risk in the intervention area reported improvements in perceived health during the last year, compared to controls.

Risk assessment by clinical scores and heel osteoporosis

Clinical risk factors related to hip fracture, fragility fracture and mortality risk
These four risk factors in the FRAMO Index were found to be significant as binary variables for HF after univariate logistic regression. Low weight and prior fragility fracture remained multivariately significant, with around 2-fold risks. Both age and weight as continuous variables were significant for HF, as in other studies.[22, 25] For every five-year increase in age, the HF and FF risk was doubled, as in another study.[70]
A majority of women (63%) had 0–1 FRAMO Index risk factors, associated with a very low absolute annual risk of HF; 0.4%. The predicted HF risk increased 7.5-fold for the 37% of women with at least two risk factors and identified 81% of all incident HF. The risk estimates remained significant after the index was adjusted for continuous age. The FF risk was increased nearly 7-folded for the 34% with at least two risk factors; this was calculated in only two of three subpopulations (with available out-patient registers for FF).
The FRAMO Index score requires only four simply-worded Yes/No questions and no BMD assessment, yet it predicts HF over a two-year period as well as four other, more

complex, risk scoring systems,[22, 25, 86, 144] further described in Table VII, and in "Introduction" at "Risk factor models for hip fracture" (page 23) The FRAMO Index has a sensitivity of 81%, a specificity of 64% and a positive predictive value of 5.4%. Our index was calculated on a participation rate of 83% compared to 70% in another population-based risk model study (see Table VII below).[144] A prediction period of two years is rather short, but our simple 4-item score is easy to revaluate and possible to calculate without using a written form. The risk factor "impaired ability to rise" is especially modifiable (in both directions); exercise or inactivity may change it, possibly altering the HF risk.

Using the Risk Model II, in which the risk factor "fall during last year" is used instead of "impaired ability to rise", 38% of the 1248 women scored 2–4, yielding an absolute HF risk of 2.3% annually, a 4-fold increase, compared to the low-risk group. The corresponding sensitivity and specificity were 71% and 63%, respectively.

The mortality risk according to the FRAMO Index was increased more than 9-fold for the 37% who had 2–4 risk factors. The annual absolute mortality risk was 12%, evaluated during 2002–2003. There was an obvious mortality correlation for an increased number of risk factors.

Osteoporosis prevalence, assessed with DXL

Other main findings; in 2003, 60% of 285 women aged 72–98, had T-score ≤ -2.5 SD (osteoporosis) and 41% (70/172) of these women had also previously sustained a fragility fracture (manifest osteoporosis). Very low T-scores (≤ -3.5 SD) were found in 24%. The prevalence of osteoporosis in the heel, diagnosed by DXL, was higher than that reported (38–47%) among Swedish women aged 75-84, diagnosed by the DXA reference method at the hip.[71]

We measured hip BMD in 41 women using DXA, finding heel T-scores 0.7 SD lower using DXL technique. Since we measured BMD in both heels, choosing the lowest value, the mean T-score was lowered by 0.2 SD. The remaining difference was close to findings in a previous study, with a 0.5 SD lower DXL-diagnosed BMD in the heel than in femoral neck,[143] important to take into account when defining osteoporosis assessed by DXL.

Fracture risk related exclusively to heel BMD

The HF risk and FF risk increased prospectively, by OR 2.7 and 2.3, respectively, for each SD decrease in T-score, analysed by logistic regression. The age-adjusted, BMD-related risk for HF and FF was doubled for each SD, with the HF risk approaching the significance level (p=0.051). These age-adjusted risk estimates were close to levels for other used BMD assessment techniques in the hip or heel, although our wide CIs make the comparison more uncertain.[24, 31]

Table VII: Hip fracture risk models for elderly women

Author (Index)	**Participants Country**	**Population base**	**Mean age**	**Period (years)**	**Number of clinical items**	**Binary items only**	**BMD**	**Sensitivity/ Specificity (%)**	**PPV (%)**	**OR**	**ROC-area**
Albertsson 2007 (FRAMO)	1248 Sweden	Total	79	2	4	Yes	No	81 / 63	5.4	7.5	0.72
McGrother 2002	1289 UK	Total	78	3	6	No	No	84 / 68			0.82
Black 2001 (FRACTURE)	7782 US & 7575 France	Lists	73 & ≥ 75	5	6	No	No DXA	66 / 66 79 / 62	5.6 5.8		0.71 0.77
Dargent-Molina 1996	7575 France	Lists	80	2	3	No	DPA			*	
Cummings 1995	9516 US	Lists	72	4	16	No	SPA (heel)			**	

* The 12.7% (932 of 7323) women who had a high fall-related risk and low BMD combined, sustained 36% of hip fractures reported.

** The 6% women who had ≥ 5 items and low third BMD combined, sustained 32% of all hip fractures reported.

Fracture risk related to clinical risk factors combined with low heel BMD

HF prediction with the clinical FRAMO Index seemed more accurate than using threshold heel osteoporosis (T-score ≤ -2.5 SD) alone (see Table VI). Improved fracture prediction at low BMD levels was seen among those women who also had sustained a prior fragility fracture or were at high risk according to the FRAMO Index (see Table VI). These findings stress the importance to consider the clinical risk factors before initiating treatment based on BMD assessment.[22]

Further more, based on clinical risk factors and the heel BMD-related rise in HF risk, we found a very high absolute annual fracture risk (7.8%) only in the 11% of women with very low (≤ -3.5 SD) heel T-scores combined with high FRAMO scores and prior fragility fracture. Even more interesting, the remaining 89% had a very low absolute annual HF risk (0.4%).

If only the 11% women at very high HF risk were treated for two years, assuming an 50% HF reduction effect of pharmacological treatment alone,[145] the NNT would be 13. A lowered NNT leads to more costs-effective treatment and less side effects. These treatment costs could be compared to the known high society costs after a HF.[56] The FF risk also increased with that risk factor combination, yielding a corresponding NNT of 11 among these 11% women, based on the same treatment assumptions.[145]

HF is the most severe common fracture type. Nonetheless, women with multiple vertebral fractures have considerable re-fracture risk, morbidity and mortality.[57] Since bisphosfonate treatment has a good preventive effects in this risk group,[145] treatment is usually beneficial.

Intervention

Multi-factorial intervention effects

Among women at high HF risk (according to Risk Model II) who were the objects of multi-factorial interventions, we found a significant improvement in falling tendency and ability to rise, compared to controls at the beginning of the study 2.5 years earlier. The improvements were restricted to women with falling tendency or impaired ability to rise at baseline.

There was also a significant fall reduction in the control area, which could be an effect of intervention spread from the adjacent intervention area. In that case, the intervention effect tends to be underestimated when the study areas are compared.

Since the baseline questionnaire was collected in November 2001 and the follow-up in May 2004, some of the fall reduction (seen in the whole study area) could also be due to a minor seasonal variation in falls, that was found in a Finnish study due to extrinsic mechanisms such as slipping or stumbling when walking outdoors.[146] However, falls in November equaled falls in May.[146] Further more, at age 75 and up (most women in our study) falls are more often related to intrinsic or unknown causes, with lack of seasonal

variation in that study.[146]
Two HF occurred in the intervention area during 2004–2005 after full intervention, compared to 11 in the control area. The reduction in HF was in line with that seen in other fall and fracture-preventive interventions[42, 60, 122, 130, 147] and to the observed mobility improvements for risk factors related to HF.[8, 22, 25] Since quite a few HF events were expected to occur during this observation period, the non-significant result was not surprising. When it came to FF, we saw no incidence difference between the study areas (OR 0.9; 95%CI 0.4-2.2). In our study, HF reduction was favoured by the high prescription rate of full-dose calcium and vitamin D the fracture-preventive effects of which are restricted to non-vertebral fractures, especially to HF.[37-39]

Intervention compliance and resources

Different interventions types were feasible in this population, involving the majority of the high-risk intervention population identified in Study III (64% received house calls and 80% had physician follow-up). Compliance was fair to good, with 33% of the women reporting one year of home exercise around 30 minutes per week and 54% accepting pharmacological treatment. Fewer women participated in group exercise (19% in Study III) which party could partly be explained by this only being offered in one village, distant for many participants.
One-year participation was 59% in another fall prevention RCT of exercise, offering group exercise in the community setting and some home exercise.[124] These elderly participants attained a general practice clinic, and were considered eligible only if they had physical performance impairments.
Our recommended home exercise program, around 10 minutes initially five times a week followed by at least two times weekly, was less intense than in another fall prevention study.[11, 122] Nonetheless, our home exercise program included some heavy load training for leg muscles, such as deep knee bending, which may improve the muscle strength and has been shown to be effective in more intense fall-preventive exercise programs, both for elderly community residents[125] and for very old individuals in residential care.[120]

Possible uni-factorial intervention effects

Three specific intervention types seemed related, independently on one another, to improvement in ability to rise in 2004; current home exercise, ongoing calcium-vitamin D treatment and previous physiotherapist-led group exercise. The effect of home exercise was restricted to women with impaired rising ability at the study start. In other studies, these intervention types have been related to fall reduction[11, 124, 130] but we found no previous study results showing improved ability to rise.
Home hazards were somewhat reduced and there was only a weak trend towards less falling (p=0.24), although the OR was 0.48. In another study,[60] less home hazards contributed to fall reduction among women who had fallen the year before intervention.

Home hazard reduction, combined with detailed medical assessment and treatment of elderly patients seeking care after a fall, led to marked fall reduction in another study.[126]

Limitations

Power and CI

Our studies comprise limited numbers, sometimes few events and wide 95%CIs, entailing a need for large differences between the groups in order to show statistical significance. This problem was more pronounced for binary variables and in the sub-group analysis. On the other hand, several items reached the level of significance, showing marked low/high ORs, indicating strong relationships of clinical interest. Our study was big enough to show major mobility improvements, in rising ability and falling tendency. Three significant intervention factors - home exercise, group exercise and calcium- vitamin D treatment - were all around the significance level with concurrent very low ORs between 0.1–0.3, showing improvement in ability to rise. The original validation of the FRAMO Index, in which the lower limits of the 95%CIs ORs were at least 3.0, confirmed that it was strongly fracture-predictive.

Fracture prediction method

The observation period in this study was only two years. Keeping the FRAMO Index simple and binary, with “Yes” or “No” as the response alternatives, leaves it easy to repeat during regular PHC consultations, even without using the written questionnaire. Age as a binary variable may become less predictive during a longer observation period.

The number of FF occurring during the study period is slightly underestimated, although reporting of vertebral fracture prevalence was optimized to 10% of the participants by the addition of a question about vertebral X-ray. Hip, arm and pelvis fractures are usually detected by X-ray but not all women suffering vertebral fractures are investigated and optimally diagnosed using radiology. Specific radiological deformities as lowered vertebrae/s have been found in half of the elderly population,[79] being related to subsequent fracture.[77, 78] Spinal fracture is a strong predictor for recurrent vertebral facture, especially in cases with multiple prior fractures.[27, 77] The more serious multiple vertebral fractures usually produce more clinical manifestations and were probably more accurately revealed by the questionnaire reply.

Dropouts

Although the response rates were rather high, the non-responders were older and less able to rise than responders. This probably decreased the actual risk estimates for fracture somewhat, since HF increase with age and impaired ability to rise. In Study III, before questionnaire follow-up in 2004, the high-risk women had a high dropout rate due to a high mortality; 9.7% annually. In the population-based Study IV in intervention area, the corresponding mortality dropout rate during the pre-study period was 5.2% annually.

Recall bias

Recall bias for prior falls is well known. It was estimated at 13% unreported falls during the preceding 12 months in a mostly female population aged over 60.[148] Biases were probably higher for our elderly participants. The low 3-year reliability for falls during the last year in Study I (45%) was probably a combination of incident fall variation and recall bias, in contrast to the high (94%) reliability for prior fragility fracture.[149] However, recall of previous falls is reported to be better in intervention populations than in controls,[150] which would reduce the apparent differences between the study areas.
The reported ability to rise was probably more reliable, since participants could and were encouraged to perform a self-test when responding to the questionnaire.

Intervention study design

Participants were not randomized to different interventions. This strategy probably increased the number of participants and was more similar to ordinary treatment. In the intervention area, nearly two thirds of the the participants at high HF risk received house calls and one third were continuing home exercise after one year. Only 20 women started the recommended group exercise, an intervention that is possibly more feasible in an urban area with shorter distances. There was probably some selection, with more active or agile women choosing active exercise. This bias was reduced by comparing the women from the intervention area with themselves, regarding intervention effects on the mobility change, adjusted for their age and baseline mobility. However, the individual preference for different types of intervention does not affect the analyses on the study area level. The major mobility analysis was made on the defined high-risk women group for HF. At the beginning of the study, the study groups were originally chosen from similar PHC rural districts with as age-matched controls.

Rural study population

This study was limited to white, rural, Swedish female populations with parents of Nordic origin (98%). Urban women, who have a higher fracture risk, more often have a history of fractures and are less physically active.[5, 53] Because this might be reflected in increasing the scores for prior fragility fracture and using arms to rise, the index may also be suitable for fracture prediction in urban areas.

Further studies

The fracture and mortality risk estimates needs to be replicated in larger, non-Scandinavian, urban populations, possibly in both genders (with modified variables for men), in order to obtain more precise risk estimates. In this context, separate analyses should be performed according to clinical risk factors, including the FRAMO Index, low BMD alone and clinical risk factors combined with low BMD. Also, the observation period should be extended. The role of BMD in choosing strategies for fracture prevention can thus be more clearly defined, finding optimal thresholds for good sensitivity for efficient treatment, and maintaining a reasonable specificity in order to avoid treatment of women at minimal fracture risk.
Mobility improvement lasted for over one year after major multi-factorial interventions in this group of women at high risk of HF with impaired mobility at the study start. This indicates that the observation period for mobility improvement should be extended and that the effects of repeated interventions should be evaluated in larger samples. Further evaluation of the different significant mobility-improving types of intervention is essential.
Since the OR related to the HF incidence was low (0.33) but non-significant, the fracture observation period should be extended.

Implications for clinical practice

Fracture risk assessment

The high questionnaire response rate may indicate a high level of interest in fracture prevention among this elderly female population. The simple 4-item FRAMO Index was effective in identifying elderly women at high risk of HF, as well as for predicting FF and mortality within two years. We found that including a specific question about vertebral X-ray improves the reporting of previous vertebral fractures, an important predictor of future fractures.[77] The FRAMO Index identifies even more accurately a majority of women aged over 70 with minimal fracture or mortality risk who thus have

lower fracture prevention requirements. For this group, BMD assessment may be unnecessary, which concurs with the Cummings study findings, that women with few clinical risk factors, even those with BMD in the lowest third, were less likely to fracture at hip.[22]
Age was a HF predictor in our study, concurring with general knowledge.[9] The use of age in a risk model is also motivated by age-related treatment effects, with less fractures at higher ages-up to 85-using bisphosfonates.[23, 42] This medication was more cost-effective at age 77 than at age 65 [118] among postmenopausal women with prior vertebral fracture and osteoporosis.[40, 41]

We found that 60% of our women population had heel osteoporosis, using DXL technique; heel BMD T-scores were 0.7 SD lower than DXA assessment at the hip. The fracture risk increased with decreasing heel BMD. The HF risk was increased (p=0.01) at first from BMD T-score level ≤ -3.5 SD, compared to those above that level (see Paper III, Table 2).
We predicted most HF with the combination of a high FRAMO Index score, prior fragility fracture and heel BMD T-score ≤ -3.5 SD; identifying 11% of all women at very high risk of HF within two years. The remaining 89% were at minimal risk of HF, with low benefits from fracture-preventive interventions during the two-year study period. As in other studies, these findings stress the importance of clinical risk factor evaluation for HF risk estimation[22, 25] and thus for directing the major preventive resources to women at high fracture risk. Portable DXL instruments might be practical for BMD assessment in PHC, for further fracture risk assessment among selected women with clinical risk factors for HF. Our heel BMD study results are based on few HF events and should be confirmed in larger investigations.

Interventions

Basic fracture-preventive lifestyle, changes, such as daily physical activity and spending time outdoors, smoking cessation, moderate intake of alcohol and adequate nutrition including calcium and vitamin D, should be encouraged, especially in postmenopausal women.[12, 36, 70, 96, 101, 103, 121]
When the FRAMO Index score, other clinical risk factors and possibly low BMD reveal that a patient is at high risk of fracture, several interventions should be considered. Optimal lifestyle habits are important and exercise can increase muscle strength,[120] which may also improve the ability to rise from sitting. In our multi-factorial fracture prevention study including house calls, home and group exercise and pharmacological treatment, we observed at least one-year improvement in falling and ability to rise after major intervention, in women with impaired mobility and high risk of HF. Improved ability to rise appeared to be related to home exercise, group exercise and calcium-vitamin D treatment. Fall reduction was possibly due to home hazard

reduction in our study, concurring with the results of a previous study.[60] Other exercise programs have led to fall reduction.[11, 123, 124] Also, safer home environment, medical examination, withdrawal of unnecessary psychotropic medication and vitamin D treatment reduced the tendency to fall.[60, 107, 126, 130] Hip protectors could prevent HF in elderly people in institutional care; compliance was improved by the free provision of protectors and staff education.[35, 128] Pharmacological calcium-vitamin D treatment was fracture-preventive in the elderly, and is also recommended during cortisone medication.[37-39, 67, 134, 147, 151] Bisphosfonates should be considered for women at high risk, especially of HF or multiple vertebral fractures, as well as during cortisone therapy.[26, 40, 42, 67, 77, 110, 121]

Since bisphosfonate treatment already leads to full fracture-preventive effect the first year of treatment,[110, 138] the current fracture risk should determine prescription to osteoporotic women. The HF risk is highest at advanced ages.[9, 42]

Aged women are usually more frail and suffers higher mortality, and women having higher FRAMO Index scores had high mortality. These conditions might warrant more active prevention against serious fractures, which cause additional morbidity and mortality[57] in these group. Also, after five years of treatment there is the possibility of discontinuing bisphosfonate treatment with remaining preventive effect for non-vertebral fractures during the following five years.[141]

Summary

- Questionnaire participation rates were high (73-92%) in these population-based studies of elderly women.
- Need for fracture prevention was seen among one third, at pre study 1998.
- The binary 4-item FRAMO Index identified a high-risk group sustaining 78-81% of all hip fractures, fragility fractures or deaths within in a 2-year period (2002–2003). A specific question about vertebral X-ray increased the number of reported vertebral fractures. The simple FRAMO Index is applicable even without using a written form.
- After full intervention, the revalidated FRAMO Index showed increased fracture risk (2004-2005), in parity with the previous study period.
- Multi-factorial intervention was related to fall reduction (by 54%) and less impaired ability to rise (by 79%), restricted to subjects with impaired mobility at the study start.
- The hip fracture risk difference between the intervention group and controls was non-significant, although a reduction (OR 0.33) was concurring with interventions and mobility improvements in the intervention area.
- Improved ability to rise was related to each of the interventions; home exercise, group exercise and calcium-vitamin D treatment (p= 0.04–0.06). These interventions were feasible, with 19-54% participation among high-risk group.
- The heel osteoporosis prevalence was high (60%), defined as T-score ≤ -2.5 SD with DXL technique. DXA-assessed hip osteoporosis corresponded to a DXL level of around -3.3 SD.
- Prospective hip fracture risk increased by 2.7 and fragility fracture risk by 2.3 for each decrease in heel BMD.
- The FRAMO Index, combined with prior fragility fracture and heel DXL ≤ -3.5 SD, identified 11% of women at very high absolute risk of hip fracture (15.6%). In remaining 89% the corresponding 2-year hip fracture risk was minimal (0.8%). The NNT was 13 in the high-risk group during a 2-year period, assuming a 50% hip fracture reduction from pharmacological treatment alone.

Conclusions

- Questionnaires used were feasible for population-based fracture prediction in PHC.
- The 4-item FRAMO Index provided good fracture prediction and was a practical prediction tool, applicable even without a written form.
- Heel BMD with portable DXL technique was prospectively related to hip and fragility fracture risk. Hip osteoporosis (BMD T-score –2.5 SD) corresponds to a heel BMD T-score around -3.3 SD.
- Clinical risk factors in combination with a very low heel BMD identify a small high-risk group for hip fracture within two years. This finding should be confirmed in larger studies.
- Women with impaired mobility improved in the intervention area, reporting better mobility more than one year after major intervention. Intervention methods were feasible, with fair to good participation and compliance.
- Hip fracture incidence showed non-significant OR 0.33, comparing the study areas. The evaluation period for hip fracture and mobility outcomes should be extended. Effects of regularly repeated interventions should be tested.
- This simple 4-item risk assessment tool (FRAMO Index) and feasible intervention program, of 1-2 years duration, is probably useful in population-based hip fracture prevention, although the results require confirmation in larger studies.

Sammanfattning på svenska (Summary in Swedish)

Bakgrund

Benbrott har ökat påtagligt sedan 1950-talet. Var fjärde kvinna bryter höften under sin livstid. Fall föregår som regel en höftfraktur (HF), men flera andra samtidigt förekommande risk faktorer, som hög ålder, tidigare fraktur, låg bentäthet, avgör om benet verkligen bryts. Efter en HF kvarstår ofta rörelsehinder och smärta, och var femte kvinna avlider inom 1 år. För varje förebyggd HF har samhällskostnaderna under första året beräknats minska med cirka 150 000 kr.
Fall och benbrott kan förebyggas genom exempelvis dagliga promenader, undvika rökning, fysisk rörelseträning och förbättrad läkemedelsbehandling. Allt detta tillämpas i begränsad utsträckning i dagens sjukvård.

Forskningsfrågor

Kan vi i förväg identifiera de kvinnor som riskerar att bryta höften?
Går det att förebygga fall och HF, med begränsade insatser till kvinnor inom ett vanligt primärvårdsområde?
Vår avsikt var att bedöma risken för höftfraktur utifrån ett risk-score med fyra enkla frågor (benämnt FRAMO Index) och att utvärdera en enklare bentäthetsmätare (DXL teknik) för hälbenet, samt utveckla och pröva enklare metoder för att förebygga fall och höftfraktur för kvinnor över 70 år i en befolkning.

Metod

Vid Studie I skickades 1998 en 46-frågors provenkät, om frakturrisk till 100 slumpvis utvalda kvinnor över 70 år i Vislanda området, med en uppföljande enkät 2001. Under 1999-2001 framtogs informationsmaterial, samt utvecklades och prövades metoder för fysisk träning och hembesök.

Vid Studie II, skickades 2001 en enkät med 22-frågor om HF-risk till 1498 kvinnor över 70 år, boende i 3 landsbygdsområden. Risk-score beräknat utifrån 4 enkät frågor, utvärderades under kommande 2 år (2002–2003) mot benbrott och dödlighet. Alla 501 kvinnor som bodde i Vislanda området (interventionsgruppen) inbjöds att delta i undersökningen. Dessa kvinnor fick även besvara 15 tilläggsfrågor, då de sedan erbjöds extra fall- och frakturförebyggande behandling. De övriga 997 kvinnorna i kontrollgruppen åldersmatchades mot interventionsgrupp och fick sedvanlig behandling.

Vid Studie IV inbjöds interventionsgruppen från 2003 att besvara en liknande enkät om HF risk samt genomgick bentäthetsmätning i hälen, med enkel bärbar DXL teknik. Aktuellt risk-score samt täthet i hälbenet jämfördes mot nya frakturer under följande 2 år (2004–2005). Bentätheten i häl jämfördes också mot bentäthet i höft och ländrygg.

I Studie III prövades förändrad uppresningsförmåga och falltendens, utifrån svar i enkät 2001 och upprepad enkät 2004. I denna studie deltog enbart kvinnor med ökad HF risk, som 2001 klassade enligt risk-score för HF. I interventionsområdet genomfördes hembesök hos 61%, hemträning och gruppträning initierandes, och fall-risker i hemmiljö åtgärdades. Farmakologisk behandling övervägdes för 80% efter bentäthetsmätning. Effekten av intervention för såväl rörelseförmåga som för nya frakturer under 2004–2005 jämfördes mellan interventions- och kontrollgrupp.

Resultat

Pilotenkäten 1998 besvarades av 92% (Studie I). Var tredje kvinna hade behov av någon fraktur-preventiv insats. Hela 94% kunde efter 3 år bekräfta att de haft tidigare benskörhetsfraktur.

Enkät 2001 besvarades av 83% (n=1248 kvinnor) i Studie II. Fyra riskfaktorer – ålder ≥80, vikt <60kg, tidigare benskörhetsfraktur och att hjälpa till med sina armar vid uppresning fem gånger från stol – kombinerades till riskfaktormodellen FRAMO Index. För merparten kvinnor (63%), med 0–1 riskfaktorer, var absoluta HF risken 0.8% under 2 år. Resterande deltagare (37%), med 2–4 riskfaktorer, hade 7.5 gånger högre HF risk (5.4%) och deras dödlighet var 24% under 2 år. Dessa signifikanta skillnader kvarstod även efter åldersjustering. Deltagare som besvarade en riktad fråga om ryggröntgen rapporterade oftare att de haft kotfrakturer.

Sju HF och 14 fragilitetsfrakturer (FF) inträffade bland de 285 deltagarna i Studie IV, som utvärderades inom interventionsområdet under 2004–2005. 60% hade osteoporos i hälbenet (T-score ≤ -2.5 SD). Kvinnor med 2–4 riskfaktorer i FRAMO Index hade 6-faldigt ökad HF risk och 4-faldig FF risk. Sjunkande bentäthet i hälen medförde ökad risk för HF och FF (med 2.7 respektive 2.3 gånger per SD). De 11% kvinnor med högt FRAMO Index + tidigare fragilitetsfraktur + låg bentäthet (T-score ≤ -3.5 SD) hade mycket hög absolut HF risk (7.8%), medan resterande 89% hade påtagligt låg årlig HF risk (0.4%).

Intervention av deltagare i Studie III som alla hade ökad HF risk, gav en minskning av fall mellan 2001 och 2004 bland kvinnor med 22% (absolut risk) i interventionsområdet, och med 12% bland kontroller. Uppresningsförmågan försämrades enbart i kontrollgruppen. I interventionsgruppen, föll färre kvinnor (OR 0.46) och färre kvinnor hade uppresningssvårigheter (OR 0.21) 2004, jämfört med kontrollgruppen. Skillnaden sågs enbart bland de kvinnor som vid studiestarten 2001 hade nedsatt rörelseförmåga. Fysisk hemträning ökade i interventionsgruppen. I interventionsområdet hemtränade 34%. 54% medicinerade med calcium-vitamin D under 2004, och 20% hade deltagit i sjukgymnastledd gruppgymnastik 2003. För kvinnor som genomförde någon av dessa 3 interventioner var uppresningsförmågan förbättrad under 2004 (p=0.04-0.06), men för hemträning sågs förbättringen enbart bland de kvinnor som hade nedsatt uppresningsförmåga 2001. Två HF inträffade i interventionsgruppen jämfört med 11 bland kontrollerna, vilket ej var signifikant (p=0.23) OR 0.33.

Slutsatser

Våra frågeformulär var praktiskt användbara för prediktion av frakturrisk inom en äldre kvinnlig primärvårdsbefolkning. FRAMO Index med 4 frågor hade god prediktion för HF, men även för FF och mortalitet. Fler kvinnor rapporterade tidigare kotfrakturer om de fick en särskild fråga om ryggröntgen. FRAMO Index är möjligt att beräkna även utan ett frågeformulär, och gör det därför lätt att använda för att kunna förbättra riskskattning inom primärvård vid vanliga läkarbesök.

Låg bentäthet i häl var relaterad till ökad HF och FF risk, mätt med enklare bärbar DXL teknik. Osteoporos i häl var vanligt (60%) med T-score ≤ -2.5 SD. Osteoporos i höften motsvarade en bentäthet på -3.3 SD i hälen. Kliniska riskfaktorer kombinerade med en låg bentäthet (≤ -3.5 SD) i hälen avgränsade en liten riskgrupp på 11% med påtagligt hög HF risk under 2 år, vilka resultat bör verifieras i en större studie.

Kvinnor med nedsatt rörelseförmåga förbättrade sin uppresningsförmåga och minskade sin falltendens i interventionsgruppen jämfört med kontroller, rapporterat mer än 1 år efter inledd huvudintervention. Bland kvinnor med ökad HF risk i interventionsområdet så genomförde 15-54% fysisk hemträning, tidigare gruppträning eller hade calcium och D-vitamin behandling. Dessa interventioner visade sig var för sig vara relaterade till förbättrad uppresningsförmåga. HF incidensen mellan studieområdena visade ett icke-signifikant OR 0.33. Utvärderingsperioden bör förlängas för rörelseförmåga och HF incidens.

Detta program för riskvärdering och intervention mot fall och HF, med en varaktighet på 1-2 år, är troligen användbart inom en kvinnlig primärvårdsbefolkning. Resultaten bör bekräftas i en större studie, där även effekterna av upprepad intervention bör prövas.

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