EXERCISE AND RISK FACTORS OF OSTEOPOROTIC FRACTURES IN ELDERLY WOMEN

RAIJA KORPELAINEN

Faculty of Medicine,
Department of Public Health Science and General Practice, Department of Neurology,
University of Oulu;
Unit of General Practice, Oulu University Hospital;
Department of Sports Medicine,
Oulu Deaconess Institute

OU LU 2005
RAIJA KORPELAINEN

EXERCISE AND RISK FACTORS OF OSTEOPOROTIC FRACTURES IN ELDERLY WOMEN

Academic Dissertation to be presented with the assent of the Faculty of Medicine, University of Oulu, for public discussion in the Great Hall of the Deaconess Institute of Oulu (Uusikatu 50) on August 26th, 2005, at 12 noon

OU Lun Yliopisto, Oulu 2005
Abstract

The aim of this study was to examine lifestyle risk factors for low bone mass, falls and fractures, and to determine the effect of 30-month exercise trial on bone mass, balance, muscle strength and gait in elderly women. Reliability of an inclinometric method for assessing postural sway was evaluated.

Data on risk factors, falls and fractures were collected by questionnaires, and calcaneus and radius bone mass were measured from 1,222 women. Lifetime physical activity, low occupational physical activity, type 2 diabetes, hypertension, hormone replacement, thyroid hormone and thiazide use were associated with increased bone mass, while low current physical activity, high coffee intake and late menarche were associated with low bone mass in lean women. Factors associated with fractures were: low lifetime habitual physical activity, diabetes, living alone and calcaneum bone mass.

One hundred and sixty women with low femoral neck bone mass were randomly assigned to the exercise group (n = 84) or to the control group (n = 76). The outcomes included radius, proximal femur and calcaneus bone mass, postural sway, muscle strength, gait speed and endurance. Bone mineral density (BMD) at proximal femur decreased in the control group, while no change occurred in the exercise group. Mean trochanter bone mineral content (BMC) decreased more in the control group. The women in the exercise group improved their performance in walking speed and endurance, body sway and leg strength compared to the control group. There were six falls that resulted in fractures in the exercise group and 16 in the control group. The inclinometric method proved to be reliable.

In conclusion, lifestyle factors are determinants of bone mass in lean elderly women. Long-term exercise has a site-specific effect on BMC but not on BMD in elderly women. Weight-bearing exercise can modify risk factors for fractures, and may even prevent fall-related fractures in elderly women.

Keywords: balance, falls, lifestyle factors, muscle strength, population based, randomized
To my family
Acknowledgements

This study was carried out in the years 1997-2004 at the Department of Sports Medicine, Deaconess Institute of Oulu, Department of Public Health Science and General Practice, Unit of General Practice, Oulu University Hospital, and the Department of Neurology, University of Oulu. I owe my deepest gratitude to Professor Timo Takala and the Deaconess Institute of Oulu for offering excellent conditions during all stages of the work.

I wish to express my deepest gratitude to my supervisors, Professor Sirkka Keinänen-Kiukaanniemi, docent Juha Korpelainen from the Department of Neurology, University of Oulu and docent Jorma Heikkinen from the Clinic of Osteoporosis, Deaconess Institute of Oulu.

I want to especially thank Professor Keinänen-Kiukaanniemi for her encouragement and optimism during these years, and for the opportunity to work in the Department of Public Health and General Practice.

I would like to express my sincere thanks to the Head of the Clinic of Osteoporosis, Deaconess Institute of Oulu, docent Jorma Heikkinen, for introducing me to the subject and trusting me during these years. His expert guidance and enthusiasm have been extremely valuable during these years.

I would like to thank Professor Kalervo Väänänen for his encouragement in the beginning of the study, and for his valuable comments on original articles and especially on this thesis. His constructive criticism developed and improved the content of the thesis.

I express my sincere gratitude to my co-authors Hannu Kaikkonen and Ville Kampman for their contribution during the development of the method for assessing postural sway. I am also grateful to Ville Kampman for developing a new software for analyzing the strength measurements.

I am very grateful to the official referees, Professor Urho Kujala and Professor Heikki Kröger for their valuable comments and careful revisions of the manuscript.

I wish to thank Gordon Roberts and Anna Vuolteenaho for careful revision of the language of the original articles and thesis.

My sincere thanks go to my former and present colleagues and other staff in the Department of Sports Medicine, Deaconess Institute of Oulu, for their encouragement and friendship during these years. I realize it was sometimes hard to understand why,
when and what I was doing, and I am grateful to my colleagues, especially to Sari Pitkänen and Mirja Levo, for being so patient. I am most grateful to my colleague Tarja Pietarila-Heikkinen for her help with the exercise sessions and functional capacity tests.

I also wish to acknowledge Paavo Soini, late Paavo Mäkinen and Markku Koiranen from the Department of Public Health and General Practice, University of Oulu, for maintaining the computer systems and helping with the problems concerning computers. I wish to thank Arja Retsu for performing the hip bone density measurements during all these years. I also thank Sarianna Vaara for performing the first screening tests in 1997-1998, and performing the radial bone density measurements and calcaneal ultrasound measurements during the follow-up. I am deeply grateful to Professor Matti Uhari, docent Marjo Renko, docent Pentti Nieminen and Tytti Pokka for their excellent guidance during the three years in Clinical-Epidemiologic graduate school, Faculty of Medicine, University of Oulu. Those years taught me to find my way out of the dark forest called biostatistics, and finally I learned how fascinating the world of science can be.

I wish to express my warmest gratitude to my parents, Marjatta and Einar, for all their loving care and support over the years. There are no words to tell how grateful I am to them for their unselfish help whenever I needed it. My sister Kaisu and my brother Voitto deserve a big hug for just being the best little sister and big brother in the world. My sincere thanks go also to the families of my sister and brother for their friendship and many joyful moments. During the past few years, Kaisu has also been my boss, and I want to thank her for the good research facilities and inspiring spirit in the Department of Sports Medicine, Deaconess Institute of Oulu.

My thanks and warm hugs go to my dear mother-in-law Eila and father-in-law Aulis, for their encouraging positive attitude and interest in my work. I wish to thank Heini Korpelainen and Jari and Kuusma Rautio for their good company and many bright and happy moments, especially in their beautiful home town Porvoo.

I want to warmly thank my dear friend Katri Polojärvi for sharing so many exciting and sometimes dangerous weekends with heavy physical work full of sweat, laugh and tears. I warmly thank my friends Susanna and Jussi Lähdesmäki for their hospitality in Kuusamo and for many long, non-scientific conversations. I thank my dear friend Tuula Kuukasjärvi for being such a long-lasting friend. My warm thanks go to my friend and colleague Anna-Liisa Rasila for keeping my running shoes going on.

I am grateful to the subjects of this study, who volunteered to participate in spite of the long duration of the trial.

My warmest and loving thanks belong to my husband Juha for his love, encouragement and endless support throughout these years together. His optimism is never-ending, and without him I would have never completed this work. He has also been one of my main supervisors, and I am grateful for the systematic and logical way of solving problems that he has taught me.

My loving thanks go to my sunshines, Pekka and Paavo, who have taught me a lot of the basics of life. I am grateful to them for bringing so much life, joy and sometimes noise into my life.

This work was supported by the Ministry of Education, Juho Vainio Foundation, Finnish Cultural Foundation, Miina Sillanpää Foundation, the Research Foundation of Orion Corporation, Oulu University Scholarship Foundation and the Northern Ostrobothnia Hospital District.
Abbreviations

BMD bone mineral density
BMC bone mineral content
BMI body mass index
BMU basic multicellular unit
BUA broadband ultrasound attenuation
CI confidence interval
COG center of gravity
COP center of pressure
DXA dual-energy x-ray absorptiometry
GDS Geriatric Depression Scale
HSA hip structural analysis
MMSE Mini Mental State Examination
MRI magnetic resonance imaging
OR odds ratio
pDXA peripheral DXA
pQCT peripheral quantitative computed tomography
QCT quantitative computed tomography
QUS quantitative ultrasound measurement
RA radiographic absorptiometry
RR risk ratio
SD standard deviation
SOS speed of sound
TUG Timed Up and Go -Test
VDR vitamin D receptor
WHO World Health Organization
List of original articles

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


Contents

Abstract
Acknowledgements
Abbreviations
List of original articles
Contents
1 Introduction ................................................................................................................... 15
2 Review of the literature ................................................................................................. 17
   2.1 Aging skeleton........................................................................................................17
      2.1.1 Childhood and adolescence .............................................................................19
      2.1.2 Adulthood ........................................................................................................19
      2.1.3 Old age ............................................................................................................20
   2.2 Definitional osteoporosis and osteopenia ...............................................................22
   2.3 Epidemiology of the osteoporotic fractures............................................................23
   2.4 How to measure skeletal health ..............................................................................24
      2.4.1 Material properties of bone..............................................................................24
      2.4.2 Structural properties of bone ...........................................................................26
      2.4.3 Bone turnover ..................................................................................................27
   2.5 Risk factors for osteoporotic hip fractures in elderly women.................................29
      2.5.1 Genetic factors.................................................................................................29
      2.5.2 Bone mass and structure..................................................................................29
      2.5.3 Body weight.....................................................................................................30
      2.5.4 Physical activity................................................................................................31
      2.5.5 Muscle strength ...............................................................................................32
      2.5.6 Balance and gait ..............................................................................................33
      2.5.7 Other lifestyle factors ......................................................................................33
      2.5.8 Falls .................................................................................................................34
   2.6 Effect of exercise on risk factors for hip fracture ...................................................34
      2.6.1 Bone mass and structure..................................................................................34
      2.6.2 Muscle strength ...............................................................................................36
      2.6.3 Balance and gait ..............................................................................................36
      2.6.4 Falls .................................................................................................................37
3 Purpose of the present study.......................................................................................... 39
4 Subjects and methods ............................................................................................................ 40
  4.1 Study design .................................................................................................................. 40
  4.2 Subjects ....................................................................................................................... 40
  4.3 Methods ....................................................................................................................... 44
    4.3.1 Questionnaires ..................................................................................................... 44
    4.3.2 Anthropometry .................................................................................................... 44
    4.3.3 Bone measurements ......................................................................................... 45
    4.3.4 Balance and gait .............................................................................................. 46
    4.3.5 Maximal isometric strength ............................................................................. 47
    4.3.6 Exercise program .............................................................................................. 49
    4.3.7 Statistical methods ........................................................................................... 49
5 Results .................................................................................................................................. 52
  5.1 Determinants of bone mass, falls and fractures in elderly women (I,II) ............... 52
    5.1.1 Calcaneum ultrasound measurements .............................................................. 52
    5.1.2 Radius BMD measurements ............................................................................ 58
    5.1.3 Falls and fractures ............................................................................................ 59
  5.2 Effect of 30-month exercise program on risk factors for fractures (III, IV) ........... 61
    5.2.1 Bone mass (III) ................................................................................................. 62
    5.2.2 Maximal isometric strength (IV) ..................................................................... 65
    5.2.3 Balance and gait (IV) ...................................................................................... 65
    5.2.4 Functional capacity ......................................................................................... 66
  5.3 Reliability of the inclinometric method for assessing body sway (V) ................. 67
    5.3.1 Test-retest reliability ........................................................................................ 67
    5.3.2 Comparison of the methods ............................................................................. 68
6 Discussion ......................................................................................................................... 69
  6.1 Methodology (Studies I-V) ....................................................................................... 69
  6.2 Determinants of low bone mass (Studies I, II) .......................................................... 72
  6.3 Effect of exercise on risk factors for hip fractures ................................................... 73
    6.3.1 Bone mass (Study III) ...................................................................................... 73
    6.3.2 Muscle strength, balance and gait (Study IV) .................................................... 75
  6.4 Reliability of the inclinometric method (Study V) .................................................... 76
7 Conclusions ..................................................................................................................... 78
References
1 Introduction

Osteoporosis and related fractures are a devastating disorder with significant physical, psychosocial, and financial consequences. Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone structure, resulting in bone fragility and increased susceptibility to fracture (NIH 2000). The diagnosis of osteoporosis thus centers on assessment of bone mineral density (BMD) and quality. Since there are no satisfactory clinical means to assess bone quality, diagnosis of osteoporosis depends on the measurement of skeletal mass.

Hip fractures place the greatest demands on resources and have the greatest impact on patients because of increased mortality, long-term disability and loss of independence. Most hip fractures occur after the age of 70, and the predicted aging of populations will accentuate the burden of these fractures on health-care systems. In Finland, the absolute number of hip fractures is expected to triple in the period from 1997 to 2030. The age-adjusted incidence of fractures is also rising, suggesting that the trend can be partially explained by factors other than demographic changes (Kannus et al. 1999b). The risk of fracture increases proportionately with decrease in BMD (Marshall et al. 1996), and in 90% of all hip fracture cases, a fracture is sustained through a fall (Youm et al. 1999). More than three-quarters of all hip fractures occur in women (Cummings & Melton 2002).

Like other complex chronic diseases, the pathogenesis of bone fragility and hip fractures is multifactorial, and no single factor can completely account for their occurrence. The risk factors for osteoporosis, as reflected by low BMD, and the risk factors for fracture overlap, but are not identical. It has been estimated that 50-85% of the variance in bone mass, bone structure and bone turnover is genetically determined (Krall & Dawson-Hughes 1993, Gueguen et al. 1995, Arden et al. 1996, Garnero et al. 1996a), (Eisman 1999), but the heritability of fracture itself is low (Recker & Deng 2002, Seeman 2003a). In women, estrogen deficiency is the main factor in the pathogenesis of postmenopausal bone loss. At advanced ages, risk factors for fracture may operate by increasing bone fragility or by increasing the likelihood of falls. There are many clinical predictors of hip fracture that are independent of BMD (Cummings et al. 1995), and many fractures arise in women without osteoporosis (Kanis et al. 2002b). Suggested nonskeletal factors associated with the risk of falling and fractures include reduced balance
(Tinetti et al. 1988, Campbell et al. 1989, Nevitt et al. 1989, Lord et al. 1994), reduced lower limb strength (Campbell et al. 1989, Lord et al. 1994), reduced walking speed (Campbell et al. 1989, Nevitt et al. 1989), low physical activity (Cummings et al. 1995) and reduced visual acuity (Ooms et al. 1994). Other factors, which are independent of BMD, include bone turnover and bone quality (Woolf & Akesson 2003). The risk of fracture increases when several risk factors are present (Cummings et al. 1995).

Several studies have suggested that low body weight is associated with low BMD and fractures (Cummings et al. 1995, Burger et al. 1998, Dargent-Molina et al. 2000, van der Voort et al. 2001, Farahmand et al. 2003), but it is not known whether the association is due to hormones, nutrition, lifestyle, the amount of impact during weight-bearing activities, or other factors. Although many lifestyle factors, such as physical inactivity and sedentary work (Greendale et al. 1995, Kohrt et al. 1995, Weiss et al. 1998, Lunt et al. 2001), low calcium intake (Dawson-Hughes et al. 1997), high caffeine intake, smoking (Cummings et al. 1995, Burger et al. 1998) and high alcohol intake (Grainge et al. 1998) have been reported to place elderly women at risk of skeletal fragility, the relative importance of the effects of these lifestyle factors on bone health in elderly women is not fully established.

Many risk factors can be prevented or modified. Previous studies demonstrate that regular exercise can positively affect muscle strength even in the elderly (Fiatarone et al. 1990), but results concerning the impact of exercise on gait and balance in elderly women are conflicting, some reporting significant improvements (Sauvage, Jr. et al. 1992, Judge et al. 1993, Buchner et al. 1997, Carter et al. 2001b, Barnett et al. 2003), and others reporting weak to negligible effects (Lichtenstein et al. 1989, Crilly et al. 1989). Regular exercise has been suggested to prevent falls and fall-related fractures in older adults (Campbell et al. 1997, Kannus 1999). Exercise programs overall have been suggested to be effective (Chang et al. 2004), and a recently updated Cochrane review (Gillespie et al. 2003) concluded that home-based programs of balance retraining, walking and strength training may be the most effective. The type of exercise, however, has varied considerably between the trials, and in many studies the type of activity may not have been optimal to affect the known risk factors for falls and fractures. Previous studies have been performed on selected samples of healthy postmenopausal women, and the programs have usually lasted one year or less. Since most of the benefits of exercise are maintained only as long as the exercise regimen is maintained, longer follow-up studies are needed.

There is an urgent need to develop effective public health strategies for preventing fractures. Strategies to prevent fractures in an elderly population must ensure maximum bone strength, reduce the occurrence of falls, and reduce the trauma associated with falls. Identification of the determinants of bone fragility and fractures is of critical importance to help focus efforts on prediction of fractures in those at greatest risk. The aim of this population-based study was to investigate the contribution of lifelong lifestyle factors to bone mass, falls and fractures, and to evaluate the effectiveness of long-term weight-bearing exercises on risk factors for fractures in elderly women.
2 Review of the literature

2.1 Aging skeleton

The human skeleton is defined externally by its outer (periosteal) surface and by endocortical, trabecular and intracortical components of its inner (endosteal) surface. Cellular activity on these surfaces produces net bone formation or resorption during growth and aging, modifying the size, shape, architecture, mass and strength of the skeleton (Seeman 2002). The cross-sectional area (CSA) of the bone is defined by periosteal bone formation, whereas the proximity of the endocortical and periosteal surfaces (cortical thickness) is determined by endocortical bone formation. Thus, endocortical bone formation thickens the cortex, and endocortical resorption thins the cortex. Bone formation on each side of the trabeculae thickens them, whereas resorption thins them and makes them perforated and fragile. (Seeman 2002)

The skeleton serves several functions for the body: support, locomotion, protection of vital organs and housing of bone marrow. The primary function of bone is to be stiff, i.e. to resist deformation in response to both internal (primarily muscular) and external forces (Currey 2002). In addition, bone must also be sufficiently strong (resist breakage) in order to remain stiff. Bone strength can be increased and maintained by adding bone mass, by changing bone geometry to redistribute the forces (stress) that it must resist, or by alterations of its microstructure (Currey 2002). Throughout life, bones change in size, shape and position. Two processes guide these changes - modeling and remodeling. When a bone is formed at one site and broken down at a different site its shape and position is changed. This is called modeling. However, much of the cellular activity in bone consists of removal and replacement at the same site, a process called remodeling. (Seeman 2003b)
Fig. 1. Etiology of osteoporosis and fractures.
2.1.1 Childhood and adolescence

Osteoporosis is not always the result of bone loss, and bone fragility in the elderly may have its origin in growth (Seeman 2002) (Figure 1). An individual who does not reach optimal bone mass during childhood and adolescence may develop osteoporosis without the occurrence of accelerated bone loss. Hence, suboptimal bone growth in childhood and adolescence is an important factor in the development of osteoporosis (U.S. Department of Health and Human Services 2004). Peak bone mass is achieved as a result of growth and modeling (Matkovic et al. 1994, Haapasalo et al. 1996). European women achieve their peak bone mass between 16-26 years of age (Theintz et al. 1992, Teegarden et al. 1995, Haapasalo et al. 1996). Failure to achieve optimized bone mass at the end of adolescence leaves an individual with much less reserve to withstand the normal losses during later life. Most gains in bone mass during puberty are due to an increase in bone length and size rather than bone density (Katzman et al. 1991).

During childhood and adolescence bones are sculpted by modeling, which allows individual bones to grow in size and to shift in space. Bones grow because resorption occurs inside the bone while formation of new bone occurs in its outer (periosteal) surface. The cortex has a thickness determined by the growth of the endocortical surface relative to the periosteal surface. The increase in mass occurs in proportion to the enlarging whole bone, so the volumetric BMD is constant or increases slightly during growth, and is not different in boys and girls (Zamberlan et al. 1996). Thus, the greater strength of long bones in men vs. women is the result of differences in size and geometry, not density. During prepubertal growth, the extent of periosteal apposition and net endocortical resorption is similar in males and females, so that the dimensions of long bone cross-sections, periosteal diameter and cortical thickness do not differ. Sex differences in bone width are established during the peripubertal period. At puberty, long bone growth slows down, whereas axial growth accelerates. Cortical width increases by further periosteal apposition in males, while in females, periosteal apposition decreases and endocortical apposition increases (Bass et al. 1999, Bradney et al. 2000, Schoenau et al. 2000). Androgens, growth hormone and the growth hormone insulin-like growth factor I axis stimulate periosteal apposition in boys, whereas estrogens inhibit periosteal apposition, resulting in narrower bone in girls than in boys. Estrogen stimulates endosteal apposition in girls. Thus boys build larger, longer and wider bones with a slightly thicker cortex than girls. The cortical mass is placed further from the neutral axis of the long bone in males, conferring greater resistance to bending. (Seeman 2003a)

2.1.2 Adulthood

After the cessation of longitudinal growth, the adult skeleton is continuously remodeled by the removal of old matrix and the deposition of new bone by a team of juxtaposed osteoclasts and osteoblasts, comprising the so-called basic multicellular unit (BMU). Osteoblasts, the bone-forming cells, are fibroblast-like cells derived from mesenchymal cells. They are localized on endosteal bone surfaces, in Haversian systems, and also occasionally on periosteal surfaces. (Aubin 1998) The two major proteins produced by
osteoblasts are type I collagen and osteocalcin. Osteoclasts originate from macrophage-like cells, and are involved in the actual resorption of bone by secreting proteolytic enzymes and hydrogen ions that are required for removal of the deposited matrix. Osteoclasts resorb a volume of bone, leaving a focal resorptive cavity on the trabecular and endocortical surfaces or a cutting cone within the cortex. After a delay, osteoblasts fill the cavity with a volume of new bone that undergoes rapid primary and then slower secondary mineralization (Boyce et al. 1999, Manolagas 2000). Provided that the volumes of bone removed and replaced within each remodeling or BMU are the same, no net bone loss or structural damage occurs. For bone to be lost, the volume of bone resorbed must be greater than the volume of bone formed (Seeman 2003a). The resorption process is regulated by systemic and local factors that affect both osteoblasts and osteoclasts. Bone remodeling is regulated by polypeptides, steroid and thyroid hormones, as well as local factors that are produced by skeletal cells and include growth factors, cytokines, and prostaglandins (Manolagas & Jilka 1995, Marie 1997). Circulating hormones may act on skeletal cells either directly or indirectly by hormone receptor activation or by modulating the synthesis of receptors associated with bone formation and bone resorption (Manolagas & Jilka 1995). BMD decreases at the spine and proximal femur in women before menopause (Riggs et al. 1986, Gilsanz et al. 1988). Bone is lost during the early adult years in men and women because the negative BMU balance probably begins in the third decade, before menopause in women. Bone loss accelerates in women at menopause because estrogen withdrawal increases the rate of bone remodeling (Parfitt 1994, Manolagas & Jilka 1995, Manolagas et al. 1995). More bone is resorbed than replaced, producing a negative BMU balance, which is the basis of bone loss (Seeman 2003a). Furthermore, an increase in bone marrow adiposity is observed, resulting in further reduction in trabecular bone volume (Rozman et al. 1989).

A recent population-based study (Riggs et al. 2004) revealed that at both central and peripheral sites, young adult men had 35-42% larger bone cross-sectional areas than women, consistent with their larger body size. Young adult women had a bone mass that was 18-21% less than in young adult men. Bone area increased equally over life in both sexes by 15% at central sites and by 16% and slightly more in men at peripheral sites. Decreases in trabecular BMD began before midlife and continued throughout life, whereas cortical BMD decreases began in midlife. Average decreases in trabecular BMD were greater in women than in men at central sites, whereas they were similar at peripheral sites (Riggs et al. 2004).

### 2.1.3 Old age

Bone material and structural properties degrade with age because the mechanisms constructing (modeling) and reconstructing (remodeling) the skeleton eventually fail (Seeman 2002). Remodeling repairs microdamage; however, during aging, less bone is deposited than removed in each remodeling or BMU. The increased remodeling and negative bone balance produce bone loss, trabecular thinning and loss of connectivity, cortical thinning and porosity. Older, more mineralized interstitial bone accumulates microdamage, while more superficial bone is replaced with younger less mineralized
bone, reducing stiffness (Duan et al. 2001). During aging changes take place in trabecular bone, cortical bone and bone marrow. Reductions in trabecular volume, number, and width have been shown in specimens of older bones (Parfitt et al. 1983, Bergot et al. 1988). These alterations are due to many factors, including changes in gonadal status, nutrition and physical activity. Despite the accelerated loss of bone in women, the overall loss of trabecular bone in men and women is similar in quantitative terms, suggesting that trabecular bone loss continues longer in men than in women (Seeman 2003a).

Late in life, endocortical and intracortical remodeling increases and bone loss comes primarily from cortical bone, because remodeling is surface-based and the surfaces within cortical bone increase due to increased intracortical porosity (Seeman 2003a). Thus, besides a reduction in trabecular bone volume in the elderly, there is also a reduction in cortical bone (McCalden et al. 1993). The reduction in cortical bone is mainly attributed to bone resorption on the endosteal surface that occurs at a greater rate than periosteal appositional growth. The result is a reduction in cortical bone width as aging progresses (Parfitt 1984, McCalden et al. 1993). As the cortical bone gets thinner, the bone at the interface adjacent to cancellous bone becomes porous, bearing more resemblance to cancellous than cortical bone (Parfitt 1984, Bousson et al. 2001). As people get older, resorption occurs on inner surfaces while formation occurs on outer surfaces, which can partially compensate for the loss of strength due to the thinning of the cortex. Bone modeling by periosteal apposition reduces compressive stress by distributing loads on a larger area, thus maintaining bending strength (Duan et al. 1999, Duan et al. 2001). It has been suggested that the true material density of bone tissue remains quite constant with age (Sievanen et al. 1999a), whereas the size, geometry and trabecular architecture of bones vary considerably between different sites and individuals, and like other bones, the femoral neck expands slowly with aging (Heaney et al. 1997, Beck et al. 2000, Crabtree et al. 2000, Beck et al. 2001, Kaptoge et al. 2003b). Periosteal apposition continues slowly on the shafts of long bones, so that the external dimensions of the diaphyses of a 70-year-old’s bones may be subtly thicker than they were in young adulthood, but the cortices will be substantially thinner (Lazenby 1990).

A recent population-based study revealed that the relative differences in bone cross-sectional area in favor of men are largely maintained over life (Riggs et al. 2004). With aging, the cortical area decreased slightly, and the cortex was outwardly displaced by periosteal and endocortical bone remodeling. Over life, cortical BMD decreased more in women than in men, consistently with menopausal-induced increases in bone turnover and bone porosity (Riggs et al. 2004).

While osteoporosis occurs in both sexes, it is two to three times more common in women than men. This is partly due to the fact that women have two phases of age-related bone loss - a rapid phase that begins at menopause and lasts 4-8 years, followed by a slower continuous phase that lasts throughout the rest of life, while men go through only the slow, continuous phase (Riggs et al. 2002). The rapid phase of bone loss in women results in losses of 5-10 percent of cortical bone and 20-30 percent of trabecular bone. The slow phase of bone loss results in losses of 20-25 percent of cortical and trabecular bone over a long period of time (Riggs et al. 2002). Both the rapid phase and the slow phase of bone loss in aging women appear to be largely the result of estrogen deficiency. The rapid phase is initiated by a dramatic decline in estrogen production by the ovaries at menopause. The loss of estrogen action on estrogen receptors in bone
results in large increases in bone resorption combined with reduced bone formation. The end result is thinning of the cortical outer shell of bone and damage to the trabecular bone structure (Ahlborg et al. 2003). The slower phase of bone loss is thought to be caused by a combination of factors including age-related impairment of bone formation, decreased calcium and vitamin D intake, decreased physical activity, and the loss of estrogen’s positive effects on calcium balance in the intestine and kidney as well as its effects on bone (Riggs et al. 2002).

2.2 Definitional osteoporosis and osteopenia

Osteoporosis is a complex disorder of bone tissue with multifactorial origin characterized by compromised bone strength, predisposing to an increased risk of fracture (NIH 2000). The clinical consequence of osteoporosis is a fracture.

The diagnosis of osteoporosis is currently based on BMD measurement at the hip, most commonly with dual-energy x-ray absorptiometry (DXA), expressed as grams of mineral per area or volume. In 1994, a working group of the World Health Organization (WHO) developed a classification system for osteoporosis for women based on BMD using the known gradient of the risk of fracture in the population as a whole. They sought to define osteoporosis so that the proportion of individuals identified as having osteoporosis would be related to the lifetime risk of fracture in the population. Four general diagnostic categories were proposed for assessments done with DXA (Table 1) (Kanis 1994, World Health Organization 1994, Kanis 2002). BMD in young healthy adults is normally distributed. An individual’s BMD can be compared to the mean value in a reference population, such as young healthy adults. The difference between an individual’s BMD and the mean BMD for the reference population can be expressed in standard deviation (SD) units; a score of 0 indicates BMD equal to the mean; a score of +1 indicates one standard deviation above the mean, and a score of -1 is one standard deviation below. When an individual’s BMD is compared to the mean BMD score in a young healthy population, this standard deviation measurement is referred to as a T-score. The T-score is calculated using the following formula: T-Score = patient’s BMD – young normal mean/Standard Deviation of young normal mean (U.S. Department of Health and Human Services 2004). Thus, osteoporosis is defined as a BMD value ≥2.5 standard deviations (SD) below the reference mean of women 20–29 years of age. It should be noted that the classification is based solely on BMD values, while a more general description of osteoporosis also includes changes in microarchitecture and strength.

The risk of fracture increases proportionately with decrease in BMD at any site (Marshall et al. 1996). However, fractures do also occur in women who have normal BMD: the lifetime risk of hip fracture for a white woman aged ≥ 50 years who has normal BMD is 10% to 17% (Cummings et al. 2002). Furthermore, a recent large multicenter study revealed that BMD was not a predictor of upper limb fractures (Kaptoge et al. 2005).
Table 1. Diagnostic categories for osteoporosis determined with DXA.

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
<th>T score value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Hip BMD&lt;1 SD below the young adult female mean</td>
<td>≥-1</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>Hip BMD 1-2.5 SD below the young adult female mean</td>
<td>&lt;-1 and &gt;-2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Hip BMD ≥ 2.5 SD below the young female adult mean</td>
<td>≤-2.5</td>
</tr>
<tr>
<td>Severe osteoporosis</td>
<td>Hip BMD ≥ 2.5 SD below the young female adult mean in the presence of one or more fragility fractures</td>
<td>≤-2.5 + fracture</td>
</tr>
</tbody>
</table>

*(Patient's BMD - young normal mean/SD of young normal mean)*

Osteoporosis is further classified into primary and secondary osteoporosis. Secondary osteoporosis is associated with several medical disorders, such as chronic diseases and medications. The most common type of osteoporosis is known as primary osteoporosis - that is, osteoporosis not caused by some other disorder or medication. Primary osteoporosis is mainly a disease of the elderly, the result of the cumulative impact of bone loss and deterioration of bone structure that occurs as people age. Since postmenopausal women are at greater risk, the term postmenopausal osteoporosis is also used (Seeman 2003a).

2.3 Epidemiology of the osteoporotic fractures

Kanis et al. (Kanis et al. 2001) defined osteoporotic fractures as occurring at a site associated with low BMD and which at the same time increased in incidence after the age of 50 years. The following fractures in women are considered to be due to osteoporosis: vertebral fractures, hip fractures, wrist-forearm fractures, humeral fractures, other femoral fractures, rib fractures, pelvic fractures, clavicular, scapular and sternal fractures, and tibial and fibular fractures. Hip fractures are the most severe complications of osteoporosis, and in most parts of the world, they result in hospitalization and are fatal up to 20-30% of the time during the first year after the fracture. An increase in mortality has been reported especially in persons with reduced mental or somatic health and low physical ability (Meyer et al. 2000). Hip fracture patients also have an increased risk of long-term disability and loss of independence, and only 50% of the patients regain their prefracture status as judged by the ability to walk and the need for aids at home (Sernbo & Johnell 1993, Meyer et al. 2000, Willig et al. 2001).

The lifetime risk for a hip, spine or forearm fracture at the age of 50 years in women has been estimated to be 40% - 46% (Melton, III et al. 1992, Kanis et al. 2001), and in industrialized societies, the lifetime risk of hip fracture is about 18% in women (Meunier 1993). Prevalence of hip fractures increases from about 3 per 100 women aged 65-74 to 12.6 per 100 women aged 85 or older (Hochberg et al. 1998). This rise in fracture risk results from an age-related decrease in BMD and an age-related increase in falls, which are responsible for at least 90% of all hip fractures (Youn et al. 1999). The mean age of hip fracture has been reported to be 80 years for women in Scandinavia (Kanis et al. 2002a). In 1990, there were 1.7 million hip fractures worldwide; with changes in population demographics, this figure is expected to rise to 6 million by 2050 (WHO Scientific Group 2003). The steepest increases will be observed in Asia and Latin
America due to the greater increase in population size in those regions. The absolute number of hip fractures in Finland increased fivefold from 1968 to 1998, and the number is expected to triple in the period from 1997 to 2030 (Kannus et al. 1999b, Luthje et al. 2001). The age-adjusted hip fracture incidence has also risen, from 292/100,000 in 1970 to 467/100,000 in 1997 among women aged 50 or over in Finland, suggesting that the trend is partially explained by other than demographic changes (Boyce & Vessey 1985, Kannus et al. 1996, Kannus et al. 1999a). The risk of fracture varies markedly in different countries, and this is best documented in the case of hip fracture risk (Kanis et al. 2002a). The age- and sex-adjusted hip fracture rates are higher in northern Europe than in southern Europe (Kanis et al. 2002a).

2.4 How to measure skeletal health

A fracture occurs when the load applied generates an internal stress that exceeds the strength of the material (bone) (Jepsen 2003). As such, fracture risk is related to bone strength, and in order to understand why bones break, it is necessary to examine the factors that affect bone strength (Bouxsein 2003a, Bouxsein 2003b). Bone is a complex, damageable, viscoelastic composite material, and its strength is affected by a number of mechanical properties. Skeletal fragility is influenced by bone size, shape, structure, microarchitecture, material properties and quantity of the tissue. These are affected by the rate of bone turnover (Felsenberg & Boonen 2005). Thus, age-related increase in fracture risk cannot be fully explained by BMD alone, and therefore, noninvasive techniques for measuring structural properties and quality of bone are needed. The limitations of the presently available techniques include cost, availability, and clinical meaningfulness (Felsenberg & Boonen 2005).

2.4.1 Material properties of bone

The material properties of bone include its mineral and collagen composition as well its microdamages (Felsenberg & Boonen 2005). Bone tissue is principally composed of inorganic bone apatite crystals that mineralize an organic type I collagen matrix. The degree of mineralization, the material properties of the collagen matrix, crystal size, and the mineral-to-matrix ratio are all important for bone strength (Boivin et al. 2000, Ottani et al. 2001, Follet et al. 2004). Bone densitometry measurements reflect the degree of mineralization of the bone, but they cannot distinguish whether the decrement in density is the result of lost bone mass and content, or whether bone turnover is occurring at a higher rate, replacing more mineralized old bone with less mineralized new bone. Thus, BMD and the degree of mineralization are not interchangeable (Meunier & Boivin 1997). Reduced concentration of collagen cross-links in bone has been suggested to result in reduction of the material strength of the bone trabeculae and increased risk of fractures in individuals with osteoporosis (Oxlund et al. 1996, Paschalis et al. 2004). Summary of the different densitometry techniques is presented in Table 2.
The most commonly used central method for the measurement of BMD or bone mineral content (BMC) is DXA, and it has been adopted as the golden standard for bone mass measurements. The radiation dose is comparable to daily background radiation exposure (Njeh et al. 1999) and the precision (coefficient of variation, CV%) is 1-2% (Fogelman & Blake 2000b). With the newest DXA, both the spine and the hip can be scanned in a few minutes. Owing to the plane image of DXA, the measurement obtained is the BMC per unit projected bone area of the bone in the coronal plane, or an areal BMC (g/cm²). BMC per unit projected area is called BMD (Seeman 2001). Thus, DXA only measures areal BMD values, not true volumetric density (g/cm³) and, because wider bones are also thicker, it overestimates substantially the BMD of larger bones, significantly confounding the interpretation of age- and sex-related changes (Seeman 1997). Furthermore, an increase in the projected area as a result of increased bone size, e.g. from subperiosteal expansion, would lead to a decrease in BMD even if the BMC remains unchanged (Carter et al. 1992, Seeman 1997). On the other hand, this type of subperiosteal expansion has been shown to increase structural rigidity of long bones independently of the BMC (Beck et al. 2000, Beck et al. 2001). Thus, it has been suggested that studying geometry along with conventional bone measurements could lead to a better understanding of the processes leading to increased fracture risk.

Peripheral DXA (pDXA) is a peripheral application of the central DXA for measuring bone density. The radiation dose is extremely low and the precision 1-2% (Fogelman & Blake 2000b). Peripheral DXA is predictive of fractures, but does not predict hip or vertebral fractures as well as central DXA. However, peripheral measurements are cheaper than central DXA and are thus more easily available for clinical use (Cummings et al. 2002).

Quantitative computed tomography (QCT) has been applied both to the appendicular skeleton and to the spine. QCT has the advantage of determining the true three-dimensional, volumetric bone density of both trabecular and cortical compartments of bone (Genant et al. 1996). Cancellous bone is more responsive than cortical bone to many interventions. Computed tomography can therefore be used to monitor the effect of treatment (Genant et al. 1996). Additionally, the technique avoids the effect of degenerative disease, a particular drawback to DXA at the spine. The main disadvantages of computed tomography are high exposure to radiation, difficulties with quality control, and high cost compared to DXA (Kanis 2002). Peripheral QCT (pQCT) has lower radiation dose and cost, and it has been found to be useful for measurement of appendicular skeleton (Genant et al. 1996, Sievänen et al. 1998).

Radiographic absorptiometry uses conventional x-rays of the phalanges to assess bone density in the hand (Gluer et al. 1997). The radiographic image is captured on a personal computer and then processed automatically using a specially developed software application. The main advantage of RA is its potential for general use on the basis of the widespread availability of conventional film radiography. Furthermore, it seems to predict fracture risk as well as DXA (Bouxsein et al. 1997).

The only established methods for noninvasive assessment of bone status that do not require radiation are ultrasound-based techniques measuring ultrasound velocity (speed of sound, SOS) and broadband ultrasound attenuation (BUA) at the calcaneus and other bone sites. Quantitative ultrasound measurements (QUS) of the heel could possibly yield information about the qualitative mechanical properties of bone and bone strength in
addition to the ability to reflect bone density and fracture risk (Agren et al. 1991, Kaufman & Einhorn 1993, Turner et al. 1995, van Daele et al. 1996a). Ultrasonographic heel measurements have been found to predict the risk of hip fracture in elderly women living at home equally to DXA of the hip (Hans et al. 1996). The clinical usefulness of the QUS method is limited by its relatively poor precision (1-5%) (Gluer 1997).

Table 2. Different bone densitometry techniques*.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Regions of interest</th>
<th>Units reported</th>
<th>Precision (%CV)</th>
<th>Radiation exposure (μSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXA</td>
<td>Spine, hip, total body</td>
<td>BMD (g/cm²)</td>
<td>1%-2%</td>
<td>1-10</td>
</tr>
<tr>
<td>pDXA</td>
<td>Radius, calcaneus</td>
<td>BMD (g/cm²)</td>
<td>1%-2%</td>
<td>0.1</td>
</tr>
<tr>
<td>QCT</td>
<td>Spine</td>
<td>BMD (g/cm²)</td>
<td>3%</td>
<td>50-500</td>
</tr>
<tr>
<td>pQCT</td>
<td>Radius, Tibia</td>
<td>BMD (g/cm³)</td>
<td>1%-2%</td>
<td>1-3</td>
</tr>
<tr>
<td>RA</td>
<td>Phalanx</td>
<td>BMD (g/cm²)</td>
<td>1%-2%</td>
<td>10</td>
</tr>
<tr>
<td>QUS</td>
<td>Calcaneus, tibia, multisite</td>
<td>BUA (dB/MHz)</td>
<td>0.1%-5%</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOS (m/s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>Peripheral, multisite</td>
<td>app. BV/TV (%)</td>
<td>2%-9%</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>app. Tb.Th (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>app. Tb.N (mm⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>app. Tb.Sp (mm)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Modified from (Fogelman & Blake 2000b, Newitt et al. 2002b). DXA, dual energy x-ray absorptiometry; pDXA, peripheral DXA; QCT, quantitative computed tomography; pQCT, peripheral QCT; RA, radiographic absorptiometry; QUS, quantitative ultrasound; BUA, broadband ultrasound attenuation; SOS, speed of sound; MRI, magnetic resonance imaging; app. BV/TV, apparent bone volume fraction; app. Tb.Th, apparent trabecular thickness; app. Tb.N, apparent trabecular number; app. Tb.Sp, apparent trabecular separation

2.4.2 Structural properties of bone

The structural properties of bone include its geometry (size and shape) as well as its microarchitecture (trabecular architecture and cortical thickness/porosity) (Felsenberg & Boonen 2005).

Conventional pelvic radiography is widely available at low cost, and it offers sufficient spatial resolution and contrast to assess the macroscopic structure of the proximal femur (Gluer et al. 1994a). Several studies using pelvic radiography measurements have revealed an association between proximal femur geometry and the risk of hip fracture in postmenopausal women, but the measured variables reflecting hip structure have been mutually conflicting in these studies (Gluer et al. 1994a, Peacock et al. 1995, Karlsson et al. 1996, Michelotti & Clark 1999).

Linear and angular geometric parameters of the proximal femur and their relation to the risk of hip fracture risk have also been measured from DXA scans. Beck et al. (Beck et al. 1990, Beck et al. 2000) have developed a method called hip structural analysis (HSA) that uses areal BMD for measurements made by DXA at the femoral neck to estimate cross-sectional geometry and indices of bone strength, but this approach
provides only rough approximation of these structural indices (Duan et al. 2003). There is evidence (Melton et al. 2005) that direct measurement of hip BMD is as effective as HSA in predicting fracture risk. Some studies have shown increased hip axis length measured with DXA to be an independent risk factor for hip fractures in postmenopausal women (Faulkner et al. 1993, Boonen et al. 1995), while controversial findings also exist (Center et al. 1998, Dretakis et al. 1999, Alonso et al. 2000).

QCT makes it possible to describe true cross-sections in vivo, and it is able to determine the true three-dimensional, volumetric bone density of both trabecular and cortical bone separately (Genant et al. 1996). Cortical and trabecular areas can be differentiated from each other, and the true geometry of the bone can be described. The most sophisticated pQCT devices incorporate multislide data acquisition capability, which could potentially give a more representative three-dimensional picture of bone size, structure and entire body strength (Genant et al. 1996).

QUS of the heel could possibly yield information about the qualitative mechanical properties of bone and bone strength that cannot be measured with absorptiometric techniques alone, and it has been shown to predict risk of fractures (Agren et al. 1991, Kaufman & Einhorn 1993, Turner et al. 1995, Hans et al. 1996, Heaney & Kanis 1996, van Daele et al. 1996a). QUS has been shown to reflect bone structure, and a combined analysis of QUS and BMD has been suggested to allow for a more comprehensive assessment of skeletal status than either method alone (Gluer et al. 1994b). Most QUS devices use calcaneus as the measurement site, because it encompasses a large volume of trabecular bone and is readily accessible for transmission measurements (Fogelman & Blake 2000b). BUA is reduced in patients with osteoporosis, because there are fewer trabeculae in the calcaneus to attenuate the signal, and SOS values are reduced because, with the loss of mineralized bone, the elastic modulus of bone is decreased (Fogelman & Blake 2000b).

Magnetic resonance imaging (MRI) permits visualization of musculoskeletal tissues without using ionizing radiation. Clinical high-resolution MRI scanners have recently reached sufficient spatial resolution to quantify microstructural parameters of trabecular bone at peripheral skeletal sites in vivo (Ouyang et al. 1997, Link et al. 1999, Majumdar et al. 1999, Laib et al. 2002, Newitt et al. 2002a). These parameters typically include apparent bone volume fraction, apparent trabecular thickness, apparent trabecular number, and apparent trabecular separation. Previous studies have reported only moderate correlations between structural indices of trabecular bone and bone density (Ouyang et al. 1997, Majumdar et al. 1999, Newitt et al. 2002a, Link et al. 2003), suggesting that microstructural parameters may contribute independent information in predicting bone strength.

### 2.4.3 Bone turnover

The bone turnover rate is a function of the bone renewal process, including both modeling and remodeling processes, in which old or damaged bone is resorbed and new bone is created to replace it (Felsenberg & Boonen 2005). BMD is a static measure of bone composition, reflecting its "history", and detectable changes take an extended period
of time (years). In the past 10 to 15 years, several assays measuring biochemical markers of bone turnover have been developed. Biochemical markers of bone metabolism measured from serum or urine offer inexpensive and generally available tools for detecting short-term changes in bone metabolism in the whole skeleton. While these markers are of limited use for diagnosis, they offer the advantage of a short time frame (months) for assessment of changes in the rates of bone turnover, and changes in bone markers predict improvement in bone density and strength (Nishizawa et al. 2001).

Bone metabolic markers have been traditionally classified into two categories 1) Bone formation markers that are released by osteoblasts and are measured from serum or plasma and 2) Bone resorption markers that are released from bone matrix or osteoclasts during bone resorption and are measured from urine or serum (Delmas et al. 2000, Seibel 2000, Looker et al. 2000). Osteocalcin has been considered to be a marker of osteoblastic function. However, it was recently shown also to be released during bone resorption, and the authors suggested that it should be considered a marker of bone turnover rather than a marker of formation (Ivaska et al. 2004). Most of the bone metabolic markers are present in tissues other than bone and may therefore be influenced by nonskeletal factors (Delmas et al. 2000). Different markers reflect different steps in bone formation and resorption. They reflect enzymatic activity of the bone cells, excess products from the formation or fragments released during the degradation of matrix components (Gerdhem et al. 2004). The list of principal current markers of bone formation, resorption and turnover is given in Table 3.

Table 3. Currently available bone biochemical markers.

<table>
<thead>
<tr>
<th>Formation markers</th>
<th>Resorption markers</th>
<th>Turnover markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total alkaline phosphatase</td>
<td>Hydroxyproline</td>
<td>Osteocalcin</td>
</tr>
<tr>
<td>Bone alkaline phosphatase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I collagen propeptides</td>
<td>Hydroxylysine-glycosides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Free and total pyridinolines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Free and total deoxypyridinolines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type I collagen telopeptides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bone sialoprotein</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tartrate-resistant acid phosphatase 5b</td>
<td></td>
</tr>
</tbody>
</table>

Bone markers are increased after the menopause, and the results of several studies indicate that the rate of bone loss varies according to the marker value. Thus a potential clinical application of biochemical indices of skeletal metabolism could be in assessment of fracture risk. Findings of prospective studies indicate an association between osteoporotic fracture and indices of bone turnover, independently of bone density in elderly women (Garnero et al. 1996b). In elderly women, increased levels of biochemical markers of bone turnover, more specifically of bone resorption, have been shown to predict fractures independently of BMD, and in particular fractures that engage trabecular bone, possibly because of trabeculae perforation that decreases bone strength (Riis et al. 1996, van Daele et al. 1996b, de Vernejoul 1998, Garnero et al. 2000, Johnell et al. 2002, Gerdhem et al. 2004). In elderly women with values for resorption markers that exceed the reference range for premenopausal women, fracture risk is increased about two-fold.
after adjustment for BMD. These results suggest that a combined approach with BMD and indices of bone turnover could improve fracture prediction in elderly women (Johnell et al. 2002)

2.5 Risk factors for osteoporotic hip fractures in elderly women

2.5.1 Genetic factors

Findings of the studies over the last 30 years in twins and family members have established that differences in traits such as bone size, shape, and BMD between individuals of the same age are largely attributable to differences in their genes (Peacock et al. 2002). It has been estimated from twin studies that 50-85% of the variance in BMD, quantitative ultrasound, femoral neck geometry and bone turnover markers is genetically determined (Krall & Dawson-Hughes 1993, Gueguen et al. 1995, Arden et al. 1996, Garnero et al. 1996a). Although associations between these traits and polymorphisms in candidate genes encoding type I collagen, estrogen, androgen, vitamin D receptors, and many local factors have been reported, the associations are inconsistent (Seeman 2003a). In human subjects, no gene has been shown to account for differences in formation or thickening of trabecular numbers, endosteal remodeling, activation frequency, the volumes of bone formed or periosteal apposition. Nor is there any evidence reporting that individuals with a given genotype are more sensitive to calcium supplementation or exercise (Seeman 2003a).

Although a family history of fracture is a risk factor (Cummings et al. 1995), the heritability of fracture itself is relatively low (25-35%) (Recker & Deng 2002), and no gene has been shown to identify individuals at risk for fractures (Seeman 2003a).

2.5.2 Bone mass and structure

According to previous studies, BMD has been suggested to be the best single predictor of fracture risk. The incidence of hip fractures is increased in women with low central and peripheral BMD, and the lower the bone density, the higher the risk of hip fracture (Kanis et al. 1994, Lips 1997, Miller et al. 2002, Taylor et al. 2004). Nonetheless, the proportion of fractures attributable to osteoporosis is modest, ranging from <10% to 44% based on the most commonly used definition of osteoporosis (BMD T-score < -2.5) (Marshall et al. 1996, Stone et al. 2003). Data from the National Osteoporosis Risk Assessment in elderly women show that more than two-thirds of hip fractures occur in women who were not classified as osteoporotic (Siris et al. 2001). Ultrasonographic measurements of the calcaneus have been shown to predict the risk of hip fracture in elderly women living at home equally well as DXA of the hip both in cross-sectional and prospective studies (Hans et al. 1996, Welch et al. 2004, Khaw et al. 2004). Measurements of ultrasound speed and attenuation are also associated with the risk of hip fracture in elderly women in the upper third of BMD (Robbins et al. 2005). In the most comprehensive report to date,
a wide set of potential risk factors for hip fracture was assessed in the Study of Osteoporotic Fractures, a prospective study of 9,516 white and Asian-American women (Cummings et al. 1995). Hip fracture incidence was 17 times greater among the women who had five or more of the risk factors, exclusive of bone density, compared to women with two or less risk factors.

In the past decade, several measures of hip structure and geometry have been studied as possible risk factors for hip fracture, because the strength of an object is also a function of its geometry according to basic engineering principles (Karlsson et al. 1996). Increased hip axis length (HAL), femoral neck length (FNL), neck shaft angle (NSA) and femoral neck width (FNW) have often been considered independent risk factors for fractures, but studies have not always shown this to be the case (Faulkner et al. 1993, Gluer et al. 1994a, Boonen et al. 1995, Karlsson et al. 1996, Center et al. 1998, Dretakis et al. 1999, Michelotti & Clark 1999, Gnudi et al. 1999, Alonso et al. 2000, Partanen et al. 2001, Crabtree et al. 2002, Gnudi et al. 2002, Bergot et al. 2002). Some studies have revealed that elderly women with hip fractures have reduced cortical thickness, but increased femoral neck periosteal diameter (Duan et al. 2003, Filardi et al. 2004). The most recent study showed no improvement in fracture prediction by HSA compared to the direct assessment of BMD (Melton et al. 2005). On the contrary, Karlamangla et al. (Karlamangla et al. 2004) found that bone size and body size factors contributed to hip fracture risk independently of areal BMD, and that composite femoral neck strength indices constructed from DXA measurements improved hip fracture assessment.

2.5.3 Body weight

In elderly women, low body weight and weight loss, low body mass index (BMI) and low fat mass have been suggested to be associated with reductions in bone mass in the total body, lumbar spine, hip region and radius (Lindsay et al. 1992, Reid et al. 1992, Bauer et al. 1993, Edelstein & Barrett-Connor 1993, Felson et al. 1993, Ooms et al. 1993, Holbrook & Barrett-Connor 1993b, Flier et al. 1995, Glauber et al. 1995, Aloia et al. 1995, Orwoll et al. 1996, Burger et al. 1998, Dargent-Molina et al. 2000, van der Voort et al. 2001, Reid 2002, Wildner et al. 2003, Gerdhem et al. 2003b), although there is some discordance among these studies as to the relative importance of lean or fat mass in predicting bone mass. The differences in the study results may reflect differences in study design; for example, in Aloia's study (Aloia et al. 1995) obese women were excluded. Data from previous studies (Nguyen et al. 1998, Dennison et al. 1999, Hamann et al. 2000, Knoke & Barrett-Connor 2003) have also indicated that changes in weight are associated with concurrent changes in bone density at the hip in older women. The strength of the association between fat and lean mass and BMD probably depends on the age of the population studied. After the menopause, fat mass and weight increase while lean mass decreases (Evans 1992).

The positive relationship between increased weight and increased BMD may partly be a result of increased mechanical forces on the bone (Slemenda 1995), higher levels of sex hormones and their precursors (Ribot et al. 1988, Edelstein & Barrett-Connor 1993, Tremolieres et al. 1993, Reid et al. 1993), and lower bone turnover (Ribot et al. 1988).
Although DXA measurement is currently the golden standard technique for osteoporosis diagnosis, it has limitations; i.e. artefacts due to a degenerative disease or fat folds overlying the proximal femur that may confound BMD results in a nonion manner, particularly so for osteopenic, osteoporotic, and elderly patients (Binkley et al. 2003, Bolotin et al. 2003). Positive correlations between soft tissue anthropometrics and BMD may also be confounded by these inaccuracies (Bolotin et al. 2003). Furthermore, bone densitometry provides only a two-dimensional areal view of the three-dimensional bone. The length and width of the scanned bone is known, but not its depth. Thus, a bone with greater depth will attenuate more photons and will be reported as being denser. The fact is, the bone is not more denser, it is just larger, and the association between weight and bone density might be a pure misconception due to this technical limitation (Seeman 2001).

Both low body weight, low BMI, weight loss and low triceps skinfold thickness have also been associated with an increase in hip fracture risk in older women (Kiel et al. 1987, Farmer et al. 1989, Paganini-Hill et al. 1991, Cummings et al. 1995, Ensrud et al. 1997a, Burger et al. 1998, Dargent-Molina et al. 2000, van der Voort et al. 2001, Langlois et al. 2001, Reid 2002, Farahmand et al. 2003). It is unclear whether being overweight reduces the risk of fracture. Some older studies have reported a lower risk of fracture in overweight women (Farmer et al. 1989), but a more recent study reported that women of average weight had a risk of hip fracture that was similar to that of heavier women (Ensrud et al. 1997b). Low body weight and unintentional weight loss are a particular problem for the elderly, as they may signal a variety of medical problems, often manifested by overall frailty, a syndrome that is predictive of incident falls, hip fractures, disability and mortality (Vanitallie 2003). A large prospective study of older women found that women who experienced weight loss in later years also had increased rate of bone loss and a two-fold risk of subsequent hip fracture, irrespective of current weight or intention to lose weight. These findings indicate that even voluntary weight loss in overweight elderly women increases hip fracture risk (Ensrud et al. 2003).

### 2.5.4 Physical activity

Physical activity has been demonstrated to be associated with the bone density at various sites in elderly (Hannan et al. 2000, Nguyen et al. 2000, Lunt et al. 2001, Siris et al. 2001, Yamazaki et al. 2004), but contradictory evidence also exists (Bauer et al. 1993, Brahm et al. 1998, Snelling et al. 2001, Gerdhem et al. 2003b). Leisure physical activity level was an independent predictor of the heel QUS parameters and of femoral neck BMD, but no such association was observed for BMD of the lumbar spine (Blanchet et al. 2003). In a population-based study of 4,000 subjects aged 50-80 years, both current and lifetime physical activity were positively associated with BMD (Lunt et al. 2001). The effect was stronger with hip BMD than spine BMD, and the largest beneficial effect was found in lean women. A recent population-based study revealed that current or previous physical activity explained less than 1% of the variation in bone mass at different bone sites in 75-year-old women (Gerdhem et al. 2003a, Gerdhem et al. 2003b). A lifetime of physical activity has been suggested to be associated with the external...
dimension of bone (area and width) and bone mass more than density (Brahm et al. 1998). Several studies have shown the relationship between physical activity and QUS parameters of the heel, reflecting that the bone quality might be affected by physical activity rather than bone density (Yamaguchi et al. 2000, Blanchet et al. 2003).

Data from longitudinal observational studies have shown a link between physical activity and reduced fracture risk. Recent reviews of the epidemiologic evidence suggest that physical activity is associated with reduction in the risk of hip fracture in elderly women and that there is a "dose-response" effect, i.e. the risk goes down as physical activity level goes up (Gregg et al. 2000, Karlsson 2002). In large prospective studies of older women, moderate or high levels of leisure time physical activity and household chores have been associated with an overall 28-36 percent reduction in hip fractures (Cummings et al. 1995, Gregg et al. 1998, Hoidrup et al. 2001). Moreover, walking at least 4 hours per week was associated with 41 percent lower risk of hip fracture compared with walking less than an hour per week (Feskanich et al. 2002). Decline in the physical activity level over time was also shown to be an important risk factor for hip fracture, although there was no evidence of fracture-protective effect from increasing activity. (Hoidrup et al. 2001) Jaglal et al (Jaglal et al. 1995) showed that lifelong heavy activity at work reduces the risk of hip fracture in postmenopausal women. On the other hand, Van der Voort and colleagues (van der Voort et al. 2001) reported that moderate to heavy occupational exercise in the past is associated with fractures after the age of 50.

### 2.5.5 Muscle strength

In some studies, grip strength has been shown to be positively related to BMD at various bone sites in elderly women (Kritz-Silverstein & Barrett-Connor 1994, Kröger et al. 1994, Blain et al. 2001). On the contrary, a recent study revealed that muscle strength explained less than 1% of the BMD variability (Gerdhem et al. 2003b). Muscle strength has been described as an independent predictor of femoral neck BMD in some (Pocock et al. 1989, Snow-Harter et al. 1990, Hyakutake et al. 1994), but not all studies (Seeman et al. 1996). Muscle mass also has been shown to be associated with total hip BMD (Pluijm et al. 2001). It is unclear whether muscle strength partially determines the BMD or whether strength and BMD are associated only because of similar genetic regulation, since individuals with a larger skeleton and higher BMD also have a larger muscle volume (Pocock et al. 1989, Snow-Harter et al. 1990, Kritz-Silverstein & Barrett-Connor 1994, Hyakutake et al. 1994).

Impaired lower extremity muscle strength has been identified as one of the major risk factors for falling and hip fractures among elderly (Campbell et al. 1989, Lord et al. 1994) (Tinetti et al. 1988, Nguyen et al. 1993). Inability to rise from a chair was associated with an increase in hip fracture risk in two prospective population-based studies. (McGrother et al. 2002) (Cummings et al. 1995) Partanen et al. (Partanen et al. 2002) revealed in their case-control study among elderly women that the mean femoral muscle strength was better in the control group than in the hip fracture group. Grip strength and arm muscle strength have been suggested to be associated with hip fractures especially in women with high BMD (Nevitt & Cummings 1993, Robbins et al. 2005).
2.5.6 Balance and gait

Balance control is very complex behavior and the beneficial effects of exercise interventions may be a function of individual postural control deficits and the type of exercise intervention adopted. Slowing gait, caused mainly by a prolongation of the stance and double support phases of the gait cycle and decreased step and stride length is commonly reported in elderly individuals (Woollacott 1993). In epidemiological studies, impaired postural balance has been shown to contribute to the risk of falling and fractures in older women (Tinetti et al. 1988, Nevitt et al. 1989, Nguyen et al. 1993). Decrease in static balance and increase in body sway was associated with falls especially in frequent fallers (Tinetti et al. 1988, Nevitt et al. 1989). Impaired neuromuscular function, measured as gait speed and ability to do tandem walk, was an independent fall-related predictor of hip fracture in a prospective cohort study of 6,933 women aged 75 years or older (Dargent-Molina et al. 2002). Slower walking speed independently predicted a 1.17- to 1.83-fold increase in hip fracture risk (Taylor et al. 2004). Impaired functional mobility (ability to get about the house and to get out of the house and go shopping) was associated with the occurrence of fracture in a cross-sectional study. Walking ability was better among elderly women without hip fractures compared to the women with hip fractures in a case-control study of 74 female hip fracture patients and 40 control subjects (Partanen et al. 2002).

2.5.7 Other lifestyle factors

Cigarette smoking has been suggested to be associated with lower BMD and increased bone loss in postmenopausal women (Nguyen et al. 1994, Law & Hackshaw 1997, Burger et al. 1998). A recent meta-analysis on smoking and fracture risk revealed that current and previous smoking resulted in hip fracture risk that was substantially greater than that explained by measurement of BMD (Kanis et al. 2005).

Moderate alcohol intake has been associated with increased BMD (Holbrook & Barrett-Connor 1993a, Nguyen et al. 1994), while alcohol consumption has been associated with increased (Felson et al. 1988, Boonyaratavej et al. 2001), decreased (Baron et al. 2001) and unchanged (Cumming & Klineberg 1994a, Johnell et al. 1995, Hoidrup et al. 1999) risk of fracture. Caffeine consumption may predispose to bone loss at proximal femur in elderly women (Cooper et al. 1992).

Evidence exists that low dietary calcium intake in middle age predicts low BMD in older age in women independent of other major determinants of BMD (Holbrook & Barrett-Connor 1995). The slower phase of bone loss in elderly women has been suggested to be caused by a combination of factors including decreased calcium and vitamin D intake, and the loss of estrogen’s positive effects on calcium balance in the intestine and kidney as well as its effects on bone (Riggs et al. 2002). This has been shown to result in further impairment of absorption of calcium by the intestine and reduced ability of the kidney to conserve calcium. If the amount of calcium absorbed from the diet is insufficient to make up for the obligatory calcium losses in the stool and urine, serum calcium begins to fall. Parathyroid hormone levels will then increase,
removing calcium from bone to make up for the bone loss (Riggs et al. 2002). The net result of this process is an increase in bone resorption. A negative balance of only 50-100 mg of calcium per day over a long period of time has been shown to be sufficient to produce the disease (U.S. Department of Health and Human Services 2004). Calcium supplementation has been shown to be useful in the prevention and treatment of postmenopausal osteoporosis especially when combined with vitamin D (Cumming 1990, Kanis 1999), but the increment in skeletal mass may be only modest and ill-sustained (Kanis et al. 1999). According to a recent meta-analysis, observational studies failed to show any association between dietary calcium intake and risk of hip fracture (Xu et al. 2004).

Vitamin D deficiency is common among community-dwelling elderly and very common among institutionalized elderly, geriatric patients and patients with hip fractures (Mosekilde 2005). Vitamin D has been suggested to have a protective effect on bone loss and risk of fractures in elderly women in some studies (Chapuy et al. 1992, Heikinheimo et al. 1992, Chapuy et al. 1994, Dawson-Hughes et al. 1995, Ooms et al. 1995, Papadimitriou et al. 2002, Gerdhem et al. 2005), while there are studies showing no relationship between vitamin D and fracture risk (Kanis et al. 1992, Lips et al. 1996, Michaelsson et al. 2003). Moreover, elderly with low intake of calcium and vitamin D, with reduced cutaneous production of vitamin D or decreased renal production of calcitriol have been shown to be at increased risk of falling (Chapuy et al. 1983, Lips 2001). Some studies have revealed increased sway (Pfeifer et al. 2001) and affected psychomotor function (Dhesi et al. 2002) with increased risk of falling among vitamin D deficient elderly.

2.5.8 Falls

In persons aged 65 years or more, falls are a factor in over 90 percent of fractures of the hip, and a history of falls is associated with an increased risk of hip fractures (Cumming & Klineberg 1994b, Cummings et al. 1995, Young et al. 2001, Geusens et al. 2002, Porthouse et al. 2004). Approximately one per cent of all falls of the elderly result in a hip fracture (Nevitt et al. 1991). In addition to the number of falls, fracture risk is influenced by the direction of the fall and the protective responses of the faller (Cummings & Nevitt 1989, Greenspan et al. 1994, Luukinen et al. 2000). Since hip fractures are usually caused by the impact of a fall, risk factors for fracture may operate by increasing the likelihood of falls (Lips 1997).

2.6 Effect of exercise on risk factors for hip fracture

2.6.1 Bone mass and structure

It is known that mechanical loading primarily influences the juvenile skeleton, when most of the skeleton's growth in size occurs. As osteoprogenitor cells senesce, they
decline in number and become less sensitive to many stimuli, including those from mechanical loading (Chan & Duque 2002). In vitro and comparative studies indicate that in older individuals, osteoblasts are less responsive to strains than osteoblasts in growing individuals. In addition, comparative studies of the effects of exercise on the skeleton in different age groups show that mechanical loading stimulates periosteal growth mostly prior to skeletal maturity, and primarily acts to slow down the rate of bone loss in older individuals (Bass et al. 1998, Wolff et al. 1999, Kohrt 2001). Older humans tend to show only minor gains in bone mass in response to exercise interventions intended to build bone mass or slow its loss (Karlsson et al. 2001). However, studies of the effects of exercise in older adults indicate that exercise can act to slow down the rate of bone loss, primarily by downregulating osteoclastic activity, but it is much less effective than exercise earlier in life in triggering osteoblastic activity. Low-impact exercise, such as nonstrenuous calisthenics or walking, seems to produce no benefits, and only higher-impact or more strenuous activities appear to be effective in slowing the rate of bone loss in older adults (Kerr et al. 1996, Heinonen et al. 1998, Uusi-Rasi et al. 1999, Brooke-Wavell et al. 2001).

The Cochrane Collaboration reviewed 18 trials of exercise for preventing or treating osteoporosis in postmenopausal women specifically, and these analyses indicated that walking was only effective in increasing BMD at the spine and hip (Bonaiuti et al. 2002). Furthermore, the reviewers concluded that the quality of the reporting of the trials was low, which limits the conclusions that can be drawn from the review. Another meta-analysis by Wolff et al. (Wolff et al. 1999) concluded that exercise prevents femoral bone loss, while Berard concluded that weight-bearing exercises are effective on the spine but not on the hip (Berard et al. 1997). The inconsistencies between these meta-analyses are due to different search and selection criteria. Nevertheless, several studies suggest that high-impact loading such as jumping, strength-training exercises, or a combination of these can slightly increase or conserve hip bone mass in postmenopausal or elderly women (Bassey & Ramsdale 1995, Kohrt et al. 1995, Kohrt et al. 1997, Going et al. 2003). Few randomized controlled exercise interventions have been performed in the elderly, and they have revealed a maximum of two per cent increase in BMD during the study period (Lau et al. 1992, Prince et al. 1995, Pruitt et al. 1995, Ebrahim et al. 1997). Although Lau et al. (Lau et al. 1992) found a joint effect of calcium supplements and exercise at the femoral neck, exercise alone had no effect on BMD at any bone site. No randomized, prospective studies have been done to evaluate the skeletal effects of lifelong exercise. The Rancho Bernardo Study (Greendale et al. 1995) showed that both current and lifetime exercise were correlated with hip BMD - i.e. differences in BMD between persons in the highest and lowest categories of exercise being 5% and 8%, respectively.

While several studies have examined associations between physical activity and BMD in the elderly, there are little data on the relationship between physical activity and bone strength in the elderly. Recently it has been suggested that studying bending resistance and geometry along with conventional bone mass measurements could lead to a better understanding of the effect of physical activity on bone. A large population-based prospective study revealed that changes in hip loading are associated with mechanistically appropriate alteration in the section modulus, an index of bending and torsional strength (Beck et al. 2001). The biomechanical strains from enhanced physical activity may
promote increases in bone size that can help preserve bone strength even in the face of bone loss (Kaptoge et al. 2003a). Kaptoge et al. (Kaptoge et al. 2003a) found that hip section modulus, proximal femur diameter and cross-sectional area were more strongly related to reported lifetime physical activity than BMD in elderly women after adjusting for weight and height.

Based on a review of published studies on the effects of exercise training in humans and evidence from experimental studies on mechanical loading in animals, Lanyon and Skerry (Lanyon & Skerry 2001) evaluated the hypothesis that postmenopausal osteoporosis is the result of a failure of bone's adaptation to mechanical loading rather than a multifactorial systemic disorder described by WHO. They concluded that loading history and related bone cells' adaptive responses are the primary functional determinant of bone architecture and bone strength.

2.6.2 Muscle strength

Exercise may have the potential to slow the age related deterioration in structure and function of skeletal muscles. The trainability of skeletal muscle appears unaffected by age, and strength loss seems to be modifiable even in the oldest members of the population (Fiatarone et al. 1994, Chandler & Hadley 1996). Resistance training of varied duration and intensity has been shown to increase strength by 28% to 226% in elderly people (Frontera et al. 1988, Fiatarone et al. 1990, Charette et al. 1991, Fiatarone et al. 1994, Vandervoort 2002). Results from previous studies have also suggested that community-based general aerobic exercise programs can be effective in improving lower extremity strength (Lord et al. 1995, Lord et al. 1996a). A recent trial with home-based multidimensional exercises had no effect on strength in community-dwelling men and women over 70 years (Nelson et al. 2004). The lack of significant improvement in the strength outcome in this study may reflect the specificity of training that differed from the conditions for testing. Although it seems that training interventions can partially reverse losses of strength even in the very old, the extent to which lifelong patterns and training can prevent age-related declines in strength has not been prospectively examined (Doherty 2003).

2.6.3 Balance and gait

Previous studies suggest that older females who exercise demonstrate less postural sway than sedentary females (Lord et al. 1993), and the more active the individual, the less the degree of postural sway (Voorrips et al. 1993). Older females who have participated in regular activity for periods ranging from six weeks to 10 years or more possess better balance than inactive females of the same age (Rikli & Busch 1986, Ringsberg et al. 2001). The interventions shown to be effective in improving balance in elderly women have involved disparate exercise regimens, including tai chi (Wolf et al. 1997), combined weight-bearing and flexibility exercises (Bravo et al. 1996) and multidimensional home-based exercises (Campbell et al. 1997, Campbell et al. 1999, Nelson et al. 2004).
Supervised general group exercise has also been found to be effective (Day et al. 2002, de Vito et al. 2003). Lord et al. reported significant improvements in static and dynamic postural stability and coordination after 12 months of supervised weight-bearing strengthening and balancing group activities (Lord et al. 1995, Lord et al. 1996b). However, the same study group reported no improvement in standing balance in frail older people living in retirement villages (Lord et al. 2003). Many other studies have also failed to demonstrate any significant effects of exercise on balance in the elderly (Judge et al. 1993, Mills 1994, Buchner et al. 1997). Limited literature exists concerning the effects of exercise on gait in elderly people. Twelve months of home-based exercise, and 12 months of strengthening and balancing group activities resulted in improvements in gait measures (Lord et al. 1995, Lord et al. 1996b, de Vito et al. 2003), while another 12-month trial failed to demonstrate significant differences in gait measures between exercisers and nonexercisers among community-dwelling elderly women (MacRae et al. 1994). Similarly, eight weeks of resistance training and six months of home-based progressive strength, balance, and general physical activity showed to have no effect on gait velocity and step time in older adults (Berg & Lapp 1998, Nelson et al. 2004).

Few trials have focused on balance and gait measures in elderly women with low bone mass. Carter et al. found a clinically minor and statistically nonsignificant improvement in static and dynamic balance after 10 weeks of twice-weekly strengthening and stretching exercises among elderly women with osteoporosis (Carter et al. 2002). Resistance and balance training resulted in significantly better postural stability than stretching in women aged 75 to 85 with low bone mass (Liu-Ambrose et al. 2004).

### 2.6.4 Falls

Recent meta-analyses have concluded that exercise is effective in reducing fall risk and preventing falls in elderly people, although the optimal exercise prescription to prevent falls has not yet been defined (Province et al. 1995, Carter et al. 2001a, Gillespie et al. 2003, Chang et al. 2004). Multifaceted interventions that have included balance and strengthening exercises have been suggested to be the most effective interventions (Gillespie et al. 2003), although in these studies it is not possible to separate the specific fall-reducing effect of exercise. The most recent review by Sherrington et al. (Sherrington et al. 2004) provides an update of the evidence on the effects of various physical activity or exercise intervention strategies for the prevention of unintentional falls among older people. Six systematic reviews and three randomized controlled trials not incorporated in previous reviews were included. The authors concluded that there is clear evidence that a targeted supervised home exercise program of strength and balance exercise and walking practice, prescribed by a trained health professional, can prevent falls among older community dwellers. They also suggested that there is an indication that untargeted group exercise (ie. not individually prescribed) can prevent falls among community dwellers, particularly if it involves tai chi or other exercises which challenge balance. The authors also concluded that individual prescription of exercise is more important in frailer groups of elderly people.
Of all the methods of fracture prevention, regular physical activity is the only one that provides other considerable health related benefits that may have a positive, albeit indirect, effect on fall and fracture risk in older adults. Thus, regular exercise should be recommended to all elderly individuals and especially to those with a history of recurrent falls.
3 Purpose of the present study

The main purposes of the present study were to identify risk factors for osteoporosis and fractures with special emphasis on lifelong physical activity, and to assess the effects of long-term supervised exercise on bone health and functional ability in elderly women at risk for fall related fractures.

The more specific aims of the individual studies were:

1. To evaluate the relationship between lifestyle factors, bone mass and fractures in elderly women.
2. To study how a 30-month supervised weight-bearing exercise program affects bone loss in elderly women with low bone mass.
3. To study how a 30-month supervised weight-bearing exercise program affects muscle strength, balance, gait and functional ability in elderly women with low bone mass.
4. To evaluate the repeatability of the inclinometric method developed within the study for measuring postural sway, and the agreement between the inclinometric method and the conventional force platform method.
4 Subjects and methods

This study was carried out during the years 1998-2004 at the Department of Sports Medicine, Oulu Deaconess Institute and the Departments of Public Health Science and General Practice and Neurology, University of Oulu. The approvals of the local Ethics Committee and written informed consent from all subjects were obtained before the study. The principles of the Declaration of Helsinki were observed.

4.1 Study design

The contribution of lifelong lifestyle factors for bone mass in elderly women were investigated using a population-based historical cohort study, in which the data of the explanatory factors were collected retrospectively and longitudinally, and the bone mass was evaluated cross-sectionally (Studies I and II). A population-based, randomized controlled trial was carried out to assess the effect of exercise on bone mass and selected risk factors for fractures in elderly women with osteopenia (Studies III and IV). Repeatability and validity of the inclinometric method for assessment of body sway was examined using an experimental design with simultaneous measurements with the inclinometric and force platform method, and two repeated measurements with the inclinometric method (Study V).

4.2 Subjects

The number of subjects at each phase of the studies I, II, III and IV as well as the reasons for exclusion and withdrawal are presented in Figure 1. The clinical characteristics of the subjects in studies I-IV are presented in Table 4. The original total cohort population in studies I-IV consisted of all the 1,690 women aged 70 to 73 years (born in the period 1924-1927) who were residing in Oulu, Finland in November 1997. The name, address and date of birth of the subjects were obtained from the National Population Register of Finland. Seventy-two per cent of the women (n=1222) attended the study center after
invitation and agreed to participate in the study (Study I). The women were screened for weight, height and BMI, and the women were divided into three subgroups according to the BMI tertiles (BMI < 25.1, 25.1 < BMI < 28.5, BMI > 28.5). The women with BMI < 25.1 (n=407) were included in study II. The WHO classification (WHO 1997) of BMI was not used, because the basis for this BMI classification scheme stems from observational and epidemiologic studies in younger populations, and the nadirs for risk of morbidity and mortality seem to increase with age (Heiat et al. 2001).

Screening tests were used to ensure that the exercise intervention was aimed at those at risk. Of the 1,222 women, who attended the clinic, 1,203 women underwent measurement of BMD at the distal radius, and 1,071 women assessment of calcaneum bone status. Eighty-nine women were excluded due to medical reasons (see exclusion criteria below). Those who had a distal radius BMD value of more than 2 SD below the young adult female mean (n = 430) were invited to the second screening visit, which included hip densitometry. Finally, those who had a hip BMD value of more than 2SD below the young adult female mean, and who agreed to participate (n=160) were enrolled in the intervention study in August 1998. The exclusion and withdrawal criteria before and during the exercise intervention were: use of walking aid device other than a stick, bilateral hip joint replacement, unstable chronic illness, malignancy, medication known to affect bone density, severe cognitive impairment and involvement in other interventions (Studies III and IV). The women were randomly assigned to an exercise group (n=84) and a control group (n=76) using computer-generated random numbers. The randomization was performed after recruitment, and it was provided by a technical assistant not involved in the conduction of the trial.

In Study V, to examine the repeatability of the inclinometric method for assessment of body sway, 51 women were randomly selected from the original population-based cohort of women. In the method comparison study, twenty-nine consecutive old subjects (18 men and 11 women, aged 69 to 86 years) admitted for inpatient rehabilitation at the Rokua Rehabilitation Center in May 1999 were included.
Eligible subjects (n=1690)
Women born 1924-1927

Baseline postal questionnaire and an invitation to clinical examination (n=1689)
(1 woman died before mailing)

1222 (72.4%) responded and attended the clinic
463 did not respond
4 could not be contacted
Calcaneus QUS (n=1071)
Radius BMD (n=1203)

Second postal enquiry (n=1222)

1114 (91.2%) responded

677 excluded:
Radius BMD ≥ 2 SD
n=526

89 excluded:
Medical reasons
n=437

Proximal femur BMD

277 excluded:
Hip BMD ≥ 2 SD (n=207)
or medication for osteoporosis (n=7)

160 randomised

84 allocated to exercise group
15 did not complete study
9 withdrew consent
6 excluded due to medical reasons
69 completed the study
84 available for intention-to-treat analyses

76 allocated to control group
9 did not complete study
3 withdrew consent
6 excluded due to medical reasons
67 completed the study
76 available for intention-to-treat analyses

Exercise intervention 1998-2001

Fig. 2. Flow chart of studies I, II, III and IV.
Table 4. Characteristics of the subjects in studies I-IV.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III and IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All women</td>
<td>BM≤25.1</td>
<td>BM&gt;25.1&lt;28.6</td>
</tr>
<tr>
<td></td>
<td>n=1222</td>
<td>n=407</td>
<td>n=408</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>72.1 (1.2)</td>
<td>72.2 (1.2)</td>
<td>72.0 (1.2)</td>
</tr>
<tr>
<td>Mean weight (kg) (SD)</td>
<td>68.5 (11.1)</td>
<td>58.2 (5.9)</td>
<td>67.7 (5.4)</td>
</tr>
<tr>
<td>Mean height (cm) (SD)</td>
<td>158.0 (5.7)</td>
<td>158.1 (5.8)</td>
<td>158.0 (5.6)</td>
</tr>
<tr>
<td>Calcium intake (mg)(SD)</td>
<td>805 (346)</td>
<td>795 (365)</td>
<td>814 (373)</td>
</tr>
<tr>
<td>Estrogen (n) (%)</td>
<td>39 (4.8)</td>
<td>21 (5.2)</td>
<td>24 (5.9)</td>
</tr>
<tr>
<td>Other medication for osteoporosis (n) (%)</td>
<td>37 (3.0)</td>
<td>15 (3.7)</td>
<td>12 (2.9)</td>
</tr>
<tr>
<td>Hypertension (n) (%)</td>
<td>436 (35.7)</td>
<td>108 (26.5)</td>
<td>144 (35.3)</td>
</tr>
<tr>
<td>Type 2 diabetes (n) (%)</td>
<td>173 (14.2)</td>
<td>38 (9.3)</td>
<td>68 (16.7)</td>
</tr>
<tr>
<td>Thiazide diuretics (n) (%)</td>
<td>191 (15.6)</td>
<td>45 (11.1)</td>
<td>59 (14.5)</td>
</tr>
<tr>
<td>Statins (n) (%)</td>
<td>114 (9.3)</td>
<td>30 (7.4)</td>
<td>47 (11.5)</td>
</tr>
<tr>
<td>Oral corticosteroids (n) (%)</td>
<td>21 (1.7)</td>
<td>7 (1.7)</td>
<td>6 (1.5)</td>
</tr>
<tr>
<td>Weekly consumption of alcohol (n) (%)</td>
<td>108 (9.9)</td>
<td>41 (11.5)</td>
<td>40 (10.9)</td>
</tr>
<tr>
<td>Daily smoking (n) (%)</td>
<td>65 (5.3)</td>
<td>33 (8.1)</td>
<td>16 (3.9)</td>
</tr>
<tr>
<td>No regular physical exercise (n) (%)</td>
<td>133 (10.9)</td>
<td>32 (7.9)</td>
<td>23 (5.7)</td>
</tr>
<tr>
<td>Bone measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean calcaneal BUA (dB/MHz) (SD)</td>
<td>64.81 (17.96)</td>
<td>60.83 (17.57)</td>
<td>64.02 (15.63)</td>
</tr>
<tr>
<td>Mean distal radial BMD (g/cm²) (SD)</td>
<td>0.373 (0.086)</td>
<td>0.323 (0.069)</td>
<td>0.368 (0.075)</td>
</tr>
<tr>
<td>Mean ultradistal radial BMD (g/cm²) (SD)</td>
<td>0.297 (0.074)</td>
<td>0.256 (0.059)</td>
<td>0.294 (0.063)</td>
</tr>
<tr>
<td>Mean femoral neck BMD (g/cm²) (SD)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean trochanter BMD (g/cm²) (SD)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Baseline value
4.3 Methods

4.3.1 Questionnaires

In November 1997 a baseline self-administered health questionnaire was mailed to 1689 of the women (one woman died before mailing). There were questions about demographic features, physical activity, medical history and current diseases, number of pregnancies, the duration of breast-feeding, menarcheal and menopausal age, consumption of dairy products and fish, smoking and consumption of alcohol. The subjects were asked to bring the completed questionnaire and all their pills and prescriptions to the study center for confirmation of current medication use before the clinical investigation.

A second questionnaire was mailed to all the 1,222 women who participated in the clinical examination. The questionnaire included a complete lifetime occupational history that recorded the following: job titles and duties, the type of activity the job required, and the duration of employment for each job held. The number of years at each occupational activity level was calculated for each subject by summing the number of years in each job with a similar activity rating (Jaglal et al. 1995). To assess leisure time physical activity, a modified Paffenbarger questionnaire was used (Greendale et al. 1995). The subjects were asked to recall their participation in activities during four time periods in their life span, corresponding to the ages of 15, 30, 50, and their current age. Calcium intake during the same four time periods of the lifespan was computed as the sum of intakes of milk and cheese (Tuppurainen et al. 1994). To ascertain functional capacity in the extended activities of daily life (EADL), the self-report version of the Frenchay Activities Index (Carter et al. 1997) was used. Depressive symptoms and cognitive functions were evaluated with the Geriatric Depression Scale (GDS) (Yesavage & Brink 1983) and Mini Mental State Examination (MMSE) (Folstein et al. 1975). Medical history and occurrence of fractures were ascertained with the questions: “Has a doctor ever told you that you have any of the following?” - followed by a list of conditions including fractures, and “If yes, when (what year) did that happen?” Fractures occurring in connection with motor vehicle and bicycle accidents were not included. Medical records were reviewed to confirm the diagnosis of type 2 diabetes. The subjects were asked to account for the number of falls during the last three months, the occurrence of any fractures beyond the age of 40, and the age at the time of each fracture.

4.3.2 Anthropometry

The weight of the subjects was measured with a standard mechanical scale (Seca, Vogel&Halke, Hamburg, Germany). Body height was measured in the upright position (accuracy 0.1 cm). BMI was calculated as weight (kg) divided by height (m) squared (Studies I-V). Percentage of fat and lean mass were assessed while lying with bioimpedance equipment (Bodystat 1500, Bodystat Ltd., Douglas, Isle of Man, UK) (Studies III and IV) (Fig. 3).
4.3.3 Bone measurements

Areal BMD and BMC at the left proximal femur were measured by a DXA (Dexa, Lunar Corporation, Madison, Wisconsin, USA) (Fig. 4). The scanner was calibrated daily by bone phantoms (Hologic Corp., Bedford, MA, USA). The coefficient of variation of the measurement in our laboratory is 0.5% (Studies III and IV). Areal BMD of the dominant distal and ultradistal radius were measured by a peripheral DXA (Osteometer DTX 200, Osteometer Meditech, Roedovre, Denmark) ((precision range according to previous studies 1%-2%) (Fogelman & Blake 2000a)). The distal site is defined as the 24-mm long section of bone immediately proximal to the reference line where the separation between radius and ulna is 8 mm. It consists of 87% cortical bone and 13% of trabecular bone. The ultradistal site is the area distal to the 8-mm reference line, and contains 45% cortical and 55% trabecular bone (Patel et al. 1998). Assessment of calcaneal BUA (dB/MHz) and speed of sound (SOS, m/s) was performed by a QUS (Sahara, Hologic, Bedford, MA) (Fig. 5) ((precision range 0.1%-5%) (Fogelman & Blake 2000a)) (Studies I-IV). All the scans and analyses with each item of equipment were performed by the same experienced operators unaware of the women's trial status.
4.3.4 Balance and gait

In studies III, IV and V, postural sway measurements were performed under standardized conditions using an inclinometry-based method (Viitasalo et al. 2002) The device (Fig. 6) consisted of a belt fastened firmly at the level of the iliac crest, an inflexible measuring rod, an inclinometric module, a joint structure lying on the ground, a power unit and a computer with a data acquisition card. The deviating movement of the measuring rod was calculated separately for the side-to-side and forward-backward directions. The measured sway parameters were the maximum deflection for lateral and antero-posterior directions, the total path length of postural sway and total sway area. The path length was obtained by calculating the distance between the sequential location points of each sample, and after that, summing the values. After that, the algorithm of the software approximated the outlines of the measured x/y sway and calculated the assessed area. In study V, body sway was also measured with a force platform device (In Good Balance Trigon, Metitur
Ltd., Finland). The total path length of the center of pressure (COP) movement in the lateral and antero-posterior directions was calculated (at the height of 0.55 times body height).

In the test-retest reliability study for the inclinometric device the test was repeated 20 minutes after the first measurement by the same tester. The subjects were instructed to remove their shoes and stand with their feet together and arms down their sides. During the measurement the subjects were instructed to gaze at a fixation point located 4 m in front of them and not to move their feet. In the method comparison study, two different procedures were used: standing with eyes open and standing with eyes closed, and postural sway was recorded simultaneously using the inclinometric device and the force platform device.

Basic mobility and dynamic balance were measured with the Timed Up and Go -Test (TUG) (Podsiadlo & Richardson 1991) and walking endurance was measured as the distance (m) walked in two minutes (Butland et al. 1982). Time (s) spent on a 30-m walk (Frändin & Grimby 1994) was assessed, and the walking speed (m/s) was calculated.

Fig. 6. Measuring sway with the inclinometric method. The movement of the measuring rod (D_{x,y}) is calculated separately in lateral (x) and antero-posterior (y) directions at the level of the estimated height (h) (0.55 times body height) of the center of gravity, \( \alpha \) being the measured inclination.

4.3.5 Maximal isometric strength

The maximum isometric leg extensor strength and the simple reaction time were assessed bilaterally with a computerized strain-gauge dynamometer (Digitest, Muurame, Finland) in the seated position, the hip and knee set at 90° (Fig. 7). The grip strength and reaction time were measured using a standard grip strength meter (Digitest, Muurame, Finland) (Fig. 8). The force data were analyzed using computer software (Force Measurement
System, Oulu, Finland), and in all strength measurements, the best result of the three consecutive recordings was used in the final statistical analysis. Calibration of the dynamometer was carried out daily before the measurements.

Fig. 7. Measuring maximal isometric strength of the lower extremities.

Fig. 8. Measuring maximal isometric grip strength.
4.3.6 Exercise program

The women in the exercise group were asked to attend hour-long training sessions, supervised by a qualified physiotherapist, once a week for a six-month period each year. Additionally, the participants were asked to train 20 minutes daily at home following a program that consisted of patterns of exercise similar to those in the supervised sessions. From April to September, the exercises took place only at home. Both the supervised and home exercise programs were updated on a bi-monthly basis to ensure progression and versatility. Each group session included a warm-up period, and approximately 45 minutes of each session was devoted to jumping, stamping, lower extremity strength and balance exercises. The intervention group kept a diary of their daily physical activity, and the supervising physiotherapist was responsible for monitoring their daily logs. Subjects assigned to the control group were asked to continue their daily routine activities (Studies III and IV).

The participants of both groups were contacted every three months to record possible changes in their state of health. The women were asked whether a fall had occurred, along with their assessment of the cause and consequences of the fall events and the need for medical treatment. Where there had been a need for medical treatment, the self-reported information was checked from the medical records. Falls and fractures occurring in connection with motor vehicle and bicycle accidents were not included in the analyses. All of the women in both groups were invited to attend seminars led by experts twice per year. Topics included general information on nutrition, health, medical treatment and fall prevention (Studies III and IV).

4.3.7 Statistical methods

The null hypothesis of the data analysis was that lifetime lifestyle factors would not be associated with bone mass and fractures in elderly women (Studies I and II), and that there would be no difference in bone loss or change in selected fracture risk factors between the exercise group or control group during the intervention (Studies III and IV). The alternative hypothesis was that lifestyle factors would be associated with bone mass and that there would be a difference in changes in bone, balance and strength measures depending on group assignment. In study V, the null hypothesis was that the difference between the means of the two repeated measurements with the inclinometric method would differ significantly from zero, and that the results of the simultaneous measurements with the two devices would not be linearly related and they would not agree. The alternative hypotheses were that the repeated measures with the inclinometric method would be identical, and that there would be agreement between the two methods.

The main endpoints were radial BMD and calcaneal BUA in studies I and II, upper femur BMD and BMC in study III, body sway and maximal isometric leg strength in study IV and body sway in study V. The data were analyzed with the SPSS for Windows software, versions 9.0, 10.0 and 11.0, and the Stats Direct Statistical Software, versions 1.8.9 and 2.4.1. All the BMD and functional ability and physical performance measures were normally distributed.
In study I, association between the response and explanatory factors in the aggregated data was first analyzed using crosstabulation and the Pearson product-moment correlations. Since BMI was strongly related to all the responses and most of the explanatory variables, the data were disaggregated into three subgroups by the BMI tertiles (lean: BMI ≤ 25.1, normalweight: 25.1 < BMI < 28.5, obese: BMI ≥ 28.5) to reveal strata-specific relative risks. Thereafter, the one-way Anova was used to evaluate the statistical significance of the differences between the BMI subgroups for continuous variables. For the dichotomous variables, the \( \chi^2 \) test was used to evaluate the significance of the differences. To determine those factors that predicted low BMD and BUA in each BMI class, the response variables were dichotomously divided as follows: low distal and ultradistal radial BMD (BMD value < -1 SD of the mean BMD of the entire study population) and normal BMD (value ≥ -1 SD of the entire study population), low heel BUA (BUA < -1 SD of the mean BUA of the entire study population) and normal BUA (value ≥ -1 SD of the entire study population). For analysis related to leisure exercise exposure, physical activity indices at different ages, and a lifetime activity index were calculated. The exercise level indices were divided into tertiles and for the final analysis the variables were dichotomized. To test the possible linear trend between the strata, the \( \chi^2 \) -test for linear trend was used.

In study II, the Student's test and the chi-square test for two independent proportions for statistical comparison between the study population and total population were used. To assess how well the various measured risk factors could predict BUA and BMD, multiple linear regression analysis using all variables possibly associated with BUA and BMD in univariate analyses was used. Logistic regression analysis was performed to calculate odds ratios and 95% confidence intervals for having experienced fractures beyond the age of menopause. Variables were grouped into categories and forward stepwise regression procedures (p<0.05) were used to select the most predictive variables within each category. For analysis related to leisure exercise exposure, physical activity indices at different ages, and lifetime activity were calculated (Greendale et al. 1995). The exercise level indices were divided into tertiles, and for the final analysis the variables were dichotomized. A similar stepwise analysis was then used to select the most predictive variables from all categories of predictors. The significant risk factors in the final model were reported using odds ratios (ORs) and their 95% CIs.

In study III, it was estimated that at 5% significance level 64 women would be required in each group to give an 80% power to detect a 0.02g/cm\(^2\) difference in femoral neck BMD between the groups. In study IV, it was estimated that at a 5% level 50 women would be required in each group to give an 80% power of detecting a 20% difference in body sway between the groups. The study also had 80% power at the 5% significance level to show a 20% difference in lower extremity strength. The absolute and percentage changes from baseline were calculated for each characteristic (Studies III and IV). The means with 95% confidence intervals were calculated for change within a group and for difference between the groups. The paired samples \( t \) test was used to analyze the within group change from baseline, and the \( t \) test for independent samples was used to compare the treatment group with the control group. The analysis of variance for repeated measures was used to analyze the intra-group-by-time-effect and the group-by-time interaction over the study period. (Studies III and IV) Multiple linear regression analysis using all variables associated with BMD and BMC in univariate analyses was performed...
to evaluate the determinants of bone response within the exercise group and the pooled groups in study III. For the number of fractures, the $\chi^2$ test was used to evaluate the significance of the difference between the groups. Data was analyzed on an intention-to-treat basis, and missing outcome values were imputed by the last observation carried forward strategy, even if this was the baseline value.

In study V, reliability from the test-retest measurements was assessed using the two-tailed paired Student t-test, linear regression analyses and the Bland and Altman analysis (Bland & Altman 1986). To assess the level of agreement between the inclinometric method and the force platform method the Pearson product-moment correlation coefficients and linear regression analyses were used. Level of significance for all tests was set at $p < 0.05$. 
5 Results

The main results of each study are presented in Table 5. The detailed results are presented in the original publications I-V.

5.1 Determinants of bone mass, falls and fractures in elderly women (I,II)

Table 4 shows the characteristics of the subjects in each study in 1997-1998. The mean age of the women at the first clinical examination was 72 years. BMI varied between 15 kg/m² and 46 kg/m², averaging 27 kg/m². Mean current weight was 68 kg (range 40 kg to 113 kg) and mean current height was 159 cm (range 139 cm to 177 cm). Thirty per cent of the women (363) reported having any fractures after the age of 40, and 328 (90.4%) of them were postmenopausal low-trauma fractures. One woman in the exercise group had unilateral hip joint replacement.

5.1.1 Calcaneum ultrasound measurements

Table 6 shows the significant predictors of low calcaneum BUA after the crude and stratified analysis in the study population according to the current BMI tertiles (Study I). The crude analysis of the aggregated data revealed a significant inverse association between the level of occupational activity and the calcaneum BUA value (RR 0.5, 95% CI 0.3 to 0.9), and this remained true after the stratified analysis in the lowest BMI subgroup (RR 0.4, 95% CI 0.2 to 0.8) but not in the other groups.

After stratification, physical inactivity at all stages of life other than teenage was significantly associated with a low BUA value in the lowest BMI strata (RR 1.3 to 1.7). Lean women with low current daily activity also had moderately increased risk of reduced calcaneum BUA. Poor self-rated mobility was associated with decreased calcaneum BUA in the aggregated data (RR 1.5, 95% CI 1.1 to 2.2), and the relationship was strengthened in the lowest category of BMI after the stratified analysis (RR 1.9, 95% CI 1.2 to 3.0).
CI 1.2 to 3.0). A low score (< 15 s) in the Timed Up and Go Test was also a statistically significant predictor of a low calcaneum BUA value in the leanest group of women (RR 1.9, 95% CI 1.1 to 3.2). Current coffee intake of more than five cups per day was found to be significantly associated with a low calcaneal BUA value in the lowest BMI group after stratified analysis (RR 1.7, 95% CI 1.1 to 2.7).

Type 2 diabetes strongly protected lean women from decreased BUA value (RR 0.3, 95% CI 0.1 to 0.9) and the presence of hypertension also reduced the risk of calcaneal bone loss in lean women (RR 0.5, 95% CI 0.3 to 0.8).

Table 7 shows the statistically significant predictors of calcaneum BUA in the multiple linear regression analysis adjusted for all significant variables in the univariate analysis (Study II). Low lifetime occupational activity, current hormone replacement and type 2 diabetes were associated with higher calcaneum BUA, while low current habitual physical activity was associated with low BUA. The final model explained 12% of the BUA variance.
Table 5. The main results of studies I-V.

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim of study</th>
<th>Study type and subjects</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Risk factors for low bone mass</td>
<td>Retrospective cohort 1,222 women</td>
<td>Increased risk for low calcaneal BUA: BMI↓, Low habitual exercise at the ages 30, 50 and currently, Poor self-rated mobility, Coffee intake ≥ 5 cups/day, Increased risk for low radial BMD: BMI↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Risk factors for low bone mass and self-reported fractures in lean women</td>
<td>Retrospective cohort 407 women</td>
<td>Increased risk for low calcaneal BUA: Low physical activity, Increased risk for low radial BMD: Late menarche</td>
</tr>
</tbody>
</table>

*Percentage change in exercise group minus percentage change in control group. A positive value indicates a positive effect of exercise. Only statistically significant differences are presented. ** Percentage change in exercise group minus percentage change in control group. A negative value indicates a positive effect of exercise. Only statistically significant differences are presented. TUG = Timed Up and Go - Test
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim of study</th>
<th>Study type and subjects</th>
<th>Main results</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Exercise effect on bone mass</td>
<td>Randomized controlled trial</td>
<td>% difference* in BMD at any site and heel BUA: No difference % difference* in trochanter BMC: 4.8</td>
<td>Fall related fractures: Exercise group 6 Control group 16</td>
</tr>
<tr>
<td>IV</td>
<td>Exercise effect on risk factors for hip fractures</td>
<td>Randomized controlled trial</td>
<td>% difference** in sway length: -26.4 % difference* in leg strength: 29.8 % difference* in gait velocity: 19.4</td>
<td>% difference* in endurance: 14.6 % difference* in grip strength: 10.6 % difference** in TUG-score: -15.4</td>
</tr>
<tr>
<td>V</td>
<td>Repeatability and validity of the inclinometric method</td>
<td>Experimental methods</td>
<td>Test-retest $r^2$: sway path length: 0.683 sway area: 0.500 Agreement with the force platform method: $r^2 = 0.466 - 0.694$</td>
<td></td>
</tr>
</tbody>
</table>

*Percentage change in exercise group minus percentage change in control group. A positive value indicates a positive effect of exercise. Only statistically significant differences are presented. ** Percentage change in exercise group minus percentage change in control group. A negative value indicates a positive effect of exercise. Only statistically significant differences are presented. TUG = Timed Up and Go -Test.
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>All women (n=1071)</th>
<th>BMI ≤ 25.1 (n=357)</th>
<th>BMI 25.1 &lt; BMI &lt; 28.5 (n=358)</th>
<th>BMI ≥ 28.5 (n=356)</th>
<th>χ² for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>%</td>
<td>RR (95% CI)</td>
<td>N</td>
</tr>
<tr>
<td>Occupational physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary to light activity work (vs. moderate to heavy activity job)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>188</td>
<td>17</td>
<td>9.0</td>
<td><strong>0.6 (0.4-0.9)</strong></td>
<td>69</td>
<td>6</td>
</tr>
<tr>
<td>773</td>
<td>20</td>
<td>15.5</td>
<td>241</td>
<td>58</td>
<td>24.1</td>
</tr>
<tr>
<td>Low lifetime occupational activity (vs. moderate-to-heavy-activity)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>290</td>
<td>31</td>
<td>10.7</td>
<td>0.7 (0.5-1.1)</td>
<td>106</td>
<td>17</td>
</tr>
<tr>
<td>599</td>
<td>92</td>
<td>15.4</td>
<td>188</td>
<td>41</td>
<td>21.8</td>
</tr>
<tr>
<td>Exercise level at various ages (low or moderate activity vs. high activity)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teenage</td>
<td>186</td>
<td>21</td>
<td>11.3</td>
<td>1.0 (0.6-1.6)</td>
<td>75</td>
</tr>
<tr>
<td>694</td>
<td>78</td>
<td>11.2</td>
<td>197</td>
<td>42</td>
<td>21.3</td>
</tr>
<tr>
<td>30 years</td>
<td>253</td>
<td>37</td>
<td>14.6</td>
<td>1.0 (0.7-1.5)</td>
<td>87</td>
</tr>
<tr>
<td>599</td>
<td>83</td>
<td>13.9</td>
<td>189</td>
<td>35</td>
<td>18.5</td>
</tr>
<tr>
<td>336</td>
<td>52</td>
<td>15.5</td>
<td>1.2 (0.8-1.6)</td>
<td>108</td>
<td>31</td>
</tr>
<tr>
<td>563</td>
<td>74</td>
<td>13.1</td>
<td>178</td>
<td>30</td>
<td>16.9</td>
</tr>
<tr>
<td>336</td>
<td>52</td>
<td>15.5</td>
<td>1.2 (0.8-1.6)</td>
<td>108</td>
<td>31</td>
</tr>
<tr>
<td>563</td>
<td>74</td>
<td>13.1</td>
<td>178</td>
<td>30</td>
<td>16.9</td>
</tr>
<tr>
<td>Current</td>
<td>498</td>
<td>67</td>
<td>13.5</td>
<td>1.0 (0.7-1.4)</td>
<td>104</td>
</tr>
<tr>
<td>400</td>
<td>54</td>
<td>13.2</td>
<td>193</td>
<td>32</td>
<td>16.6</td>
</tr>
<tr>
<td>Lifetime</td>
<td>577</td>
<td>77</td>
<td>6.8</td>
<td>1.0 (0.7-1.5)</td>
<td>184</td>
</tr>
<tr>
<td>225</td>
<td>30</td>
<td>13.3</td>
<td>78</td>
<td>14</td>
<td>17.9</td>
</tr>
</tbody>
</table>

BUA, broadband ultrasound attenuation; BMI, body mass index. * BUA < -1 SD of the mean BUA of the entire study population. † One hundred and fifty-one women were excluded from the analysis because of missing calcaneal BUA data.
Table 6. Continued.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>All women (n=1071)</th>
<th>BMI ≤ 25.1 (n=357)</th>
<th>25.1 &lt; BMI ≤ 28.5 (n=358)</th>
<th>BMI ≥ 28.5 (n=356)</th>
<th>χ² for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Referent category)</td>
<td>N</td>
<td>N</td>
<td>%</td>
<td>RR (95% CI)</td>
<td>N</td>
</tr>
<tr>
<td>Poor self-rated mobility (vs. moderate to very good)</td>
<td>150</td>
<td>31</td>
<td>20.7</td>
<td>1.5 (1.1-2.2)</td>
<td>34</td>
</tr>
<tr>
<td>Timed Up and Go &gt; 15 s (vs. &lt; 15 s)</td>
<td>120</td>
<td>22</td>
<td>18.3</td>
<td>1.3 (0.9-2.0)</td>
<td>32</td>
</tr>
<tr>
<td>Nutritional and dietary factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean daily current dietary calcium intake ≤ 654.0 mg (vs. &gt; 654.0 mg)</td>
<td>325</td>
<td>43</td>
<td>13.2</td>
<td>0.9 (0.6-1.3)</td>
<td>114</td>
</tr>
<tr>
<td>Current daily smoking (vs. not smoking)</td>
<td>54</td>
<td>11</td>
<td>20.4</td>
<td>1.4 (0.8-2.5)</td>
<td>27</td>
</tr>
<tr>
<td>Weekly consumption of alcohol (vs. less than weekly)</td>
<td>90</td>
<td>6</td>
<td>6.7</td>
<td>0.5 (0.2-1.0)</td>
<td>31</td>
</tr>
<tr>
<td>Current coffee intake ≥ 5 cups/day (vs. &lt; 5 cups/day)</td>
<td>215</td>
<td>41</td>
<td>19.1</td>
<td>1.5 (1.1-2.1)</td>
<td>65</td>
</tr>
<tr>
<td>Other factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (vs. no hypertension)</td>
<td>397</td>
<td>48</td>
<td>12.1</td>
<td>0.8 (0.6-1.0)</td>
<td>103</td>
</tr>
<tr>
<td>Type 2 diabetes (vs. no type 2 diabetes)</td>
<td>674</td>
<td>108</td>
<td>16.0</td>
<td>0.6 (0.5-1.2)</td>
<td>254</td>
</tr>
<tr>
<td>Self reported fractures since age of 40 (vs. no fractures)</td>
<td>732</td>
<td>91</td>
<td>12.1</td>
<td>0.7 (1.1-2.3)</td>
<td>240</td>
</tr>
</tbody>
</table>

BUA, broadband ultrasound attenuation; BMI, body mass index. * BUA < -1 SD of the mean BUA of the entire study population. † One hundred and fifty-one women were excluded from the analysis because of missing calcaneal BUA data.
Table 7. Significant predictors of calcaneum BUA (dB/MHz) in stepwise multiple linear regression analysis adjusted for all significant variables in the univariate analysis in the leanest tertile of women (n = 407) (Study II).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcaneum BUA: Model R² = 0.117, P &lt; 0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low lifetime occupational physical activity vs. moderate to heavy activity (referent)</td>
<td>6.754 (1.633 to 11.876)</td>
<td>0.010</td>
</tr>
<tr>
<td>Low current habitual physical activity vs. moderate to high (referent)</td>
<td>-7.942 (-15.881 to -0.004)</td>
<td>0.050</td>
</tr>
<tr>
<td>Current hormone replacement vs. none (referent)</td>
<td>12.473 (3.889 to 21.057)</td>
<td>0.005</td>
</tr>
<tr>
<td>Type 2 Diabetes vs. none (referent)</td>
<td>8.988 (1.608 to 16.368)</td>
<td>0.017</td>
</tr>
<tr>
<td>Constant</td>
<td>59.757 (57.237 to 62.278)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BUA, broadband ultrasound attenuation; * Model adjusted for other significant variables in univariate analysis (impaired distant vision, Timed Up and Go > 11s)

5.1.2 Radius BMD measurements

A positive (RR 1.3, 95% CI 1.0 to 1.7) association between current height and the ultradistal radial BMD measure was observed in the crude analysis, but no association was found after stratification by BMI tertiles (Study I). The crude analysis also revealed a significant (RR 0.5, 95% CI 0.3 to 0.9) inverse association between daily physical exertion and the ultradistal radius BMD, but the relationship was not found in the stratified data.

The type of activity in the main occupation during working life and lifetime occupational activity were associated with radial BMD after stratification, low activity reducing the risk of low ultradistal BMD (RR 0.7, 95% CI 0.5 to 1.0). Poor self-rated mobility was associated with decreased radial BMD values in the aggregated data, but a positive relationship was not observed after the stratified analysis.

The presence of type 2 diabetes and hypertonia were associated with increased BMD in the aggregated data. After stratification, diabetes was found to be a strongly protective (RR 0.1, 95% CI 0.1 to 0.5) factor for low ultradistal BMD in those women with low BMI.

Table 8 shows the statistically significant predictors of radius BMD in the multiple linear regression analysis adjusted for all significant variables in the univariate analysis. The final models explained 7% of the distal radius variance and 6% of the ultradistal radius variance. The predictors of radius BMD were different from BUA, except for type 2 diabetes that was significantly associated with higher calcaneum BUA and higher BMD at the radius. Late menarche was associated with lower radius BMD, and current use of thiazide diuretics and current use of a thyroid hormone protected from low BMD.
Table 8. Significant predictors of radius BMD (g/cm²) in stepwise multiple linear regression analysis adjusted for all significant variables in the univariate analysis in the leanest tertile of women (n = 407) (Study II).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal radius BMD: Model R² = 0.072, P &lt; 0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menarche age &gt; 15 years vs. ≤ 15 years (referent)</td>
<td>-0.019 (-0.033 to -0.005)</td>
<td>0.008</td>
</tr>
<tr>
<td>Thiazide diuretics vs. none (referent)</td>
<td>0.025 (0.003 to 0.046)</td>
<td>0.027</td>
</tr>
<tr>
<td>Thyroid hormone vs. none (referent)</td>
<td>0.024 (0.001 to 0.048)</td>
<td>0.042</td>
</tr>
<tr>
<td>Type 2 Diabetes vs. none (referent)</td>
<td>0.034 (0.011 to 0.058)</td>
<td>0.005</td>
</tr>
<tr>
<td>Constant</td>
<td>0.325 (0.315 to 0.335)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Ultradistal radius BMD: Model R² = 0.064, P < 0.001† |

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menarche age &gt; 15 years vs. ≤ 15 years (referent)</td>
<td>-0.013 (-0.025 to -0.001)</td>
<td>0.032</td>
</tr>
<tr>
<td>Thyroid hormone vs. none (referent)</td>
<td>0.021 (0.000 to 0.041)</td>
<td>0.045</td>
</tr>
<tr>
<td>Type 2 Diabetes vs. none (referent)</td>
<td>0.039 (0.019 to 0.060)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Constant</td>
<td>0.257 (0.248 to 0.265)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMD, bone mineral density; * Model adjusted for other significant variables in univariate analysis (educational level, hypertension, calcium intake); † Model adjusted for other significant variables in univariate analysis (educational level, hypertension, calcium intake, alcohol consumption)

5.1.3 Falls and fractures

The women in the lowest category of BMI reported having sustained slightly more fractures beyond the age of 40 than the women with BMI over 25 kg/m² (P=0.25) (Study I). The proportion of women who reported having at least one postmenopausal fracture also was higher among the leanest women compared to the total population ((124 (30.4%) vs. 328 (26.8%)) (P=0.157) (Study II). The number of self-reported postmenopausal fractures was 455 in the total population, and the leanest group of women had 171 fractures (Table 9). Over half of the fractures were located in the wrist, followed by the foot and ankle. There were 15 hip fractures in the study population. There was no difference in the distribution of fractures between the women in the lowest category of BMI and the total population.
Table 9. Sites and number (%) of the self-reported postmenopausal low-trauma fractures reported by the 124 women with BMI < 25.1 (n=407) and 328 women in the total population (n=1222).

<table>
<thead>
<tr>
<th>Site</th>
<th>Women with BMI &lt; 25.1</th>
<th>Total population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Leg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foot and ankle</td>
<td>17 (9.9)</td>
<td>60 (13.2)</td>
</tr>
<tr>
<td>Tibia and fibula</td>
<td>3 (1.8)</td>
<td>11 (2.4)</td>
</tr>
<tr>
<td>Patella</td>
<td>4 (2.3)</td>
<td>15 (3.3)</td>
</tr>
<tr>
<td>Femur</td>
<td>4 (2.3)</td>
<td>15 (3.3)</td>
</tr>
<tr>
<td>Total</td>
<td>28 (16.3)</td>
<td>101 (22.2)</td>
</tr>
<tr>
<td><strong>Trunk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvis</td>
<td>2 (1.2)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Vertebra</td>
<td>11 (6.4)</td>
<td>26 (5.7)</td>
</tr>
<tr>
<td>Sternum</td>
<td>1 (0.6)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Rib</td>
<td>10 (5.9)</td>
<td>26 (5.7)</td>
</tr>
<tr>
<td>Clavicle</td>
<td>5 (2.9)</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>Total</td>
<td>29 (17.0)</td>
<td>65 (14.3)</td>
</tr>
<tr>
<td><strong>Arm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humerus</td>
<td>10 (5.9)</td>
<td>26 (5.7)</td>
</tr>
<tr>
<td>Elbow</td>
<td>5 (2.9)</td>
<td>6 (1.3)</td>
</tr>
<tr>
<td>Wrist</td>
<td>95 (55.6)</td>
<td>243 (53.4)</td>
</tr>
<tr>
<td>Hand and fingers</td>
<td>4 (2.3)</td>
<td>12 (2.6)</td>
</tr>
<tr>
<td>Total</td>
<td>114 (66.7)</td>
<td>287 (63.1)</td>
</tr>
<tr>
<td>Site unknown</td>
<td>2 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>171 (100%)</td>
<td>455 (100%)</td>
</tr>
</tbody>
</table>

In study II, low lifetime habitual activity (OR 2.7, 95% CI 1.5 to 4.7), low current habitual activity (OR 2.0, 95% CI 1.2 to 3.2), incapacities for IADL (OR 2.0, 95% CI 1.2 to 3.2), living alone (OR 2.0, 95% CI 1.3 to 3.0), type 2 diabetes (OR 0.4, 95% CI 0.2 to 1.1) and recent falling (OR 2.6, 95% CI 1.5 to 4.7) were associated with postmenopausal fractures in the univariate analysis. Calcaneum BUA was associated with self-reported fractures beyond the age of menopause, each 1SD decrement in calcaneum BUA increasing the risk of fractures by 50% (OR 1.5, 1.2 to 2.0).

Multivariable logistic regression analysis disclosed that low or moderate lifetime exercise level compared to high activity (OR 3.7, 95% CI 1.9 to 7.1) and living alone (OR 1.7, 95% CI 1.0 to 3.0) were independently associated with postmenopausal fractures among the women in the lowest stratum of BMI (Table 10). A decrease of 1 SD in calcaneum BUA increased the risk of fractures 80% (OR 1.8, 95% CI 1.3 to 2.4), while type 2 diabetes was associated with a decrease in risk of fractures (OR 0.2, 95% CI 0.1 to 1.0).
Table 10. Multivariate model of risk factors for postmenopausal low-trauma fractures in the study population (n = 407).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted odds ratio* (95% CI)</th>
<th>P value to remove</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime habitual exercise level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low or moderate vs. high activity (referent)</td>
<td>3.7 (1.9 - 7.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type 2 diabetes vs. no diabetes (referent)</td>
<td>0.2 (0.1 - 1.0)</td>
<td>0.023</td>
</tr>
<tr>
<td>Living alone vs. living with somebody (referent)</td>
<td>1.7 (1.0-3.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Calcaneum ultrasound BUA (per 1SD decrease)</td>
<td>1.8 (1.3-2.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Variables significant (p < 0.07) in the univariate analysis and radial BMD were entered and adjusted for in the forward stepwise logistic regression analysis. The final model is presented. BUA = broadband ultrasound attenuation

We also analyzed the possible lifestyle risk factors for recent falling. After adjustment for other factors significant in the crude analyses, poor self-rated mobility (OR 3.0, 95% CI 1.3 to 7.1), Timed Up and Go – score > 11s (OR 2.0, 95% CI 1.0 to 4.1) and presence of symptoms of depression (OR 2.3, 95% CI 1.2 to 4.4) remained independent risk factors for falling in the logistic regression analysis. Women who consumed more than four cups coffee per day had a 2.4-fold risk of falling compared with those whose consumption was less (OR 2.4, 95% CI 1.1 to 5.2).

5.2 Effect of 30-month exercise program on risk factors for fractures (III, IV)

Baseline data on those taking exercise and the controls are presented in Table 4. Sixty-eight women (81%) in the exercise group and sixty-five women (86%) in the control group completed the study. In both groups all but four of the withdrawals occurred during the first year of the intervention. Reasons for withdrawal were unwillingness to continue (n=12), new or worsening health problems (n=7) or medication included in the initial exclusion criteria (n=5). The drop-out subjects were similar in respect to demographic features, main outcome variables and calcium intake compared to those who continued to participate.

Attendance at the exercise sessions averaged 78.1% during the first supervised six month period, 74.4% during the second supervised period and 72.6% during the last supervised six months. The average frequency of performing the home exercise program was 3 times per week. Three women in the exercise group experienced musculoskeletal problems that required minor modifications in the training regimen. All of these women completed the exercise program without further problems. Two women had to suspend...
training due to knee arthroplasty, 6 women due to neurological or cardiovascular problems and 6 women due to glaucoma surgery.

During the 30-month follow-up, there were 88 falls in the exercise group and 101 falls in the control group. The exercise group had 6 fall-related fractures, while there were 16 fractures in the control group. The distribution of types of fractures between the exercise group and the control group was as follows: exercise group (radius 4, fibula 1, clavicula 1); control group (radius 3, finger 1, fibula 2, humerus 4, elbow 2, rib 1, vertebra 2, pelvis 1). All the subjects with fractures returned to the exercise program and completed a modified regimen without problems.

5.2.1 Bone mass (III)

The bone measurement values over the 30-month trial at the radius, calcaneum and various hip sites in the two groups are presented in Table 11. Figures 9, 10 and 11 show the change in hip BMD and BMC over the study period in the exercise and control group, and the significance of the difference in the repeated-measures ANOVA. The femoral neck BMD decreased 1.1% (95% CI -2.1% to -0.1%, P=0.04) and trochanter BMD decreased 1.6% (95% CI -2.7% to -0.4%, P=0.01) in the control group while no significant change occurred within the exercise group (neck -0.6%, 95% CI -1.6% to 0.10%, P=0.07; trochanter -0.3%, 95% CI -1.6% to 0.8%, P=0.48). Trochanter BMC decreased 7.7% (95% CI -9.7% to -5.6%, P=0.001) in the control group and 2.9% (95% CI -5.3% to -0.9%, P=0.001) in the exercise group (repeated measures ANOVA, P=0.001 for the difference between the groups). In the linear multiple regression analyses adjusted for attendance (%) at the training sessions, each kg increment in weight increased the total hip BMD by 0.5% (R²=30.2%, model P<0.001) and the total hip BMC by 0.8% (R² = 38.3%, model P<0.001) within the exercise group. Also within the pooled groups, weight change over time was the most significant determinant of bone loss at the hip, with each kg increment in weight accounting for a 0.5% increase in the total hip BMD (R² = 22.2%, model P<0.001) and 0.8% of the change in the total hip BMC (R² = 29.8%, model P<0.001).

The mean BMD at the distal and ultradistal radius decreased similarly and significantly in both groups (exercise group -3.8%, 95% CI -5.2% to -2.5%, P=0.001 and -2.8%, 95% CI -4.9 to -0.7, P=0.003; control group -2.8%, 95% CI -4.4% to -1.2%, P=0.001 and -2.7%, 95% CI, -5.1% to -0.3%, P=0.01). Nor did exercise have any significant effect on the rate of bone loss at the calcaneum, where the bone mass values decreased significantly and similarly in both groups.
Table 11. Mean (95% CI) bone density values at the proximal femur, radius and calcaneum at baseline, 12 months and 30 months.

<table>
<thead>
<tr>
<th>Bone site</th>
<th>Exercise group (n=84)</th>
<th>Control group (n=76)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proximal femur</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck BMD (g/cm²)</td>
<td>0 months 0.674 (0.663 to 0.685)</td>
<td>0.670 (0.660 to 0.680)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 months 0.673 (0.661 to 0.684)</td>
<td>0.667 (0.657 to 0.678)</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>30 months 0.670 (0.657 to 0.681)</td>
<td>0.663 (0.651 to 0.674) †</td>
<td>0.61</td>
</tr>
<tr>
<td>Neck BMC (g)</td>
<td>0 months 3.22 (3.14 to 3.30)</td>
<td>3.24 (3.16 to 3.32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 months 3.24 (3.16 to 3.33)</td>
<td>3.26 (3.17 to 3.34)</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>30 months 3.23 (3.15 to 3.31)</td>
<td>3.25 (3.16 to 3.33)</td>
<td>0.95</td>
</tr>
<tr>
<td>Trochanter BMD (g/cm²)</td>
<td>0 months 0.621 (0.605 to 0.638)</td>
<td>0.618 (0.601 to 0.635)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 months 0.619 (0.602 to 0.636)</td>
<td>0.613 (0.596 to 0.630) †</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>30 months 0.619 (0.601 to 0.636)</td>
<td>0.608 (0.591 to 0.626) †</td>
<td>0.17</td>
</tr>
<tr>
<td>Trochanter BMC (g)</td>
<td>0 months 8.08 (7.74 to 8.42)</td>
<td>8.45 (8.04 to 8.86)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 months 8.10 (7.75 to 8.46)</td>
<td>8.32 (7.87 to 8.78)</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>30 months 7.84 (7.45 to 8.22) †</td>
<td>7.79 (7.39 to 8.21) §</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Total femur BMD (g/cm²)</strong></td>
<td>0 months 0.746 (0.730 to 0.762)</td>
<td>0.734 (0.718 to 0.751)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 months 0.745 (0.728 to 0.762)</td>
<td>0.737 (0.721 to 0.754)</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>30 months 0.744 (0.727 to 0.762)</td>
<td>0.740 (0.722 to 0.758)</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Total femur BMC (g)</strong></td>
<td>0 months 23.85 (23.15 to 24.55)</td>
<td>24.27 (23.49 to 25.04)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 months 23.83 (23.11 to 24.54)</td>
<td>24.30 (23.49 to 25.11)</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>30 months 23.70 (22.95 to 24.45)</td>
<td>24.03 (23.21 to 24.86)</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Radius</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal BMD (g/cm²)</td>
<td>0 months 0.290 (0.281 to 0.299)</td>
<td>0.291 (0.281 to 0.300)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 months 0.279 (0.269 to 0.289)§</td>
<td>0.282 (0.272 to 0.292)§</td>
<td>0.44</td>
</tr>
<tr>
<td>Ultradistal BMD (g/cm²)</td>
<td>0 months 0.229 (0.220 to 0.237)</td>
<td>0.234 (0.224 to 0.244)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 months 0.222 (0.213 to 0.230)†</td>
<td>0.226 (0.217 to 0.236)†</td>
<td>0.94</td>
</tr>
<tr>
<td>Calcaneum QUS BUA (dB/MHz)</td>
<td>0 months 52.78 (49.92 to 55.65)</td>
<td>53.05 (49.42 to 56.67)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 months 53.05 (50.15 to 55.95)</td>
<td>53.22 (49.57 to 56.87)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

* Difference between changes from baseline in exercise and control group, independent samples t-test.
† P<0.05; ‡ P<0.01; § P<0.001 Significance for within-group difference from baseline, paired samples t-test.
Fig. 9. Change from baseline in femoral neck bone mineral density and content (repeated measures ANOVA, P value for the difference between the groups).

Fig. 10. Change from baseline in trochanter bone mineral density and content (repeated measures ANOVA, P value for the difference between the groups).

Fig. 11. Change from baseline in total proximal femur bone mineral density and content (repeated measures ANOVA, P value for the difference between the groups).
5.2.2 Maximal isometric strength (IV)

Figure 12 shows the change (95%CI) in maximal isometric leg extensor strength and grip strength in the exercise and control group over the study period, and the significance of the difference between the groups in the repeated-measures ANOVA. The exercise group demonstrated a 19.1 kg (95% CI 13.5 kg to 24.7 kg, P<0.001) gain in leg extensor strength, while there was decrement of 8.1 kg (95% CI -12.7 kg to -3.8 kg, P<0.001) in leg strength in the control group (P for the difference <0.001). Grip strength decreased in both groups and the decrement was more pronounced in the control group (P=0.02). There was an improvement in mean leg reaction time in the exercise group (-0.04 s, 95% CI -0.08 s to -0.01 s, P=0.006), while there was no change in reaction time in the control group (-0.01 s, 95% CI -0.03 s to 0.02 s, P=0.21) (P=0.12 for the difference between the groups).

Body sway path length increased 0.38 cm (95% CI -0.31 cm to 1.08 cm, P=0.02) in the exercise group and 3.55 cm (95% CI 2.72 cm to 4.39 cm, P<0.001) in the control group (P for the difference between the groups <0.001, repeated-measures ANOVA). Body sway area increased 0.11 cm (95% CI 0.01 cm to 0.21 cm, P=0.001) in the exercise group and 0.48 cm (95% CI 0.29 cm to 0.67 cm, P<0.001) in the control group (P <0.001).

In both groups, the TUG -score improved over the first 12 months of the study, and the improvement was sustained in the exercise group (mean change over time -2.6 s, 95% CI -3.1 s to -2.2 s, P<0.001), while there was a gradual decrease in the performance towards the end of the study in the control group (mean change -1.1 s, 95% CI -1.5 s to -0.7 s, P<0.001) (P<0.001, repeated-measures ANOVA). The women in the exercise group improved their mean walking speed by 0.24 m/s (95% CI 0.18 m/s to 0.29 m/s) while the control group had a mean decrement of 0.07 m/s (95% CI -0.12 m/s to -0.02 m/s) (P<0.001). The mean distance walked in two minutes improved by 20.8 m (95% CI 16.1
m to 25.6 m, P<0.001) in the exercise group and decreased by 2.0 m (95% CI -6.2 m to 2.2, P=0.15) in the control group (P<0.001).

Fig. 13. Change from baseline in balance measures during the study period and the significance of the difference between the groups in the repeated-measures ANOVA. Bars represent 95% CIs. (n=160 at each timepoint).

Fig. 14. Change from baseline in walking tests during the study period and the significance of the difference between the groups in the repeated-measures ANOVA. Bars represent 95% CIs. (n=160 at each timepoint).

5.2.4 Functional capacity

Overall daily activity outside the program, measured with the Frenchay Activities Index, showed a similar decrease in the exercise group (P=0.002) and the control group (P=0.002). There were no significant intra-group or intergroup differences in the depressive symptoms measured with the GDS or the cognitive functions measured with the MMSE. When we compared the women with at least one fall (n=80) with those with no falls (n=61), the fallers performed worse in the MMSE test (P=0.04) and in the TUG test compared with the non-fallers (P=0.04; P=0.02, respectively). Frequent fallers (more
than three falls during the study) experienced a more profound increase in body sway than the women with less than three falls (P=0.01).

5.3 Reliability of the inclinometric method for assessing body sway

5.3.1 Test-retest reliability

There was a significant linear correlation between the two repeated inclinometric values for total sway path length ($y=0.836x + 1.318$, coefficient of determination $r^2=0.683$) and for sway area ($y=0.576x + 0.204$, $r^2=0.500$) (Figure 15). The Bland and Altman analyses for repeated measurements of total sway path length and sway area indicate that the differences between the first and second values are randomly scattered around a mean of approximately zero and there is no evidence of bias (Figure 16).

Fig. 15. Correlation of test versus retest of total body sway path length (cm) and area (cm$^2$) of the inclinometric method (n=51).

Fig. 16. Bland and Altman analysis for total body sway path length (cm) and area (cm$^2$) data from the inclinometric test-retest measurements (n=51).
5.3.2 Comparison of the methods

The mean values of sway path length assessed with the force platform method were higher than those assessed with the inclinometric method, although the calculating height of sway was similar. The amount of sway was significantly higher in the lateral direction (P < 0.001) in both inclinometric and force platform measurements.

There was a significant linear correlation between the values of total body sway path length measured with the inclinometric method and those of lateral directional sway movements measured with the force platform method (y=1.129x + 20.988, r² = 0.466). The correlation was even stronger between the inclinometric sway path length and antero-posterior directional (y=1.437x + 5.463, r² = 0.694) and combined lateral and antero-posterior directional (y=0.257x + 2.646, r² = 0.623) sway movements measured with the force platform method (Figure 17). The summary measure was used to include both lateral and antero-posterior components of body sway from the force platform measurement into the comparison, since inclinometric total body sway length measurement also includes these both components.

Fig. 17. Correlation of inclinometric body sway path length (cm) versus force platform x-length, y-length and x-length+y-length (n=29).
6 Discussion

6.1 Methodology (Studies I-V)

In this study, the target population consisted of all women aged 70 to 73 residing in Oulu, and still living at home in 1997. Among 1,222 women, we evaluated retrospectively the contribution of lifelong lifestyle factors to calcaneal and distal forearm bone mass and self-reported fractures, and prospectively the effect of long-term impact and balancing exercises on bone mass and functional ability in elderly women considered to be at risk of osteoporotic fractures on the basis of a low baseline BMD (n=160).

The strength of the study was its population-based, prospective, randomized design. The target population was a homogenous, stable and representative sample of aged Finnish women, obtained from the National Population Register of Finland, which has 100% coverage. The intervention (Studies III and IV) also had the advantage of being long-term and having extremely high attendance and adherence rates, despite the population-based approach. This suggests that the chosen regimen could have a high feasibility in the general population. Furthermore, the analysis was based on intention to treat, which eliminated the possible bias caused by drop outs.

On the other hand, several limitations need to be considered. Generalization of the present results to institutionalized or other age groups of women is not possible. Of the 1,689 originally eligible women 467 (27.6%) did not participate in the study, and we assume that those were the frailest group of our cohort, perhaps many of them nonambulatory, and may have had lower BMDs. Although the response rate was not lower than usually observed in studies of the elderly, in order to make these observations more generalizable, the findings must be replicated in institutionalized women and other age groups of women. One limitation of studies I and II was the partly cross-sectional design. Additionally, the QUS measurements were not available for 151 women. We analyzed the age, education, calcium intake, past and current physical activity, BMI, height, weight, and BMD of those 151 women and they did not differ from the total population.

In studies III and IV, for obvious reasons, it was not possible to blind patients to the intervention. Furthermore, the way we handled missing outcome data in studies III and IV may have introduced some bias. Our aim in this study was however pragmatic, and
the purpose was to answer "the public health question" by ignoring adherence when the data were analyzed. On treatment analyses would have overestimated the exercise effects and not reflected the way exercise would perform in the population.

There is no "golden standard" method for estimating physical activity, and past activity is even more difficult to estimate than present activity. Nevertheless, we wanted to collect the data on physical activity level at different age stages, and a questionnaire was the only method of choice. Although self-assessment questionnaires do not provide detailed information about specific activities, they are useful in grouping people into categories. We used a modified Paffenbarger (Greendale et al. 1995) questionnaire to assess leisure time physical activity. Although the validity of the original Paffenbarger physical activity questionnaire (Paffenbarger, Jr. et al. 1978) with respect to cardiovascular outcomes has been well documented, it estimates fitness more than the potential bone-loading character of certain activities. This may limit its sensitivity to detect bone density effects. The frequency of incomplete information concerning physical activity at the age of 15 was 21% and at the age of 30 20% which was evidently a problem of recall. Recalled information on physical activity in the distant past must be viewed with caution and prospective studies are needed to confirm our results. Unfortunately, objective instruments for measuring current physical activity, e.g. pedometers, were not available in studies III and IV.

A self-report was used to assess the frequency of fractures and falls (fall diaries) in studies I to V. Self-report of major osteoporotic fractures has been demonstrated to be a reasonably accurate method for obtaining information about the occurrence and timing of hip and distal forearm fractures in particular (Ismail et al. 2000). Dietary calcium intake during four time periods of lifespan (studies I and II) and during the intervention (studies III and IV) was computed as the sum of intakes of milk and cheese. A more accurate method for assessing current intake would have been a food frequency questionnaire or a food record. Nelson et al. (Nelson et al. 1989) have shown that at least eight days of diet records are needed to achieve a reliability coefficient for calcium intake of over 0.9.

Measurement of BMD is the basis of the diagnosis of osteoporosis, and DXA is the most commonly used technique today (Kröger & Reeve 1998). The precision of the DXA is good, it is fast, it involves a minimal radiation dose and gives regional values as well as total body values (Mazess et al. 1990). Although DXA measurement is currently the golden standard technique for osteoporosis diagnosis, it has limitations; i.e. artefacts due to degenerative disease or fat folds overlying the measurement site that may confound BMD results in a nonunion manner, particularly so for osteopenic, osteoporotic, and elderly patients (Binkley et al. 2003, Bolotin et al. 2003). Positive correlations between soft tissue anthropometrics and BMD may also be confounded by these inaccuracies (Bolotin et al. 2003). There are many possible sources of error in repeat bone density tests. Degenerative changes at the hip joint may limit rotation of the hip joint, and interpretation of serial BMD values may be confounded by the changes in the positioning of the hip during DXA scanning (Lekamwasam & Lenora 2003). Furthermore, variations from year to year in the machine readings, technologists, and positioning will decrease the reproducibility. These errors cause the phenomenon of regression to the mean; women who apparently lose bone during the first year of a trial will then apparently gain it back over the second year. In studies III and IV, we tried to overcome this by careful operator training. Furthermore, the bone density printouts were examined to see if there were
noticeable differences in the position or the area measured. In addition to BMD, we also reported the BMC value, which reflects the amount of mineral of the given bone site, and has been suggested as a measure of the cross-sectional area occupied by bone mineral. An increase in the projected bone area as a result of increased bone size, e.g. from subperiosteal expansion, would lead to a decrease in BMD even if the BMC remains unchanged (Young et al. 1994, McCreadie & Goldstein 2000). BMC changes under unchanged BMD in this study may suggest some changes in the bone area or bone geometry. However, BMC is not able to differentiate between the actual size, geometry, structure or composition of the given site (Bozolin et al. 2003) and therefore, no detailed conclusion can be made regarding the geometrical changes in the present study.

Calcaneal BUA and distal radius DXA were chosen for the measurement of bone density for several reasons (Studies I to IV). Ultrasonography and peripheral DXA are simple, safe and inexpensive methods for evaluating bone strength. Both calcaneus and distal radius encompass a large volume of trabecular bone known to be affected by postmenopausal osteoporosis, and both measurements predict independently the occurrence of fractures (Hans et al. 1996, Miller et al. 2002, Huotio et al. 2004). Previously, calcaneal BUA has been reported to be associated with high-impact activities (Jakes et al. 2001), trabecular bone volume and trabecular orientation, and to reflect structure apart from quality (Gluer et al. 1994b). Quality assurance and quality control have been shown to be problematic especially with QUS equipment (Hans et al. 2002b). Nevertheless, daily QC was performed according to manufacturer's recommendations and the transducer pads were replaced even more often than recommended. It is known, however, that the manufacturer specific phantoms that are used with QUS devices are influenced by many external factors, and they cannot be regarded as good indicators of device stability. A limitation in this study was that the precision of the QUS was not examined.

Studies I and II were mainly focused on the association of lifelong physical activity and osteoporosis, which was the rationale for choosing both a weight-bearing site and a non-weight-bearing site for the measurements. Distal radius also served as a reference bone in studies III and IV, and it was anticipated that the intervention would have no effect on radius, and the possible changes in BMD would reflect the age-related changes in a non-weight-bearing bone.

In study V, the measurements were performed in two rather large groups of aged subjects known to be at risk for falling. A novel aspect in the study was the simultaneous measurement of antero-posterior and medial-lateral postural sway. Unlike the previous inclinometric methods (Lombardi et al. 2001, Panella et al. 2002), the present portable inclinometric device was designed to avoid rotational artefacts by a particular joint structure, and to detect body movements caused by multiple simultaneous motions of the lower extremity joints. This kind of structure with a measuring rod relaying movements of the body to the detecting inclinometers has not previously been described.

A limitation in study V was that the force platform method only provided COP values, while the inclinometric method offered COG values. It is known that COP values are usually larger than the COG values, because the dynamic component of postural sway is included in the COP location. However, it was possible to compare the methods, and the analyses revealed no sign of bias.
6.2 Determinants of low bone mass (Studies I, II)

Few previous studies have evaluated the association between total current and lifetime habitual exercise and bone mass in elderly women. The results from the present studies I and II confirm the previous findings that lifetime habitual physical activity may protect lean elderly women from increased bone loss at weight-bearing sites of skeleton (Greendale et al. 1995, Lunt et al. 2001). One explanation for the result may be that the skeleton responds to mechanical stress provided by body weight with a stimulation of osteoblast activity resulting in increased BMD. Elderly women with low BMI do not have the advantage of excessive body weight, but the mechanical stress for bone can be provided by load-bearing physical activity. As a measurement site, the calcaneus is particularly sensitive to the amount of exercise the patient takes, which may explain the positive effect of current and past recreational physical activity on the calcaneum BUA values, but not on the BMD of the non-weight-bearing radius in our data. Increased fat mass is also likely to support greater estrogen production and thus contribute to bone formation (Barrett-Connor & Kritz-Silverstein 1996). On the other hand, the differences between the results of radial and calcaneal measurements may partly be due to differences between the QUS and DXA methods. While peripheral DXA measures BMD and BMC, BUA has been found to correlate with trabecular bone volume and trabecular orientation, and to reflect structure apart from quality (Gluer et al. 1994b).

Few previous studies have examined the relationship between lifetime occupational physical activity and osteoporosis, and the results are conflicting (Jaglal et al. 1995, van der Voort et al. 2001). Our results concerning job-related activity contradict the hypothesis that weight-bearing activity preserves bone mass (Studies I and II). One explanation may be the static type of mechanical loading at heavy jobs reported in this study, such as within the building industry. The most effective type of mechanical stimulus inducing bone formation according to previous studies includes both high strain rates and versatile movements (Heinonen et al. 1996). On the other hand, the women with sedentary jobs were more educated in our cohort and their nutritional awareness and thus their nutritional state may be better.

The most significant risk factors for self-reported low-trauma postmenopausal fractures in study II were low calcaneum BUA and low lifetime habitual physical activity irrespective of recent falling. It has been suggested that high kinetic energies and the orientation of the faller contribute to the occurrence of fracture (Luukinen et al. 2000). It can be assumed that physically active fallers were protected from fractures perhaps due to better motor performance, reaction time, balance, muscle strength and coordination. Prospective studies including reliable measurement of these characteristics of physical performance are needed. We also found that living alone was a risk factor for fractures. This suggests that elderly unpartnered people may have a different daily-life pattern and may be in poorer physical condition, both of which may be associated with a diminished social network. This is further supported by a recent finding that strong social networks may protect against the risk of falling in older adults (Faulkner et al. 2003).

Non-insulin-dependent diabetes has been associated with increased (van Daele et al. 1995, Lunt et al. 2001, Schwartz et al. 2001), decreased (Levin et al. 1976, Isaia et al. 1987) and unchanged (Wakasugi et al. 1993) BMD. The present study was the first to
investigate the relationship between type 2 diabetes and low bone density separately in lean, normal and obese women. In studies I and II, we found that the presence of type 2 diabetes was significantly associated with increased calcaneal BUA, increased radial BMD and self-reported fractures in the lowest tertile of BMI of the women. There may be several explanations for the higher BMD in lean women with diabetes. Type 2 diabetes is preceded by a period of hyperinsulinemia and increased level of insulin-like growth factor before the onset of diabetes (Yki-Jarvinen 1994, Stolk et al. 1996, Seck et al. 2001). Our finding may partly be explained by the differences in insulin levels and insulin sensitivity between lean and obese women. Hyperinsulinemia is associated with obesity, but after the onset of diabetes at least a relative insulin deficiency develops in all type 2 diabetic patients. This deficiency can even be more pronounced in the lean women who on the whole are more insulin-sensitive than their more obese counterparts, and do not have the advantage of the prediabetic obesity-associated hyperinsulinemia. Secondly, both endogenous and exogenous insulin may act to increase BMD in patients with non-insulin-dependent diabetes (Cornish et al. 1996). In our data, there was no difference in the frequency of insulin users between the different BMI strata, and the association between diabetes and bone density in the leanest group of women can not be explained by the medication they were receiving. Thirdly, an influence of vitamin D receptor (VDR) gene polymorphisms on BMD in nonobese postmenopausal women has been observed (Vandevyver et al. 1997), and polymorphism at the VDR gene locus has been suggested to be associated with insulin sensitivity as well (Chiu et al. 2001). Whether the answer lies in genetic-lifestyle interaction remains to be studied in future prospective studies.

6.3 **Effect of exercise on risk factors for hip fractures**

6.3.1 **Bone mass (Study III)**

Although recent systematic reviews (Wallace & Cumming 2000, Bonaiuti et al. 2004) clearly show that exercise slows the rate of bone loss at the spine in postmenopausal women, there is a great deal of heterogeneity between the study results for the proximal femur in elderly women (Lau et al. 1992, Bravo et al. 1996, Lord et al. 1996b, Ebrahim et al. 1997) (Prince et al. 1995). Two years of brisk walking had a positive effect on femoral neck BMD (mean age of the women 67 years) (Ebrahim et al. 1997) while 10 months of stepping (mean age 76 years) (Lau et al. 1992) and mixed balance- and weight-bearing exercise (mean age 72 years) (Lord et al. 1996b) had a negative effect on proximal femur BMD. The osteogenic effects of exercise training are suggested to be site-specific to the anatomic sites at which the mechanical strains occur (Tommerup et al. 1993, Haapasalo et al. 1994). This was further emphasized by a recent randomized trial, where 157 elderly osteoporotic and osteopenic women performed daily heel drop exercises monitored with a home-use force platform (Hans et al. 2002a). The authors hypothesized, based on Wolff’s law, that most participants would likely experience local BMD losses at some hip bone sites, and local increases at others, and they developed a
new statistical classification model based on individual site-specific BMD changes. Although the authors found no significant differences between the groups in overall BMD measurements, they found that the result of the impact loading was a local redistribution in BMD. In our study, the exercise regimen was chosen to induce stress and tension especially in the proximal femur and the gluteal and hip muscles inserting to the lateral part of the trochanter. The results concerning the observed BMC changes at the trochanter are consistent with the chosen regimen and indicate the site-specificity of the training effect.

The intervention showed no effect on BMD at any hip bone sites, and this may be partly explained by the DXA-based method. Although DXA measurement is currently the golden standard technique for osteoporosis diagnosis, it has several limitations mentioned before. Recently it has been suggested that studying bending resistance and geometry along with conventional bone mass measurements could lead to a better understanding of the effect of physical activity and exercise on bone. A large population-based prospective study revealed that changes in hip loading are associated with mechanically appropriate alteration in the section modulus, an index of bending and torsional strength (Beck et al. 2001). Kaptoge et al. found that hip section modulus was more strongly related to physical activity than BMD in elderly women (Kaptoge et al. 2003a). It has also been suggested that the true material density of bone tissue remains quite constant with age, whereas the size, geometry and trabecular architecture of bones vary considerably between different sites and individuals, and like other bones, the femoral neck expands slowly with aging (Heaney et al. 1997) (Sievanen et al. 1999b). In addition to BMD, we also reported the BMC value, which reflects the amount of mineral of the given bone site, and has been suggested as a measure of the cross-sectional area occupied by bone mineral. An increase in the projected bone area as a result of increased bone size would lead to a decrease in BMD even if the BMC remains unchanged (Young et al. 1994, McCreadie & Goldstein 2000). BMC changes under unchanged BMD in this study may suggest some changes in the bone area or bone geometry. However, BMC is not able to differentiate between the actual size, geometry, structure or composition of the given site (Sievanen et al. 1999b) and therefore, no detailed conclusion can be made regarding the geometrical changes in the present study.

Although the calcaneum is known to be particularly sensitive to the amount of exercise the patient takes, the exercise had no effect on the BUA and SOS values measured by QUS at the calcaneum. One explanation may be that the exercise did not induce enough gravitational forces (impacts) to strengthen the calcaneum, and the positive response at the trochanter may have been mainly a result from muscular pull through tendinous attachments at the trochanter. Secondly, quality assurance and quality control have been shown to be problematic especially with QUS equipment (Hans et al. 2002b). Nevertheless, daily quality control was performed according to manufacturer's recommendations and the transducer pads were replaced even more often than recommended. It is known, however, that the manufacturer specific phantoms that are used with QUS devices are influenced by many external factors, and they cannot be regarded as good indicators of device stability.

In this study, change in weight during the follow-up period was the main determinant of the variation in BMD and BMC of the hip, indicating that maintaining or even gaining weight seems to retard excessive bone loss at the hip in elderly women. This is in
agreement with the previous studies suggesting that weight and weight increase are associated with maintenance of bone mass and reduced bone loss, whereas thinness and weight loss lead to enhanced bone loss (Nguyen et al. 1998, Dargent-Molina et al. 2000). It is known that elderly women tend to lose weight rather than gain weight. In our study, the opposite finding may be explained by the general information on nutrition and health given to the participants. Although inaccuracies in the DXA method may confuse the interpretation of the association between soft tissue anthropometry and BMD, it should be kept in mind that low body weight and unintentional weight loss have also been reported to be manifestations of overall frailty, a syndrome that is predictive of incident falls, fractures, disability, hospitalization, and mortality (Vanitallie 2003). Maintenance of body weight should therefore be emphasized in health education and interventions targeted at elderly women.

6.3.2 Muscle strength, balance and gait (Study IV)

Our finding that comprehensive weight-bearing exercise improves postural stability, lower extremity strength and gait speed is consistent with previous randomized exercise interventions in older people (Tinetti et al. 1994, Lord et al. 1996b, Shumway-Cook et al. 1997, Carter et al. 2002). A twelve-month exercise program that included twice-weekly activities similar to our study resulted in significant improvements in muscle strength, body sway and walking velocity in community-dwelling older women (Lord et al. 1996b). Balance and mobility seem to improve consistently in interventions that employ some form of walking or balance training, while strength and cardiovascular endurance training programs do not have the same effect (Rooks et al. 1997, Shumway-Cook et al. 1997, Wolf et al. 2001). On the other hand, Campbell et al. (Campbell et al. 1997) found an improvement in balance, but not in walking speed or distance after six months of home-based strength and balance exercises, and another previous trial with 50 elderly women had contradictory findings with regard to different body sway measures (Lichtenstein et al. 1989). These slightly inconsistent findings of the previous studies may reflect the differences in the training regimens used across the studies (type, frequency, duration).

In the present study, there was a significant difference between the exercise and control group in postural sway in favor of the exercise group, reflecting the effectiveness of the chosen exercises in improving static balance. Our results are in agreement with the previous findings of exercise-related improvements in women with osteoporosis (Malmros et al. 1998) and in community-dwelling older women (Lord et al. 1996b, Liu-Ambrose et al. 2004) To provide better insight to community mobility compared to the measures of standing balance in a fixed position, we measured dynamic balance with the TUG test and a timed 30-meter walking test. Our study extends the previous finding of exercise-related improvement in dynamic balance in elderly women with osteoporosis (Carter et al. 2002) by demonstrating, in a larger, population-based cohort of women, that an exercise intervention can improve dynamic balance.

The chosen exercise regimen resulted in significant improvements in lower extremity strength. The increase in strength induced by versatile weight-bearing exercises including
standing squats complements the findings of the previous studies that have employed regimens of resistance training requiring weights and equipment (Fiatarone et al. 1990, Carter et al. 2002) In addition to the improvements in strength, there were significant improvements in strength-related walking velocity, endurance and reaction time - all factors identified as primary risk factors for hip fracture.

The distribution of fractures between the groups was somewhat different, and the fractures were located more proximally in the control group than in the exercise group. This might indicate that the type of fall may have been different among the exercisers. The chosen exercise had an effect on many physiological characteristics, that may modify the fall dynamics and improve additional absorptive mechanisms. It is known that breaking the fall with outstretched arm or eccentric action of the quadriceps during descent are probably involved in falls without hip fracture (Robinovitch et al. 1995). The difference in the distribution of fractures might reflect the altered fall mechanism in the exercisers. We acknowledge that improving bone mass, muscle strength or balance does not guarantee fewer fractures. Although there were fewer fractures in the exercise group during the follow-up (Studies III and IV), the sample size of this study was not large enough for this outcome, and no conclusions can be drawn from these data. Future research using falls and fractures as the primary outcome measures are needed to confirm this finding.

At present, there is no universally accepted policy for screening to identify individuals at high risk of fracture. Because falls and fractures result from various combinations of factors, an effective clinical strategy for risk assessment and management must take into account many predisposing factors. Brief screens such as the TUG test could easily be incorporated into short clinical encounters. Of all the methods of fracture prevention, regular physical activity is the only one that provides other considerable health-related benefits that may have a positive, albeit indirect, effect on fall and fracture risk in older adults.

### 6.4 Reliability of the inclinometric method (Study V)

When interpreting the results of the repeatability study, it should be kept in mind that postural control is a complex, dynamic interaction of vestibular, visual and proprioceptive signals analyzed by the central nervous system resulting in constantly changing motor outputs. Thus, the fluctuating nature of the response variable and momentary individual balancing body movements may partly explain the variation of individual results between the two sessions. However, the repeatability of the inclinometric measurements was moderate and there was no sign of bias. Furthermore, the measuring protocol was safe and all of the 51 women could perform both of the measurements.

The agreement study compared two different postural sway measurement systems, the inclinometric method and the force platform method. Although the calculated sway parameters were slightly different, correlation was found between the measures of the two methods indicated by moderately high coefficients of determination. Both of the methods could also detect the increased amount of spontaneous postural sway in the lateral direction compared to the forward-backward direction, plausibly explained by the
decreased area of weight bearing and the narrow base of support while standing feet together. The results indicate that the inclinometric method and the force platform method quantify similar aspects of postural stability, although the measurement parameters are different.
7 Conclusions

1. Risk factors for decreased calcaneal ultrasound attenuation and low radial bone density appear to be different among lean and normal/obese women. Lifelong recreational physical activity, low physical activity at work, type 2 diabetes and hypertension seem to be associated with increased bone density, while high coffee intake may increase the risk of lower bone density in lean elderly women.

2. Lifestyle factors, especially regular recreational physical activity, may modify the risk of low bone mass at load-bearing bone sites and the risk of falls and fractures among lean elderly women. Type 2 diabetes may have a protective role but the mechanism remains unknown. Since depressive symptoms, high coffee intake and impaired vision were also associated with risk of falling, multifactorial prevention strategies targeted at lean elderly women are recommended.

3. In elderly women with low bone mass, impact exercise seems to restrain bone loss at upper femur, and may prevent fall-related fractures.

4. Weight-bearing exercise is a safe, feasible and effective way of modifying well-recognized risk factors for falls and fractures, and may even prevent fall-related fractures in elderly women.

5. The inclinometric method is a repeatable and valid method for assessing postural sway.
References


