Mikko Määttä

ASSESSMENT OF OSTEOPOROSIS AND FRACTURE RISK

AXIAL TRANSMISSION ULTRASOUND AND LIFESTYLE-RELATED RISK FACTORS

Mikko Määttä
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ASSESSMENT OF OSTEOPOROSIS AND FRACTURE RISK
Axial transmission ultrasound and lifestyle-related risk factors

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University of Oulu Graduate School; University of Oulu, Faculty of Medicine, Institute of Biomedicine, Department of Medical Technology, P.O. Box 5000, FI-90014 University of Oulu, Finland; Infotech Oulu, P.O. Box 4500, FI-90014 University of Oulu, Finland; University of Jyväskylä, Faculty of Mathematics and Science, Department of Physics, P.O. Box 35, FI-40014 University of Jyväskylä, Finland; Oulu Deaconess Institute, Department of Sports and Exercise Medicine, Kajaaninkatu 17, FI-90100 Oulu, Finland
Oulu, Finland

Abstract
Osteoporotic hip fractures are associated with high mortality and morbidity rates as well as significant costs. Low-frequency (LF) axial transmission ultrasound is a promising modality for assessing mineral density and geometrical properties. Thus, it may yield additional information on the risk of osteoporotic fractures. This study aimed to evaluate the ability of LF ultrasound to assess osteoporotic status and the risk of fracture in postmenopausal women. Also, lifestyle-related risk factors of hip fractures and the additional discrimination value of combining lifestyle-related risk factors and LF ultrasound velocity were assessed.

Two study populations were used. The first consisted of 1,222 older women. Lifestyle-related risk factors and mobility were assessed at baseline. The women were followed for 13 years and the fractures that occurred were recorded. A subgroup of the women was later measured with LF ultrasound and dual-energy x-ray absorptiometry (DXA). The other study population included 95 postmenopausal women whose fracture history was gathered and bone status assessed with LF ultrasound, DXA and peripheral quantitative computed tomography (pQCT).

Low body mass and impaired mobility predicted hip fractures. In addition, the risk of cervical hip fracture was increased by low physical activity and decreased by moderate coffee consumption and hypertension. Smoking and old age increased the risk of trochanteric hip fracture. The LF ultrasound velocity reflected to some degree the geometry and bone mineral density of the proximal femur. Decreased low-frequency ultrasound velocity was a significant risk factor of hip fracture even when combined with lifestyle-related risk factors. The LF ultrasound method showed similar fracture discrimination ability compared to DXA and pQCT, especially on the radius.

In conclusion, the LF ultrasound method showed promising results in bone characterization and fracture discrimination. Further prospective studies with larger population are needed to confirm the combined effect of clinical risk factors and LF ultrasound.

Keywords: bone, bone density, fracture, guided wave, low-frequency, osteoporosis, postmenopausal
Määttä, Mikko, Osteoporoosin ja murtumariskin arviointi. Luun aksiaalisuuntainen ultraäänimittaus ja elintapoihin liittyvät riskitekijät

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta, Biolääketieteen laitos, Lääketieteet teknikka, PL 5000, 90014 Oulun yliopisto; Infotech Oulu, PL 4500, 90014 Oulun yliopisto; Jyväskylän yliopisto, Matemaattis-luonnontieteellinen tiedekunta, Fysiikan laitos, PL 35, 40012 Jyväskylän yliopisto; Oulun Diakonissalaitos, Oulun Liikuntalääketieteellinen Klinikka, Kajaaninkatu 17, 90100 Oulu


Oulu

Tiivistelmä

Osteoporootisiin lonkkamurtumiin liittyvät korkean sairastavuuden ja kuolleisuuden lisäksi huomattavat taloudelliset kustannukset. Tässä työssä tutkittiin matalataajuisen ultraäänitekniikan soveltuvuutta osteoporoosin ja murtumariskin arviointiin. Matalataajuista luun pituusakselin suuntaita ultraäänteekniikkaa voidaan käyttää luun mineraalitiheyden ja rakenteen tutkimiseen. Lisäksi tutkittiin elintapoihin liittyviä lonkkamurtuman riskitekijöitä sekä näiden yhdistämistä ultraäänimittauksestaan kanssa riskimallin, ja


Tutkittu ultraäänimenetelmä osoittautui lupaavaksi työkaluksi luun karakterisoinnissa ja murtumariskin arvionnissa. Laajempia seurantatutkimuksia tulee vahvistamiseksi tarvitaan erityisesti elintapoihin liittyvien riskitekijöiden ja uloraanen yhdistämisen osalta.

Asiasanat: luuntiheys, murtuma, ohjatut aallot, osteoporoosi, riskitekijä, ultraääni
To my dearest
Elina,
Lassi, and Luukas
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## Abbreviations and symbols

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>$A_n$</td>
<td>Antisymmetrical Lamb mode ($n^{th}$ order)</td>
</tr>
<tr>
<td>AT</td>
<td>Axial transmission</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under curve</td>
</tr>
<tr>
<td>BMC</td>
<td>Bone mineral content</td>
</tr>
<tr>
<td>BMD</td>
<td>Bone mineral density</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BMU</td>
<td>Bone multicellular unit</td>
</tr>
<tr>
<td>BUA</td>
<td>Broadband ultrasound attenuation</td>
</tr>
<tr>
<td>$c$</td>
<td>Velocity of ultrasound</td>
</tr>
<tr>
<td>CBMD</td>
<td>Cortical bone mineral density</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>$c_{L}$, $c_{T}$</td>
<td>Velocity of longitudinal and transverse ultrasound wave</td>
</tr>
<tr>
<td>CV$_{RMS}$</td>
<td>Coefficient of variation (root mean square value)</td>
</tr>
<tr>
<td>DXA</td>
<td>Dual-energy x-ray absorptiometry</td>
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<tr>
<td>FAS</td>
<td>First arriving signal</td>
</tr>
<tr>
<td>$f_c$</td>
<td>Center frequency</td>
</tr>
<tr>
<td>FEA</td>
<td>Finite element analysis</td>
</tr>
<tr>
<td>FN</td>
<td>Femoral neck</td>
</tr>
<tr>
<td>FND</td>
<td>Femoral neck diameter</td>
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<tr>
<td>FSC</td>
<td>Femoral shaft cortex thickness</td>
</tr>
<tr>
<td>FSD</td>
<td>Femoral shaft diameter</td>
</tr>
<tr>
<td>Fx</td>
<td>Fracture</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Classification of Diseases, 10$^{th}$ revision</td>
</tr>
<tr>
<td>INTER</td>
<td>Intertrochanteric</td>
</tr>
<tr>
<td>L1-L4</td>
<td>Lumbar vertebrae 1-4</td>
</tr>
<tr>
<td>LF</td>
<td>Low-frequency</td>
</tr>
<tr>
<td>LS</td>
<td>Lumbar spine</td>
</tr>
<tr>
<td>$n$</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>NF</td>
<td>Non-fracture</td>
</tr>
<tr>
<td>Neck Fx</td>
<td>Cervical hip fracture</td>
</tr>
<tr>
<td>OF</td>
<td>Other fracture</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>p</td>
<td>Statistical significance level</td>
</tr>
<tr>
<td>PA</td>
<td>Physical activity</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
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<tr>
<td>pQCT</td>
<td>Peripheral quantitative computed tomography</td>
</tr>
<tr>
<td>QCT</td>
<td>Quantitative computed tomography</td>
</tr>
<tr>
<td>QUS</td>
<td>Quantitative ultrasound</td>
</tr>
<tr>
<td>r</td>
<td>Distance / Correlation coefficient</td>
</tr>
<tr>
<td>$R^2$</td>
<td>Coefficient of determination</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver operator characteristics</td>
</tr>
<tr>
<td>ScBMD</td>
<td>Subcortical bone mineral density</td>
</tr>
<tr>
<td>SCV</td>
<td>Standardized coefficient of variation</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>$S_n$</td>
<td>Symmetrical Lamb mode ($n^{th}$ order)</td>
</tr>
<tr>
<td>SOS</td>
<td>Speed of sound</td>
</tr>
<tr>
<td>TBS</td>
<td>Trabecular bone score</td>
</tr>
<tr>
<td>TF</td>
<td>Total femur</td>
</tr>
<tr>
<td>TOF</td>
<td>Time of flight</td>
</tr>
<tr>
<td>Troch Fx</td>
<td>Trochanteric hip fracture</td>
</tr>
<tr>
<td>TUG</td>
<td>Timed up &amp; go</td>
</tr>
<tr>
<td>$V_{FAS}$</td>
<td>Velocity of first arriving signal</td>
</tr>
<tr>
<td>$V_{LF}$</td>
<td>Velocity of low-frequency ultrasound</td>
</tr>
<tr>
<td>WARD</td>
<td>Ward’s triangle</td>
</tr>
<tr>
<td>WB</td>
<td>Whole body</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>Wavelength</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Density</td>
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</table>
List of original publications

The thesis consists of four original articles that are referred to in the text by their Roman numerals (I-IV):


* equal contribution.

Some additional data related to study III are also presented.
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1 Introduction

Osteoporosis and consequent osteoporotic fractures are a significant public health problem. Hip fracture is the most severe osteoporotic fracture. It is also the most common cause of acute orthopedic treatment among the elderly. They are without exception associated with chronic pain, reduced mobility, disability, and an increased degree of dependence (Keene et al. 1993). Loss of function and independence among survivors is profound, with 40% unable to walk independently and 60% requiring assistance a year later (Magaziner et al. 1990). Also, a high mortality rate of up to 30% is associated with hip fractures during the first year after fracture (Parker & Johansen 2006). Approximately 1.6 million hip fractures occur worldwide each year, Scandinavia having the highest incidence worldwide (Cooper et al. 2011). By the year 2050 the number of hip fractures could reach 6.3 million while costs of fractures occurring only in Europe are expected to rise to €76.8 billion (Kanis & Johnell 2005).

At present, osteoporosis assessment is based on bone mineral density (BMD) measurements by dual-energy x-ray absorptiometry (DXA). However, most hip fractures occur among people with BMD values in the non-osteoporotic range (Schuit et al. 2004) and treatment strategies relying solely on BMD measurements will miss many people at risk for fracture. Therefore, the use of clinical risk factors as well as alternative methods for assessing bone strength has been introduced. The prime clinical risk factors are old age and history of fragility fracture. Others include low body mass index, long-term glucocorticoid therapy, and smoking (Cummings et al. 1995, Johnell et al. 1995, Kanis et al. 2005).

Recently, a fracture risk assessment tool called the FRAX® has been introduced to assess the 10-year risk of osteoporotic fracture using a set of clinical risk factors, with or without BMD (Kanis JA on behalf of the World Health Organization Scientific Group 2007). In addition, non-skeletal risk factors that increase the risk of falls (Gregg et al. 1998, Wagner et al. 2009) – e.g., impaired mobility and balance – are important to identify and address as part of a preventive treatment. Previous studies have indicated that different hip fracture types, cervical and trochanteric hip fractures, may have different risk factors and etiology (Duboeuf et al. 1997, Mautalen et al. 1996).

Quantitative ultrasound (QUS) is an inexpensive and portable method which has been shown to discriminate fractured subjects from non-fractured controls (Marin et al. 2006). Ultrasound is a relatively inexpensive and portable technique which does not expose patients to ionizing radiation. The development of a
reliable and simple ultrasound method makes population screening more effective (e.g., in primary health care) and helps the initiation of preventive treatment of persons at high risk for fracture. The QUS measurements of cortical parts of long bones are often done using an axial transmission technique where the velocity of an ultrasonic pulse propagating along the axis of a bone is calculated. When low enough ultrasound excitation frequency is used guided waves are generated (Bossy et al. 2002, Nicholson et al. 2002). The characteristics of these guided waves are determined by the geometrical and material properties of the structure (e.g., bone) (Viktorov 1967). Because of their birth mechanism, guided waves are strongly dispersive and therefore sensitive to the early endosteal bone changes seen in osteoporosis (e.g., cortical thinning and increase of intracortical porosity). A low-frequency (LF) axial transmission ultrasound device, developed at the University of Jyväskylä, is founded on the theory of guided waves. In previous studies this LF ultrasound method has shown to be a promising modality for assessing cortical thickness and subcortical bone mineral density in radius and tibia (Kilappa et al. 2011, Moilanen et al. 2003, Moilanen et al. 2007, Muller et al. 2005, Nicholson et al. 2002). However, further work is needed to test the method’s usability on bone assessment especially in terms of fragility fractures.

The present study aims to assess the ability of the LF ultrasound method to discriminate subjects with osteoporosis from those with normal BMD as well as to evaluate the method’s capability in fracture discrimination. The other aim was to assess the association of various clinical and lifestyle-related risk factors of hip fractures and the combination of low-frequency ultrasound and these risk factors.
2 Review of the literature

2.1 Bone structure and physiology

Bones form the framework for our bodies, enabling locomotion and protecting our internal organs. They also participate in the homeostasis of calcium and phosphate (Del Fattore et al. 2012). Bone is a composite material comprised of an organic phase, mineral phase, and water. The organic phase, totaling approximately 25% of bone weight, consists of collagen fibrils (mostly type I) and non-collagenous proteins. The mineral phase (i.e., inorganic, approximately 70% of bone weight) is composed of mineral salts, mostly hydroxyapatite (Ca$_{10}$(PO$_4$)$_6$(OH)$_2$) (Njeh et al. 1999). The composition where collagen fibers are surrounded and infiltrated by plate-like apatite crystals gives the bone tissue distinctive mechanical properties (Rho et al. 1998). Variation in bone mineral content leads to the balance between material stiffness and flexibility (Turner 2002) whereas water content provides the viscoelasticity (Lakes et al. 1979).

Cortical and trabecular bone

Bones come in many shapes and sizes, such as long tubular bones (e.g., tibia), flat bilaminar plates (e.g., pelvic girdle), or irregular structures (e.g., vertebrae). Long bones can be divided into three different segments: epiphysis, metaphysis, and diaphysis (Fig. 1). At macrostructural level two different bone types can be distinguished: cortical (compact) and trabecular (cancellous) bone. Cortical bone is a dense highly hierarchical material composed of osteons, which in more detail consist of regular, cylindrically shaped lamellae (Rho et al. 1998). Trabecular bone is composed of a lattice of branching rod- and plate-like bone trabeculae forming a spongy structure. Compact bone is located on the cortical parts of the bone while cancellous bone can be found in the epiphysis of long bones and in the inner parts of flat and short bones. (Njeh et al. 1999)
Fig. 1. Schematic representation of the femur showing the basic structure of a long bone.

**Bone cells**

There are four main types of bone cells: bone-lining cells, osteoclasts, osteoblasts, and osteocytes (Njeh *et al.* 1999). Bone-lining cells cover the surfaces of the inactive bone including blood channels. The layer that bone-lining cells form on the outside of the bone is called periosteum (Fig. 1). A similar layer inside the bone is called endosteum. Osteoclasts are bone-destroyer cells that are responsible for resorption of the bone. Osteoclast precursors circulate in the bloodstream where they are recruited via multistep differentiation process when needed (Del Fattore *et al.* 2012). Osteoblasts are bone-forming cells that are derived from the mesenchymal stem cells. They control bone formation by laying down an uncalcified bone matrix, called osteoid, and participating in its mineralization. During the mineralization process, part of the osteoblasts are entombed in the osteoid and transformed into osteocytes (Seeman & Delmas 2006). Osteocytes form the body of the bone. They are the most abundant and longest-living cells in the adult skeleton (Neve *et al.* 2012). They are connected to neighboring osteocytes and bone-lining cells, which enables signaling between...
the cells (Han et al. 2004). Osteocytes also serve as mechanosensors translating bone deformation into the biochemical signals which indicate the need of bone remodeling (Neve et al. 2012, Seeman & Delmas 2006).

**Modeling and remodeling**

Bone is formed and maintained through modeling and remodeling processes (Seeman & Delmas 2006). In modeling, bone is formed by the osteoblasts on the endosteal and/or periosteal surfaces changing bone size and shape. In the remodeling process bone formation is preceded by bone resorption. During remodeling osteoclasts and osteoblasts work together as a bone multicellular unit (BMU, sometimes referred to as basic multicellular unit). Positive balance in BMU (i.e., higher osteoblast activity) results in bone formation whereas negative balance (i.e., higher osteoclast activity) leads to bone resorption.

Bone modeling and remodeling serve different purposes during different phases of life. During growth the purpose is to gain bone and build up the highest peak bone mass possible. During adulthood and older age the purpose is to maintain the acquired bone strength (Seeman & Delmas 2006). In healthy bone tissue, resorption and formation are in balance. Bone is formed where it is needed and resorbed where it is not needed. Estrogen deficiency after the menopause leads to negative balance in the BMU during which bone resorption dominates and causes bone loss (Del Fattore et al. 2012, Seeman & Delmas 2006). This decreases bone strength and makes bone more vulnerable to fracture.

**Determinants of bone strength**

Bones must be stiff in order to resist bending and at the same time they must be flexible to absorb the energy imposed by loading (Seeman 2008). When applied load exceeds the bone strength, a fracture occurs. Since bone is an anisotropic viscoelastic composite material, it has complex and unique mechanical properties which are affected by multiple determinants. Bone strength is determined by bone quantity, i.e., the bulk of the bone material, and bone quality, a vague term that is used to merge the material and structural properties (Fig. 2) (Bouxsein 2006, Seeman 2008). Bone turnover affects both bone quantity and bone quality alike, and in consequence the entire bone strength.
Bone mineral density (BMD) and bone mineral content (BMC) are the usual surrogate parameters to measure bone quantity. Measurements are often done using a dual-energy x-ray absorptiometry (DXA) scanner (see section 2.4.1). BMD is a strong determinant of bone strength and also correlates with the risk of fracture (Cummings et al. 2002, Johnell et al. 2005, Marshall et al. 1996, Nguyen et al. 2005). In addition, bone strength is affected by material and structural properties. Material properties encompass variables related to bone mineral and bone matrix. These include the degree of mineralization, properties of the collagen matrix, and mineral-to-matrix ratio (Felsenberg & Boonen 2005). Material properties also cover the extent of microcracks within the tissue. Structural properties include bone geometry (i.e., size and shape) and its microarchitecture, such as trabecular architecture and cortical thickness and porosity (Felsenberg & Boonen 2005).

During aging, bones undergo multiple changes. In women, after the menopause bone resorption is rapidly increased due to hormonal changes, i.e., estrogen deficiency. This rapidly increases the remodeling rate which has adverse effects on bone strength (Seeman 2008). More densely mineralized bone is resorbed and replaced by less densely mineralized and thus less stiff bone. Due to higher osteoclast activity, resorbed sites remain unfilled longer exposing bone to microcracks. Rapid remodeling also affects collagen isomerization and maturation, which decreases bone strength. There are also changes in the orientation of collagen fibers decreasing bone toughness (Wang et al. 2002). The structural changes in cortical bone include the increase in endosteal porosity which decreases cortical thickness (Zebaze et al. 2010). The higher cortical
porosity increases the bone surface/volume ratio which further increases the remodeling in the cortex. In trabecular bone, the thinning of trabeculae and the loss of connectivity decreases bone strength (Seeman 2008).

To overcome the changes due to aging bone mass is distributed further from the central axis by forming bone on the periosteal surface (Seeman 2008). This increases the ability of bone to resist bending and torsional loads with the same absolute amount of bone (Bouxsein 2006). This morphological change is observed in femoral diaphysis (Martin & Atkinson 1977) as well as in femoral neck (Beck et al. 1992). During aging the fatigue-life of bone shortens, damage formation patterns alter and bone becomes more vulnerable to fractures (Diab et al. 2006). Under increased magnitude of loading, number of loading cycles or loading time, microcracks start to accumulate in bone (Burr 2011). In healthy bone the remodeling process is able to repair the microcracks, stopping them from coalescing, and hence prevent bone fracture. In aging bone, however, this is not always the case.

2.2 Osteoporosis

According to the World Health Organization (WHO) osteoporosis is “a systemic skeletal disease characterized by low bone density and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility” (Report of a WHO Scientific Group 2003). In adult practice, osteoporosis is divided into two main categories: primary and secondary osteoporosis. Primary osteoporosis can further be divided into type 1 and type 2 osteoporosis.

Primary osteoporosis is related to normal bone physiology and is unassociated with any other illness. There seems to be no single or direct cause for primary osteoporosis. Two main types of primary osteoporosis are met: postmenopausal (type 1) osteoporosis and age-related or senile (type 2) osteoporosis occurring after 75 years of age. Secondary osteoporosis is caused by certain diseases (e.g., hyperthyroidism or rheumatoid arthritis), medications (e.g., glucocorticoids), or life-style-related factors (e.g., malnutrition or immobilization).

Osteoporosis is sometimes considered a silent disease since it usually remains asymptomatic until fracture occurs. Osteoporosis is more common in women than in men due to hormonal changes during the menopause, longer life expectancy, and lower peak bone mass. In developed countries the prevalence among women over 70 years is approximately 20% and among women over 80 years
approximately 40% (Kanis JA on behalf of the World Health Organization Scientific Group 2007).

2.3 Osteoporotic fractures

The adverse outcome of osteoporosis is a fracture. The most typical osteoporotic fractures occur at wrist, vertebra, and hip (Cummings & Melton 2002). In the year 2000, the number of osteoporotic fractures was estimated at 3.8 million in Europe and roughly 9 million worldwide (Johnell & Kanis 2006, Kanis & Johnell 2005). The corresponding costs in Europe alone were approximately €36.3 billion and are expected to rise to €76.8 billion by the year 2050 (Kanis & Johnell 2005).

Hip fracture is the most severe osteoporotic fracture. A high mortality rate of up to one third is associated with hip fractures during the first year after the fracture (Parker & Johansen 2006). Also, among survivors, the loss of functional ability and independence is substantive, with 40% unable to walk independently and 60% requiring assistance a year later. Approximately 0.9 million hip fractures occurred in Europe (Kanis & Johnell 2005) and 1.6 million worldwide (Cooper et al. 2011) in the year 2000. According to one estimate the number of hip fractures may increase to 4.5 million by the year 2050 (Gullberg et al. 1997). However, a plateau phase in hip fracture incidence has been observed worldwide (Cooper et al. 2011) as well as in Finland (Kannus et al. 2006). In Finland the age-standardized hip fracture incidence of 293 fractures/100,000 persons among women and 180 fractures/100,000 persons among men has recently been reported (Kanis et al. 2012). However, despite the decline in incidence the total number of hip fractures is likely to rise due to increasing life expectancy and increased amount of older population (Marks 2011). The total costs of a single hip fracture in Finland during the first year after the fracture have varied between €14,000 and €36,000 depending on whether the patient managed at home or whether she/he needed to be institutionalized (Nurmi et al. 2003, Sund et al. 2011). Similar figures have been reported in other parts of the world (Budhia et al. 2012, Nikitovic et al. 2012, Zethraeus et al. 1997).

Hip fractures can be classified into two categories: intracapsular and extracapsular fractures (Parker & Johansen 2006). Intracapsular fractures include cervical fractures whereas extracapsular fractures comprise trochanteric and subtrochanteric hip fractures (Fig. 3).
Fig. 3. Hip fracture classification.

Previous studies have suggested that the etiologies of cervical and trochanteric hip fractures are different. Femoral geometry has been shown to have greater effect on the risk of cervical fractures. Subjects with cervical fractures seem to have longer hip axis length and wider neck-shaft angle compared to age-matched controls (Duboeuf et al. 1997, Gnudi et al. 2002). On the other hand, low femoral BMD seems to be more related to increased risk of trochanteric fracture (Mautalen et al. 1996, Vega et al. 1991). Also, older age is reported to predispose to trochanteric hip fractures (Fox et al. 2000, Lin et al. 2011). Additionally, in some studies higher mortality rates among subjects with trochanteric fracture have been observed (Haentjens et al. 2007, Lin et al. 2011). However, the effect of different risk factors on hip fracture types has only been studied to some extent.

2.3.1 Risk factors for osteoporotic fractures

The epidemiology of osteoporotic fractures is multifactorial. It is affected by both skeletal (e.g., bone mass and structure) and non-skeletal factors (e.g., susceptibility to fall and loss of protective reflexes). Low BMD values are associated with increased relative fracture risk at population level (Marshall et al. 1996). On individual level, however, there seems to be an overlap of BMD values of subjects with and without fractures, and most of the hip fractures seems to occur among people with a BMD T-score higher than -2.5 (Sanders et al. 2006, Schuit et al. 2004, Siris et al. 2004, Stone et al. 2003). To improve the estimate of individual fracture risk, the use of various clinical and lifestyle-related risk factors
has been adopted. These risk factors include both modifiable (e.g., diet and physical activity) and unmodifiable (e.g., age and sex) factors. Table 1 summarizes the most well known risk factors of osteoporotic fractures.

Falls are a major cause of osteoporotic fractures. Although only a few percent of falls result in hip fracture, over 90 percent of hip fractures are the result of a fall (Parkkari et al. 1999, Tinetti 2003). Thus, factors increasing the risk of falling also increase the risk of fracture. Falls are common among older population. Approximately one third of the home-dwelling older people fall each year (Salvà et al. 2004, Tinetti et al. 1988). Among institutionalized older people the corresponding figure is approximately two- to three-fold (Jensen et al. 2002, Luukinen et al. 1994). Also, during aging the risk of falling increases (Talbot et al. 2005).
Table 1. Risk factors of osteoporotic fractures according to Kanis (2002), Benetos et al. (2007), and Finnish Current care summary (2011).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Included in FRAX®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometrics and demographic variables</strong></td>
<td></td>
</tr>
<tr>
<td>Older age</td>
<td>Yes</td>
</tr>
<tr>
<td>Female sex</td>
<td>Yes</td>
</tr>
<tr>
<td>Low body mass index</td>
<td>Yes (weight, height)</td>
</tr>
<tr>
<td>Asian or white ethnic origin</td>
<td>Yes (national reference data)</td>
</tr>
<tr>
<td>Urban residence</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic disease</strong></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Yes (BMD)</td>
</tr>
<tr>
<td>Neuromuscular disorders</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Yes (secondary osteoporosis)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td><strong>Medical history and medications</strong></td>
<td></td>
</tr>
<tr>
<td>Premature menopause</td>
<td>Yes (secondary osteoporosis)</td>
</tr>
<tr>
<td>Primary or secondary amenorrhea</td>
<td></td>
</tr>
<tr>
<td>Previous fragility fracture</td>
<td>Yes</td>
</tr>
<tr>
<td>Glucocorticoid therapy</td>
<td>Yes</td>
</tr>
<tr>
<td>Poor visual acuity</td>
<td></td>
</tr>
<tr>
<td>Family history of hip fracture</td>
<td>Yes</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>Yes</td>
</tr>
<tr>
<td>Long-term immobilization</td>
<td></td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td></td>
</tr>
<tr>
<td><strong>Lifestyle-related</strong></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Yes</td>
</tr>
<tr>
<td>Excessive alcohol intake</td>
<td>Yes</td>
</tr>
<tr>
<td>Excessive caffeine intake</td>
<td></td>
</tr>
<tr>
<td>Low physical activity</td>
<td></td>
</tr>
<tr>
<td>Impaired mobility / muscle weakness</td>
<td></td>
</tr>
<tr>
<td><strong>Nutrition</strong></td>
<td></td>
</tr>
<tr>
<td>Low dietary calcium intake</td>
<td></td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td></td>
</tr>
</tbody>
</table>

FRAX® WHO fracture risk assessment tool (described in more detail in the following section).
2.3.2 Fracture risk calculators

The WHO has developed a fracture risk assessment tool called the FRAX® (Kanis JA on behalf of the World Health Organization Scientific Group 2007). It estimates the 10-year probability of a major osteoporotic fracture (hip, spine, forearm, or humerus). The algorithm of FRAX® is based on population-based cohort studies. The models include different risk factors such as age, sex, BMD at the hip (femoral neck) and several clinical risk factors (Table 1). FRAX® can also be used without inclusion of BMD.

FRAX® has some limitations (Silverman & Calderon 2010, Unnanuntana et al. 2010). Criticisms have been raised especially due to exclusion of certain risk factors, e.g., physical activity and falls. Also, since most of the variables are queried dichotomously dose-response relations are not taken into account. In addition, the question of generalizability has also been raised. FRAX® is not validated in all countries and it does not take account of geographic variation within countries. In addition, the proposed fracture probabilities may underestimate other major osteoporotic fractures than hip fractures and lead to controversial treatment propositions in some cases.

In addition to FRAX®, also other similar risk calculators are available, e.g., QFracture developed for the population of the United Kingdom, (Hippisley-Cox & Coupland 2012) and the Garvan Institute fracture risk calculator for the Australian population (Nguyen et al. 2008).

2.3.3 Bone Turnover Markers

When evaluating bone strength, bone turnover has an essential role. Bone turnover can be assessed by measuring biochemical bone turnover markers from urine or blood samples (Unnanuntana et al. 2010). These markers can be categorized as bone resorption and bone formation markers.

During bone resorption, osteoclasts break down bone matrix. Thus, a variety of collagen breakdown products is released into the bloodstream to be metabolized in the liver and kidneys, and the concentrations of these products can be measured. When osteoblast form bone, type I collagen is synthesized. During this process, collagenous proteins are cleaved into the circulation from the newly formed collagen molecule. Additionally, a variety of non-collagenous proteins is secreted into blood stream, some of which can be quantified. (Unnanuntana et al. 2010)
Association between bone turnover markers and osteoporotic fracture risk has been shown in several studies (e.g., Chapurlat et al. 2000, Ross et al. 2000). It has also been suggested that bone turnover markers may provide additional predictive information on major osteoporotic fracture independent of FRAX® (Melton et al. 2012).

2.4 X-ray-based assessment of osteoporosis and fracture risk

2.4.1 Dual-energy x-ray absorptiometry (DXA)

Dual-energy x-ray absorptiometry (DXA) was introduced commercially in 1987, after which it reached wide acceptance in clinical medicine and research (Jergas & Genant 1993). DXA measurement is based on using two different photon energies which have different attenuation properties in different tissues, i.e., in bone and soft tissue (Blake & Fogelman 1997). At high photon energies the attenuation is relatively similar in both tissues, whereas at lower photon energy a good contrast between tissues is observed. The amount of bone mineral on a defined area can thus be calculated and expressed as bone mineral density (BMD, g/cm²). Similarly, the amount of bone mineral in grams can be defined (bone mineral content, BMC). The most common sites for the BMD measurements are hip and lumbar spine (i.e., central DXA) and peripheral sites, such as calcaneus and wrist. In some cases also DXA measurements of whole body can be done, e.g., to provide information about body composition (lean and fat mass) (Griffith & Genant 2008).

Three principal roles for DXA-based BMD measurements have been suggested: 1) diagnosing osteoporosis, 2) assessing fracture risk, and 3) monitoring response to treatment (Blake & Fogelman 2009). At the moment DXA is the golden standard in osteoporosis diagnostics since the diagnostic thresholds of osteoporosis are based on BMD values measured using DXA. The advantage of DXA is that it is able to measure sites which are at high risk for osteoporotic fractures (especially hip) and which have good response to treatments (spine) (Blake & Fogelman 2009). Recorded BMD is compared to mean value of the young healthy population and the result is expressed as a T-score (difference in standard deviations). The following categories have been adopted by the WHO (Report of a WHO Scientific Group 2003):
- Normal: a value of BMD within 1 standard deviation of the young adult reference mean (T-score $\geq -1$)
- Low bone mass (osteopenia): a value of BMD more than 1 standard deviation, but less than 2.5 standard deviations below the young adult mean value ($-2.5 < \text{T-score} < -1$)
- Osteoporosis: a value of BMD 2.5 standard deviations or more below the young adult mean (T-score $\leq -2.5$)
- Severe osteoporosis (established osteoporosis): a value of BMD 2.5 standard deviations or more below the young adult mean in the presence of one or more fragility fractures.

DXA technique has also been criticized. Since DXA measurements are two-dimensional projections of a three-dimensional object, the results are strongly correlated to bone size, smaller bones having lower and bigger bones having higher density values (Griffith & Genant 2008). Also, obesity increases measurement precision error (Knapp et al. 2012). Since DXA scanners are designed to measure density they have relatively poor spatial resolution. Bone architecture (trabecular size, shape, and orientation, and cortical cross-sectional geometry) cannot be assessed, nor can cortical and trabecular bone be separated (Beck 2003, Griffith & Genant 2008). In addition, as already presented above, although BMD has a major role affecting bone strength, it cannot comprehensively predict it by itself (Griffith & Genant 2008, Kanis 2002). DXA also has limited availability and it exposes patients to ionizing radiation, even though the dose is relatively low (approximately 5 µSv from hip and spine DXA) (Griffith & Genant 2008).

The latest improvements in DXA examination include simultaneous vertebral fracture assessment and additional analysis including geometrical elements (Griffith & Genant 2012). DXA devices with built-in fan beam technology and suitable software can acquire diagnostic quality images of the lower thoracic and lumbar spine (from vertebra T7 to L4) enabling fracture assessment. In the hip region, calculation and inclusion of proximal femur structural parameters, such as hip axis length, cross-sectional moment of inertia, femoral neck shaft angle, cross-sectional area, and femoral strength index, may improve hip fracture risk assessment compared to plain BMD (Gnudi et al. 2002, Leslie et al. 2009, Zhang et al. 2011). Also, analysis of bone microarchitecture, namely trabecular bone score (TBS), based on local variations in grey-level texture measured from a DXA image has been recently introduced (Pothuaud et al. 2008). TBS can be
calculated retrospectively from DXA scans and it has been reported to be associated to increased fragility fracture risk (Bousson et al. 2012, Boutroy et al. 2012).

### 2.4.2 Quantitative computed tomography (QCT)

The quantitative computed tomography (QCT) technique reconstructs a three-dimensional image by acquiring and combining absorption profiles from multiple different angles. This approach yields the true volumetric BMD (g/cm³) as well as bone size and geometry. The analyses can be done for whole bone or separately for cortical and trabecular compartments, which is one of the main advantages compared to DXA technique.

QCT is generally considered more sensitive to bone density changes or differences compared to DXA (Griffith & Genant 2008). Femoral geometry parameters measured using QCT are related to femoral strength and thus to fracture risk (Black et al. 2008, Ito et al. 2010). However, in the study by Black et al. (2008) overall hip fracture prediction was not improved relative to plain DXA-based areal BMD. QCT measurements of the spine and hip have also shown to discriminate subjects with spinal fractures (Lang et al. 2002). One limitation for QCT usage in screening and standard diagnostics is the relatively high radiation dose (proximal femur scan approximately 2500 µSv), although it is highly dependent on the imaging protocol used (Griffith & Genant 2008). In addition, QCT devices are rarely available in primary health care.

Peripheral QCT (pQCT) can be used to measure appendicular bone sites, such as distal radius or tibia. The measurement parameters are associated with nonvertebral fractures (Sheu et al. 2011). The major advantages of pQCT devices compared to QCT devices are lower cost and smaller radiation doses. High-resolution pQCT is able to examine the distal radius or distal tibia with a nominal isotropic voxel size of approximately 90 μm³ (Griffith & Genant 2012). This allows estimation of several structural parameters, such as trabecular number, thickness, separation, connectivity, anisotropy, and cortical thickness.

QCT data can further be used in finite element analysis (FEA) to improve the estimation of bone strength and stiffness (Griffith & Genant 2011). In FEA the QCT (or magnetic resonance) imaging data is converted into a mesh model that can be used to calculate local stresses and strains and further, to estimate failure load and fracture risk.
2.5 Ultrasound-based assessment of osteoporosis and fracture risk

Ultrasound-based methods for evaluating bone strength, known as quantitative ultrasound (QUS), have been studied for several decades (Laugier 2006). The advantages of ultrasound include relatively low cost and a portable technique with no ionizing radiation. A number of different QUS approaches have been used to assess bone status and to evaluate fracture risk (Glüer 2008).

2.5.1 Basic physics of ultrasound

Ultrasound is a mechanical wave at a frequency above the audible threshold, generally defined as 20 kHz. Ultrasound obeys the laws of physics for wave motion but differs from electromagnetic wave because it needs a medium to propagate. Ultrasound waves can be divided into longitudinal (compression) and transverse (shear) waves. The longitudinal wave produces molecular vibration in the direction of propagation whereas the transverse wave generates oscillation perpendicular to the propagation direction. In biological soft tissues only longitudinal waves can be used due to rapid attenuation of transverse waves (Laugier 1999). In bones both types are possible.

The velocity of ultrasound depends on the mechanical characteristics of the medium. Velocity is lower in soft and elastic materials than in hard and stiff materials. The velocities for longitudinal ($c_L$) and transverse ($c_T$) waves, respectively, propagating in an isotropic homogeneous solid are given by

\[
c_L = \sqrt{\frac{E(1-v)}{\rho(1+\nu)(1-2\nu)}}
\]

and

\[
c_T = \sqrt{\frac{E}{2\rho(1+\nu)}},
\]

where $\rho$ is the density of medium, $E$ is Young’s modulus, and $\nu$ is Poisson’s ratio (Langton & Njeh 2004, Laugier 1999).

Each material has its characteristic acoustic impedance $Z$, which is defined as the product of material density and acoustic velocity. The behavior of ultrasound, i.e., transmission, refraction, and reflection, at the boundary between two media is
determined by the difference in acoustic impedances. For longitudinal waves on a plane surface an intensity reflection coefficient $R$ can be determined as

$$R = \frac{I_r}{I_i} = \left(\frac{Z_1 \cos \theta_1 - Z_2 \cos \theta_2}{Z_2 \cos \theta_1 + Z_1 \cos \theta_2}\right)^2$$

(3)

and intensity transmission coefficient $T$ as

$$T = \frac{I_t}{I_i} = \frac{4Z_1 Z_2 \cos \theta_1 \cos \theta_2}{(Z_2 \cos \theta_1 - Z_1 \cos \theta_2)^2},$$

(4)

where $I_i$, $I_r$, and $I_t$ are the incident, reflected, and refracted intensity, respectively, $Z_1$ and $Z_2$ are acoustic impedances for the first and second mediums, respectively, and $\theta_1$ and $\theta_2$ are the angles of incidence and refraction, respectively (Laugier 1999). In the interface of two mediums with different acoustic impedances (e.g., soft tissue and bone) ultrasound wave is refracted based on Snell’s law

$$\frac{\sin \theta_1}{c_1} = \frac{\sin \theta_2}{c_2},$$

(5)

where $\theta_1$ and $\theta_2$ are the incident and refraction angles and $c_1$ and $c_2$ are the velocities of ultrasound in mediums 1 and 2, respectively. Assuming that the wave velocity in the first medium is slower than in the second medium, the refraction angle is larger compared to the angle of incidence. As the angle of incidence increases, a point comes in which the ultrasound wave starts to propagate along the interface of the media (Camus et al. 2000). At this point the refracted wave is referred to as lateral (or head) wave. The phenomenon is called total internal reflection and the corresponding incident angle the critical angle. As the lateral wave propagates, it continuously radiates energy according to Huygens’ Principle at the critical angle (Camus et al. 2000).

An ultrasonic waveform is typically altered due to absorption and reflections while it propagates in a physical, dispersive, medium. As a result, energy associated with the wave packet may propagate at a speed (group velocity) different from that of a fixed phase of a given frequency (phase velocity) (Laugier 1999). As ultrasound propagates through medium, its intensity attenuates. The most important attenuation processes are absorption and scattering. Additional attenuation processes include beam spreading (diffraction) and mode conversion that affects the emergence of ultrasonic guided waves. (Langton & Njeh 2004, Viktorov 1967)
2.5.2 Ultrasonic guided waves

Guided waves are ultrasound waves that propagate within a bounded or layered media. They arise from the reflection, refraction, mode conversion, and interference of longitudinal and transverse waves within the structure (Fig. 4). Because guided waves are born due to boundary interactions, their characteristics are determined by the geometrical and material properties of the structure and the surrounding media. (Viktorov 1967)

The most common technique to guided wave excitation is to use an angle beam transducer and generate an oblique incident wave onto the sample (Fig. 4) (Lefebvre et al. 2002). Another technique uses a comb transducer generating ultrasound pulses in phase or out of phase (Rose 2002). There are multiple different types of guided waves, such as Rayleigh, Stonely, Love, and Lamb waves (Rose 2002). The model of Lamb waves relates to two-dimensional guided wave propagation in a traction-free homogeneous isotropic solid plate where displacements of particles both parallel to the wave propagation direction and perpendicular to the plane of the plate occur (Viktorov 1967). The model of Lamb waves has been expanded to different structures including multi-layer plates and tubes.

![Fig. 4. Schematic image of the generation of Lamb waves. Solid arrows represent longitudinal waves and dashed arrows represent transverse waves. Thick gray arrow represents the guided wave propagating throughout the plate thickness.](image)

Lamb waves exist in the form of resonant modes where the combination of frequency and phase velocity corresponds to standing waves in the thickness direction. Thus, in a plate with a known thickness at a constant frequency only a certain number of Lamb wave modes can exist (Viktorov 1967). The standing waves are only possible with certain ratios between plate thickness and wavelength sometimes referred to as critical thicknesses and frequencies. Different ratios between critical thicknesses and wavelengths give rise to different
modes. When the displacement of the particles occurs in opposite direction in the upper and lower halves of the plane, the Lamb wave motion is said to be symmetrical (corresponding modes: \( S_0, S_1, S_2, \ldots \)) (Viktorov 1967). When the displacement occurs in the same direction in both halves of the plane, the motion is antisymmetrical (\( A_0, A_1, A_2, \ldots \)).

The Lamb wave dispersion curves for the phase and group velocities for different modes can be numerically determined (Fig. 5). Lamb waves are strongly dispersive. All modes except the two fundamental modes (\( S_0 \) and \( A_0 \)) have a cut-off frequency thickness value below which they do not propagate. At the high values of the frequency thickness product the velocities converge to the Rayleigh velocity. (Viktorov 1967)

Fig. 5. Lamb wave dispersion curves for the four lowest order symmetrical (dashed lines) and antisymmetrical (solid lines) modes in acrylic plates (\( c_L=2750 \text{ m/s}, c_T=1375 \text{ m/s}, \rho=1.18 \text{ g/cm}^3 \) were used).

2.5.3 Different ultrasound methods used in bone assessment

The ultrasound assessment of the calcaneus is the most widely used technique in clinical setting. Measurements are done using a transverse (or through) transmission method where ultrasound transducers are placed on the opposite sides of the calcaneus. Speed of sound (SOS) and broadband ultrasound attenuation (BUA) are measured. In addition, different bone strength indexes based on these two measured parameters are calculated by different manufacturers. Transverse transmission can also be applied on other bone sites, e.g., tibia and finger phalanx. However, there are several reasons for the popularity of measuring ultrasound propagation in calcaneus (Prins et al. 1998).
Calcaneus is a weight-bearing bone having only thin soft tissue layers covering nearly parallel plane sides. Also, calcaneus is mostly trabecular bone, which is usually considered to be metabolically more active and thus sensitive to osteoporotic changes. Multiple studies have reported correlation between calcaneal ultrasound measurements and BMD of the central skeleton (Njeh et al. 2001a). In addition, prospective studies of calcaneal QUS measurements have been shown to be associated with the risk of fractures (Marin et al. 2006, Moayyeri et al. 2012). The International Society for Clinical Densitometry stated in its 2007 official position paper that heel QUS predicts fragility fractures in both women and men independently of DXA-based BMD measurements (Krieg et al. 2008). A novel modality of transverse transmission measures ultrasound propagation in the anteroposterior direction at proximal femur (Barkmann et al. 2007). The results of in vivo measurements have shown comparable hip fracture discrimination ability to the hip DXA (Barkmann et al. 2010). A similar measurement setup has also been used ex vivo to assess the propagation of guided waves in the cortical shell of the femoral neck (Grimal et al. 2012). The results of this pilot study showed significant correlations between QUS measurement and femoral strength (r=0.73–0.89).

Bone status can also be evaluated using pulse-echo ultrasound where ultrasonic backscattering from tissues is measured. The measurements can be done using a separate transmitter and receiver or only one transducer acting as both transmitter and receiver. Measurements of calcaneus have shown promising results in terms of age- and osteoporosis-related changes in bone as well as fracture discrimination ability (Roux et al. 2001). Recently, this method has been implemented in in vivo measurements of proximal femur (Karjalainen et al. 2012). The measured ultrasound parameters reflected femoral BMD and discriminated subjects with hip fractures from non-fractured controls.

So-called axial transmission (AT) technique has been developed for measuring the shaft of long cortical bones. This approach uses a linear arrangement of transmitters and receivers placed on the same side of the bone to measure the SOS along the cortical bone wall.

2.5.4 Axial transmission

As cited by many authors, the first report of using axial transmission dates back to 1958 when it was used to study fracture healing at the tibia by Siegel et al. Cortical bone provides a plate-like waveguide for ultrasound. It thus also supports
the propagation of Lamb modes. A simple transducer setup enables performing AT measurements on multiple bone sites. However, an adequate distance between the transducers compared to the thickness of soft tissue is needed in order to measure the ultrasound propagating in bone and not the signal traveling directly through the soft tissue (Camus et al. 2000). Typical measurement sites include tibia, radius, and finger phalanx, but also measurements of metacarpal, capitator, patella, thoracic spine, and calcaneus have been introduced (Hans et al. 1999).

All axial transmission techniques are based on the same measurement principle. The time of flight (TOF) of the transmitted ultrasound pulse propagating along the axis of the long bone is recorded and the corresponding SOS is determined. However, there are several variations of the AT technique differing e.g., by transducer setup, excitation frequency, criteria to determine time of flight (e.g., first maximum, threshold, or zero crossing), and the wave mode(s) being excited and detected.

First arriving signal and thickness-dependence

Axial transmission measurement is typically associated with assessment of the first arriving signal (FAS) and related SOS (hereafter referred to as $V_{FAS}$). $V_{FAS}$, based on TOF of the transient wave front, does not correspond with definitions of the phase or group velocity and is therefore called apparent velocity (Bossy et al. 2002). It is dependent on the thickness of the waveguide (e.g., cortical bone, Fig. 6). When the thickness is greater than the wavelength in bone ($\lambda_{\text{bone}}$), the velocity is consistent with that of the lateral longitudinal wave (Camus et al. 2000). However, when the wall thickness decreases $V_{FAS}$ tends towards the velocity of the fundamental symmetric Lamb mode ($S_0$), and can be considered consistent with that of the $S_0$ at walls thinner than $\lambda_{\text{bone}}/4$ (Bossy et al. 2002). The effect of bone anisotropy on $V_{FAS}$ was further simulated by Bossy et al. (2004a). A significant reduction in the range of $V_{FAS}$ for transversely anisotropic bone (450 m/s) compared to isotropic bone (800 m/s) was observed. Also, the thickness sensitivity was observed to occur at narrower range of wavelength-thickness ratio (between $\lambda_{\text{bone}}/4$ and $\lambda_{\text{bone}}/2$).
The results of these simulation studies by Bossy et al. (2002, 2004a) are in accordance with experimental studies on phantoms (Nicholson et al. 2002) and human bone in vivo (Prevrhal et al. 2001). FAS is thereby affected by the boundaries of the solid waveguide. It can essentially be considered as a guided mode according to Lamb wave theory, although this mode is apparent as a transient response in the time domain only (Moilanen 2008).

**Measuring $V_{FAS}$ independent from the soft tissue effect**

On in vivo measurements, passing through the overlying soft tissue inflicts delay to the TOF and hence affects the calculated $V_{FAS}$. Lowet and Van der Perre (1996) introduced a method that eliminates the delay due to a soft tissue of constant thickness. The FAS was recorded from multiple source-receiver distances and TOF was determined for each distance. Linear regression on these time-distance points then provided the $V_{FAS}$. Using the information on the increments in the TOF and distance, the $V_{FAS}$ was thus accurately determined independent of the soft tissue thickness. Any alterations in the soft tissue thickness still caused a significant error in the $V_{FAS}$, however.

To correct the impact of varying soft tissue thickness, Bossy et al. (2004) suggested recording the ultrasound signal in opposite propagation directions. In this bidirectional technique, a symmetric arrangement of at least two transmitters
and two receivers is used to record ultrasound pulse transmitted subsequentially at both sides of the receivers. The difference in the TOF between the different receivers, consequent upon the varying thickness of soft tissue, can be solved and the unidirectional velocities \( c^+ \) and \( c^- \) of the pulses propagating in opposite directions determined. \( V_{FAS} \), accurately corrected for the soft tissue thickness variation, is determined as a harmonic mean of the two unidirectional velocities, as expressed by

\[
V_{FAS} = \frac{2}{\frac{1}{c^+} + \frac{1}{c^-}} \cos \alpha .
\]  

Typically the inclination angle \( \alpha \) between the soft tissue surface and bone surface can be considered small and therefore the cosine term can be neglected (Bossy et al. 2004).

Cortical bone and overlaying soft tissue provide a fluid-solid bilayer for guided waves (Moilanen et al. 2008, Yapura & Kinra 1995). Part of the ultrasound propagating in bone is leaked into the soft tissue layer forming so-called leaky Lamb waves. However, the effect of leaky Lamb waves on modes propagating in bone is only minor (Chen et al. 2012, Moilanen et al. 2006) and should thus have no effect on \( V_{FAS} \).

**Assessment of cortical bone using axial transmission ultrasound**

Axial transmission ultrasound measurements have been reported to reflect both material and geometrical properties of the cortical bone. A relationship between \( V_{FAS} \) and bone elasticity (Lee et al. 1997, Muller et al. 2008) and microstructure (Raum et al. 2005) has been reported in vitro. \( V_{FAS} \) has also shown sensitivity to the cortical porosity in simulation studies (Bossy et al. 2004a), which was also confirmed by in vitro studies (Bossy et al. 2004b). In addition, \( V_{FAS} \) has been shown to reflect bone mass both in vitro (Lee et al. 1997) and in vivo (Sievänen et al. 2001). Higher correlations with bone mass have been reported using higher frequencies (Muller et al. 2005) whereas the use of lower frequency yields enhanced sensitivity to cortical thickness (Muller et al. 2005, Tatarinov et al. 2005). In a study on PVC (polyvinyl chloride) bone phantoms, the velocity of high-frequency ultrasound (1.25 MHz) did not correlate with local thickness whereas the low-frequency ultrasound (200 kHz) was highly correlated (\( r=0.90 \)) and variation up to 21.4% in \( V_{FAS} \) was observed as a function of local thickness.
(Moilanen et al. 2004). In a recent study, also a relationship between low-frequency AT ultrasound velocity and subcortical BMD was reported in postmenopausal women (Kilappa et al. 2011).

Cortical bone axial stiffness is strongly determined by variations in porosity (Granke et al. 2011). Reduced cortical porosity together with reduced thickness is an important factor affecting bone strength in older individuals (Yeni et al. 1997, Zebaze et al. 2010). Since AT ultrasound measurements reflect these parameters, it is expected that improved discrimination ability in terms of risk of fragility fractures is observed. So far the results of AT ultrasound fracture studies have shown promising, although partly inconsistent, results (Table 2). However, most of the studies being cross-sectional case-control studies, there is a need for prospective study to assess the fracture prediction ability of AT measurements. The guided wave ultrasound is an appealing method for bone assessment since the ultrasonic waves propagate throughout the cortical layer and the velocity is associated with both material and geometrical properties of the cortical bone.
Table 2. Selected publications on fracture discrimination using axial transmission ultrasound.

<table>
<thead>
<tr>
<th>QUS device (Ref.)</th>
<th>Measurement site(s)</th>
<th>n, F/M, Fx status (mean age ± SD [yrs.])</th>
<th>OR (per 1 SD decrease)</th>
<th>AUC</th>
<th>CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myriad Soundscan (Myriad Ultrasound systems, Israel), (f_c=250) kHz</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Augat et al. (1998)</td>
<td>Tibia</td>
<td>67 F hip Fx within 24 mo. (74.7±8.3)</td>
<td>All hip Fx: 1.4</td>
<td>0.60</td>
<td>1.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>68 F healthy controls (74.6±8.7)</td>
<td>Troch Fx: 1.7, Neck Fx: 1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stegman et al. (1995)</td>
<td>Tibia</td>
<td>157 F, 153 M (40-80 yrs)</td>
<td>Appendicular Fx: F 1.69 / M 1.93</td>
<td>-</td>
<td>0.5-0.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE Fx after age 40</td>
<td>All Fx: F 1.11 / M 1.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunlight Omnisense (BeamMed Ltd, Petah Tikva, Israel), (f_c=1.25) MHz</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al. (2010)</td>
<td>Radius, tibia</td>
<td>4619 F, 4732 M (40-69 yrs)</td>
<td>1.07-1.20 (M)^a</td>
<td>-</td>
<td>-0.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>during ~46 mo. follow-up 198 (136 F, 62 M) LE Fx</td>
<td>1.04-1.05 (F)^b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clowes et al. (2005)</td>
<td>Phalanx, radius, metatarsal</td>
<td>279 F, Fx within 6 mo. (69.9±6.6)</td>
<td>1.26-1.44</td>
<td>0.60-0.63</td>
<td>-</td>
</tr>
<tr>
<td>Nguyen et al. (2004)</td>
<td>Phalanx, radius, tibia</td>
<td>549 F, population-based controls (67.4±7.1)</td>
<td>1.75-2.23</td>
<td>0.66-0.71</td>
<td>0.4-1.0%</td>
</tr>
<tr>
<td>Damilakis et al. (2004)</td>
<td>Phalanx</td>
<td>51 F, hip Fx within 30 mo. (64.5±6.5)</td>
<td>2.63</td>
<td>0.74</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51 F, healthy controls (64.6±6.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Damilakis et al. (2003)</td>
<td>Phalanx, radius, tibia</td>
<td>53 F, osteoporotic Fx (67.2±7.4)</td>
<td>1.47-2.69</td>
<td>0.61-0.74</td>
<td>0.5-2.4%</td>
</tr>
<tr>
<td>Hans et al. (2003)</td>
<td>Radius</td>
<td>38 F, LE hip Fx within 4 days (80.0±6.1)</td>
<td>2.72</td>
<td>0.70</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38 F, NF controls (74.9±6.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knapp et al. (2002)</td>
<td>Phalanx, radius, tibia, metatarsal</td>
<td>63 F, LE Colles' Fx (69.3±7.5)</td>
<td>1.23-1.85</td>
<td>0.54-0.64</td>
<td>-</td>
</tr>
<tr>
<td>Knapp et al. (2001)</td>
<td>Phalanx, radius, tibia, metatarsal</td>
<td>191 F, healthy controls (59±7.3)</td>
<td>1.67-2.00</td>
<td>0.66-0.67</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>109 F, vertebral Fx (73.2±7.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barkmann et al. (2000)</td>
<td>Phalanx, radius, ulna, metacarpal</td>
<td>28 F, LE Fx within 6 mo. (76.8±5.0)</td>
<td>1.6-4.5</td>
<td>0.89-0.95</td>
<td>0.2-0.7%</td>
</tr>
<tr>
<td>QUS device (Ref.)</td>
<td>Measurement site(s)</td>
<td>n, F/M, Fx status (mean age ± SD [yrs.])</td>
<td>OR (per 1 SD decrease)</td>
<td>AUC</td>
<td>CV%</td>
</tr>
<tr>
<td>------------------</td>
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</tr>
<tr>
<td>Weiss et al. (2000a)</td>
<td>Radius</td>
<td>50 F, Hip Fx within 9 yrs. (mean ~1 yrs.) (76.1±6.0)</td>
<td>2.16</td>
<td>0.69</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>130 F, NF controls (71.5±5.2)</td>
<td>1.92&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.79&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hans et al. (1999)</td>
<td>Phalanx, radius, capitate, patella, thoracic spine, calcaneus, metacarpal</td>
<td>79 F, Hip Fx within 6 mo. (80±8.9)</td>
<td>1.4-3.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.77-0.92&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.6-1.7%</td>
</tr>
<tr>
<td>Talmant et al. (2009)</td>
<td>Radius</td>
<td>44 F, LE Fx (72.9±11.3)</td>
<td>1.81&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.77&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.4-0.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>122 F, NF controls (66.7±9.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n number of subjects, F female, M male, SD standard deviation, OR odds ratio (or similar) for fracture, AUC area under curve, CV coefficient of variation, LE low-energy, Fx fracture, mo. months, MP menopause, <sup>a</sup> Age, BMI and/or other adjustment, <sup>b</sup> Risk increment/100m/s, <sup>c</sup> combination
3 Aims of the study

The main purpose of the study was to assess the ability of the low-frequency axial-transmission ultrasound method to identify subjects with osteoporosis and increased risk of fragility fracture. In addition, the study assessed lifestyle-related risk factors of hip fractures and the combination of low-frequency ultrasound and lifestyle-related risk factors in fracture discrimination. The specific aims were:

1. to assess the lifestyle-related risk factors for hip fracture in older women (I),
2. to examine if femoral geometry and bone density explain the variability in low-frequency ultrasound velocity on the tibia (II), and
3. to examine whether the low-frequency axial-transmission ultrasound method is able to discriminate subjects with fragility fractures from non-fractured controls in postmenopausal subjects (III, IV).
4 Subjects and Methods

The study was conducted using two different study populations. Table 3 presents the summary of study designs, subjects, and methods used. The numbers of participants in each study as well as women included in final analysis are presented in Fig. 7.

The study protocols were approved prior to conducting the studies by the Ethics Committee of the Northern Ostrobothnia Hospital District (I-III) and by the ethical committees of the University of Jyväskylä, the Central Hospital of Central Finland, and the Finnish National Agency of Medicines (IV). All studies were done in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Fig. 7. Study flow.
Table 3. Summary of subjects and methods.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>n</th>
<th>Age [years]</th>
<th>Weight [kg]</th>
<th>Height [cm]</th>
<th>BMI [kg/m²]</th>
<th>Bone measurement (site)</th>
<th>Fracture data</th>
<th>Additional data</th>
<th>Fracture follow-up time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population-based prospective</td>
<td>1,222</td>
<td>71.3 (1.1)</td>
<td>68.5 (11.1)</td>
<td>158.0 (5.7)</td>
<td>27.4 (4.2)</td>
<td>n/a</td>
<td>Hospital discharge registers</td>
<td>Questionnaire, interview, anthropometrics</td>
<td>13 years</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>132</td>
<td>79.7 (1.2)</td>
<td>69.1 (11.9)</td>
<td>155.2 (5.7)</td>
<td>28.7 (4.7)</td>
<td>LF QUS(^1) (tibia)</td>
<td>Radiographs (hip), DXA (hip)</td>
<td>n/a</td>
<td>Anthropometrics</td>
</tr>
<tr>
<td>Cross-sectional, retrospective / prospective</td>
<td>618</td>
<td>79.9 (1.2)</td>
<td>67.9 (11.6)</td>
<td>155.2 (5.5)</td>
<td>28.2 (4.5)</td>
<td>LF QUS(^1) (tibia)</td>
<td>DXA (hip)</td>
<td>Hospital discharge registers</td>
<td>Anthropometrics</td>
</tr>
<tr>
<td>Cross-sectional, retrospective</td>
<td>95</td>
<td>64.4 (11.2)</td>
<td>68.3 (9.8)</td>
<td>161.8 (6.6)</td>
<td>26.1 (3.4)</td>
<td>LF QUS(^2), pQCT (radius, tibia)</td>
<td>DXA (hip, L2-L4, whole body)</td>
<td>Questionnaire, verified from medical records</td>
<td>Questionnaire, anthropometrics</td>
</tr>
</tbody>
</table>

Age, weight, height, and BMI are presented as Mean (SD), n number of subjects, n/a not applicable, LF QUS low-frequency quantitative ultrasound, DXA dual-energy x-ray absorptiometry, pQCT peripheral quantitative computed tomography, \(^1\)fc\(_{200}\) kHz, scanning probe, \(^2\)fc\(_{400}\) kHz, array probe.
4.1 Subjects

The study population used in studies I-III was originally recruited in 1997 to study the interconnection between physical activity and bone health (Korpelainen et al. 2003). The population gathered from the National Population Register of Finland consisted of all the 1,690 home-dwelling women born in 1924–1927 residing in Oulu, Finland, in November 1997. Seventy-two percent of the women (n=1,222) filled out the postal questionnaire, were interviewed, and participated in the clinical examination in 1998, composing the study population for study I (Fig. 7). All those women who participated in the baseline measurements were invited to take part in follow-up measurements in 2006. The measurements were part of a more extensive study to develop and evaluate new methods for assessing the individual risk of osteoporotic fracture (Osteoporotic Fracture Risk study). Altogether 618 women (37%) participated in the clinical examination. These women formed the study populations for studies II and III (Fig. 7).

The population used in study IV was part of a large random sample family study (Calex-family study) recruited from the city of Jyväskylä and its surroundings, aimed at finding effective means to prevent osteoporosis and fractures (Cheng et al. 2005, Völgyi et al. 2010). The population of study IV consisted of 95 postmenopausal women between 45 and 88 years (Fig. 7). Since 32% of the participants were currently using hormonal replacement therapy, no subjects were excluded due to medications or diseases that affect bone metabolism. A more detailed listing of medications and diseases can be found in the original publication.

4.2 Questionnaires and clinical measurements (I, IV)

In studies I and IV health and background information, including medical history, age at menopause, smoking habits, alcohol and coffee consumption, physical activity and mobility, calcium and vitamin D intakes, and fracture history, was collected using self-administrative questionnaires and interviews at baseline. In study I, also leisure-time physical activity at four time periods in the subjects’ lifespan (15 years old, 30 years old, 50 years old, and at baseline) was assessed using a method similar to Greendale et al. (1995) and divided into quartiles (very low, low, moderate, and high). Similarly, self-rated mobility was classified into four categories (poor, moderate, good, and very good). In study IV, women’s
current physical activity was expressed as hours per week and classified into four categories (none, about 1 h or less, about 2–3 h, and about 4 h or more).

The clinical examination included anthropometric measurements and in study I also the assessment of functional mobility using the “Timed Up & Go” (TUG) test (Podsiadlo & Richardson 1991). A cut-off value of 11 seconds between normal and impaired mobility was used to categorize women into two groups.

4.3 Ultrasound measurements (II-IV)

For studies II and III quantitative ultrasound (QUS) measurements were performed using a scanning axial pulse transmission ultrasound. The device version used a pair of custom-made non-focused low-frequency contact piezoelectric transducers with a diameter of approximately 5 mm. A pulser (Panametrics 5077PR) was used to excite transmitter resulting in emission of a short acoustic impulse with center frequency of 200 kHz and bandwidth of 300 kHz (-16 dB). The received signal, recorded at a known distance by the other transducer, was then amplified and digitized with a digital oscilloscope (National Instruments 5102) by using a sampling frequency of 10 MHz. The FAS was observed in the received signal at the center frequency of 250 kHz. The transducers were mounted on a rail, which enabled an automatic uniaxial scanning mechanism. The ultrasound signal was recorded from 40 fixed source-receiver distances with an interval of 0.75 mm. The transmitter was kept fixed whereas the receiver moved in 0.75 mm steps apart from the transmitter starting from a 20-mm distance. In total, the receiver scanned a 30-mm distance (Fig. 8). A custom-made Matlab (MathWorks Inc., Natick, MA, USA) code was used to analyze the recorded ultrasound signals.

Fig. 8. Transducer setup of scanner device (left) and array probe (right).

In study IV, a new array ultrasound probe was used. The probe consists of a pair of transmitters situated at the ends 20 mm apart from a receiver array composed
of six elements at a spacing (i.e., pitch) of 6 mm (Fig. 8). The transducer elements, all with a diameter of 3 mm, were fixed in a rigid base. Similarly to the scanning device, the transmitters were exited one by one using a custom pulser resulting in a broadband acoustic signal at the center frequency of 300 kHz (bandwidth 400 kHz, -16 dB). Responses at the receivers were digitized using a sampling frequency of 20 MHz (National Instruments 5102). The FAS was identified at the center frequency of approximately 400 kHz. Signal analysis was performed in real time during the measurements using a custom made LabVIEW-based (National Instruments Corporation, Austin, TX, USA) program.

The ultrasound measurements were performed at the tibial shaft (II-IV) and distal radius (IV). At the tibia the measurement site was on the medial surface, two thirds of the total length of the tibia from the medial malleolus. At the radius measurements were performed at one third from the distal end. The transducers were placed perpendicularly to the bone surface (Fig. 9). The probe was held by hand (radius) or by an automated support and compression mechanism (tibia). To ensure proper acoustic coupling ultrasound gel and a steady contact pressure against the skin were applied during all measurements. The first maximum of the FAS was used as the criterion for determining the TOF. The corrected velocity \( V_{LF} \) was obtained as the harmonic mean of the unidirectional velocities \( V^+ \) (signal propagating towards the distal end of the bone) and \( V^- \) (signal propagating towards the proximal end of the bone) according to Bossy et al. (2004). With the scanner device version the unidirectional velocities were recorded as the receiver was moving to the opposite directions. With the array probe the velocities were determined separately for both transmitters.

Ultrasound velocities of 40 subjects measured using the scanner device had to be rejected (II, III). In 29 cases the interference of the direct wave through overlying soft tissue prevented unambiguous determination of the \( V_{LF} \). In seven cases measurements needed to be aborted due to pain. In four cases ultrasound signals were too noisy for reliable TOF determination.
In vivo repeatability was characterized by the root-mean-square coefficient of variation (CV$_{\text{RMS}}$) assessed by three repeated measurements for each subject of a corresponding study with repositioning. In studies II and III CV$_{\text{RMS}}$ values of 2.2% and 3.2%, respectively, for $V_{LF}$ were recorded. With the array probe (IV) CV$_{\text{RMS}}$ was 0.5% for both the radius and tibia, showing substantial improvement in measurement precision. Standardized coefficient of variation (SCV) was calculated as the repeatability (CV$_{\text{RMS}}$) over the range/mean ratio, in which range was defined as four times the standard deviation of the subject population (Miller et al. 1993, Orgee et al. 1996). Obtained SCV values were 4.4% in study II, 6.6% in study III, and 6.4% for radius $V_{LF}$ and 9.0% for tibia $V_{LF}$ in study IV.

4.4 Radiological assessments (II-IV)

4.4.1 X-ray measurements (II)

The digital anteroposterior hip radiographs were acquired with a Kodak DR 9000 x-ray system (Eastman Kodak Company, Rochester, NY, USA) at 70 kV, automatic exposure, resolution 2560×3072, 14-bit. A standard supine position where the beam was focused on the femoral head was used. Four subjects out of 132 (3%) with a bilateral hip prosthesis were not radiographed.

Bone geometry was measured using a custom-made Matlab code based on obtaining a line intensity profile calculated from the x-ray image. Femoral shaft diameter (FSD), medial and lateral femoral shaft cortical thicknesses (FSC), and...
femoral neck diameter (FND) were measured (Partanen et al. 2001). Parameters were measured under the minor trochanter (FSD₁ and FSC₁) and at the femoral shaft 2% of the subject’s height distally from the minor trochanter (FSD₂ and FSC₂). The distance was determined using a calibration scale included in the radiographs. The diameter of the femoral neck was measured at its thinnest point.

4.4.2 DXA measurements (II-IV)

Dual-energy x-ray absorptiometry (DXA) measurements for studies II and III were made with a Hologic DXA device (Delphi QDR series; Hologic, Bedford, MA, USA). Areal bone mineral density (aBMD) and areal bone mineral content (aBMC) of the proximal femur were measured at femoral neck (FN), Ward’s triangle (WARD), intertrochanteric (INTER), and trochanteric (TROCH) regions, as well as at total femur (TF). Standard anteroposterior positioning was used.

In study IV, the aBMD of the whole body (WB), lumbar spine (L2-4), and proximal femur were assessed with a Prodigy DXA scanner (GE Lunar Corp., Madison, WI USA). Six women had missing DXA data and were thus excluded from final analysis.

4.4.3 Peripheral quantitative computed tomography measurements (IV)

Peripheral quantitative computed tomography (pQCT; XCT2000, Stratec Medizintechnik, GmbH, Pforzheim, Germany) was used to scan the tibia and radius at site-matched locations to the ultrasound measurements. The pQCT scans were performed with a voxel size of 590 µm. Apparent volumetric densities of total bone (vBMD), cortical bone (CBMD), and subcortical bone (ScBMD) as well as cortical wall thickness (CTh) were determined from the cross-sectional images. Cortical bone was separated using a threshold of 710 mg/cm³, and the subcortical region using a threshold of 100 mg/cm³.

4.5 Fracture assessment (I, III-IV)

In studies I, III, and IV fracture history of the subjects was gathered. In studies I and III the fracture histories of all women belonging to the original cohort were surveyed for 13 years, from Dec. 1, 1997, to Dec. 31, 2010. Fracture data regarding hospital-treated fractures, were collected from the hospital discharge
registers. Hip fractures were defined as a fracture with ICD-10 (International Classification of Diseases, 10th revision) code between S72.0 and S72.2. In study I different hip fracture types were analyzed separately. Fractures with diagnosis S72.0 were classified as a cervical fracture. Subdivisions S72.1 and S72.2 including both pertrochanteric (intertrochanteric and trochanteric fractures) and subtrochanteric fractures, respectively, were all classified into trochanteric fractures. The subjects were thus divided into the following groups:

- subjects with no fractures during follow-up (NF),
- subjects with any fracture (Fx), and
- subjects with hip fractures (Hip Fx), further divided into subjects with cervical fractures (Neck Fx) and subjects with trochanteric fractures (Troch Fx).

In study I, Fx group was excluded from the final analyses. The final study sample consisted of the subjects with hip fractures and the subjects with no fractures. In study III, fractures before (1997−2006) and after (2006−2010) the bone measurements were separately analyzed. Analyses were also performed over the whole follow-up time (1997−2010). In study IV, the fracture information during whole life was collected from the subjects by a questionnaire. The fractures were classified based on estimated fracture energy, fracture site, and fracture age. The fractures caused by a fall from standing height or less were classified into low- or moderate-energy (i.e., fragility) fractures whereas high-energy fractures were due to high-trauma events (e.g., motor vehicle or bicycle accidents etc.). Thus, the subjects were divided into the following groups:

- subjects with no fractures (NF),
- low- or moderate-energy fractures occurring in adulthood (21+ years) (Fx),
- other fractures (OF) which included high-energy fractures, fractures of a toe or finger, and those that had occurred in childhood or youth (20 years or younger).

If a subject had both types of fractures (Fx and OF), she was classified into the Fx group. The subjects in OF group were excluded from the final analyses. In both study populations fractures were confirmed manually from medical records to avoid the bias of recording multiple hospitalizations due to a single fracture and errors in completing the questionnaire.
4.6 Statistical Analysis

Statistical analyses were done using SPSS for Windows (Releases 16.0 and 18.0; SPSS Inc., Chicago, IL, USA). In all tests, p-values less than 0.05 were considered statistically significant.

Continuous normally distributed variables were compared using an independent samples t-test or one-way ANOVA (post hoc algorithm: Scheffé’s test). For non-normally distributed variables, comparison between groups was done using the Mann-Whitney U Test. With categorical variables a $\chi^2$-test and an independent samples Kruskal-Wallis method were used. In study I, Kaplan-Meier analysis with log rank test was used to compare the equality of survival distributions for the different physical activity indices (very low or low vs. moderate vs. high). Pearson’s correlation coefficients were calculated to study the associations between $V_{LF}$ and radiographic measurements (II).

Regression analyses with a forward stepwise method were performed to identify the best explanatory variables for $V_{LF}$ (II) and for fracture (I, III, and IV). Significant risk factors in the final model were reported using odds ratio (OR) or hazard ratio (HR) and their 95% confidence interval (CI). In all regression analysis a forward stepwise procedure was used. All regression models were adjusted with age and BMI unless otherwise specified. The follow-up time was recorded as the time between the measurements and the first fracture, death, or the end of the follow-up period. In study I, Cox regression was used to assess the relative roles of different lifestyle-related variables in hip fracture risk. The variables associated with hip fractures in univariate analyses were selected as covariates. In study II, linear regression analysis was performed to identify the combination of BMD and geometry parameters that best explained the variation in the ultrasound velocity. In studies III and IV, logistic regression analysis was used to analyze the association between different imaging modalities (QUS, DXA, and pQCT) and the risk of fracture. Logistic regression models were also calculated to analyze the effect of combining $V_{LF}$ and lifestyle-related risk factors.

To estimate the sensitivity and specificity of the different modalities in the discrimination of osteoporotic women (II) and fractured subjects (IV), the receiver operator characteristic (ROC) curves were calculated and the areas under the curve (AUC) were determined. In study IV, differences between AUCs were compared statistically using the method of Hanley and McNeil (1983).

The subjects were classified into normal, osteopenic and osteoporotic groups according to their $V_{LF}$, DXA, and pQCT T-scores based on the WHO criterion.
(Report of a WHO Scientific Group 2003). In study III, T-scores could not be calculated for $V_{LF}$ due to the lack of established reference population. Thus, $V_{LF}$ was divided into three groups based on quartiles within the study population: a) low $V_{LF}$ (0–25%), b) moderate $V_{LF}$ (25–50% and 50–75% combined), and c) high $V_{LF}$ (75–100%).
5 Results

5.1 The effect of lifestyle-related factors on hip fracture risk (I)

During the 13-year follow-up period, 366 subjects (30%) out of 1,222 sustained a bone fracture (Fig. 7). Seventy-seven subjects (6.3%) had a hip fracture. Forty-nine (4.0%) women had a cervical hip fracture and thirty-one (2.5%) a trochanteric fracture, three women having both fracture types.

The women with hip fractures were older (p=0.002), taller (p=0.012), and thinner (p=0.041) than the women without fractures. Also, the women with hip fractures were more sedentary at baseline (p=0.016) and had lower functional mobility (p<0.001) than women in the NF group. Fewer women with hip fractures had hypertension (p=0.034) compared to those with no fractures. No differences were observed in calcium intake between the women with hip fractures and those without fractures.

Impaired functional mobility was the best independent predictor for both fracture types; hazard ratio (HR) of cervical fracture was 3.4 (95% confidence interval (CI) 1.8–6.6) and of trochanteric fracture 5.3 (95% CI 2.5–11.4, Table 4). Low physical activity at baseline increased the general risk of hip fractures (HR=2.0, 95% CI 1.2–3.3) as well as the risk of cervical fractures (HR=2.5, 95% CI 1.3–4.9). However, there was no association observed between hip fractures and physical activity earlier in life. Higher BMI decreased the risk of both hip fracture types, as well as the risk of hip fracture in general (HRs between 0.8 and 0.9). Daily smoking was associated with an increase in the risk of trochanteric fractures (HR=3.2, 95% CI 1.1–9.3). On the other hand, moderate coffee consumption (more than 3 cups/day) and arterial hypertension decreased the risk of cervical fractures (HR=0.4, 95% CI 0.2–0.8, and HR=0.4, 95% CI 0.2–0.8, respectively). Neither estrogen treatment nor specific osteoporosis medication at baseline was associated with the future risk of hip fractures.
Table 4. Cox regression models for having any hip fracture, cervical fracture, and trochanteric fracture in a population-based sample of older women.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>HR 95% CI for HR Covariate p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All hip fractures</strong></td>
<td></td>
</tr>
<tr>
<td>Age / 1 year increment</td>
<td>1.3 1.0 - 1.6 0.022</td>
</tr>
<tr>
<td>BMI / 1 unit increment</td>
<td>0.9 0.8 - 0.9 &lt;0.001</td>
</tr>
<tr>
<td>TUG ≥ 11s vs. less (referent)</td>
<td>3.3 2.0 - 5.5 &lt;0.001</td>
</tr>
<tr>
<td>Low PA vs. moderate to high (referent)</td>
<td>2.0 1.2 - 3.3 0.007</td>
</tr>
<tr>
<td>Hypertension vs. none (referent)</td>
<td>0.5 0.3 - 1.0 0.040</td>
</tr>
<tr>
<td><strong>Cervical fractures</strong></td>
<td></td>
</tr>
<tr>
<td>BMI / 1 unit increment</td>
<td>0.9 0.8 - 1.0 0.004</td>
</tr>
<tr>
<td>TUG ≥ 11s vs. less (referent)</td>
<td>3.4 1.8 - 6.6 &lt;0.001</td>
</tr>
<tr>
<td>Low PA vs. moderate to high (referent)</td>
<td>2.5 1.3 - 4.9 0.008</td>
</tr>
<tr>
<td>Hypertension vs. none (referent)</td>
<td>0.4 0.2 - 0.8 0.016</td>
</tr>
<tr>
<td>Coffee consumption &gt; 3 cups/day vs. less (referent)</td>
<td>0.4 0.2 - 0.8 0.008</td>
</tr>
<tr>
<td><strong>Trochanteric fractures</strong></td>
<td></td>
</tr>
<tr>
<td>Age / 1 year increment</td>
<td>1.9 1.3 - 2.7 0.001</td>
</tr>
<tr>
<td>BMI / 1 unit increment</td>
<td>0.8 0.8 - 0.9 &lt;0.001</td>
</tr>
<tr>
<td>TUG ≥ 11s vs. less (referent)</td>
<td>5.3 2.5 - 11.4 &lt;0.001</td>
</tr>
<tr>
<td>Daily smoking vs. no (referent)</td>
<td>3.2 1.1 - 9.3 0.032</td>
</tr>
</tbody>
</table>

Hazard ratios (HR) are calculated compared to the NF group. PA physical activity, CI confidence interval, BMI body mass index, TUG “Timed Up & Go” test. Due to missing values, the number of subjects in the analyses was 1 Fx n=66, censored n=775, 2 Fx n=39, censored n=740, and 4 Fx n=31, censored n=856. Age was also added as a covariate but was not included in the final model.

A significant difference in the probability of hip fracture was found between the baseline physical activity categories (very low or low vs. moderate vs. high) in Kaplan-Meier survival analysis (Fig. 10). High physical activity protected the women from hip fractures and cervical fracture, but not from trochanteric fractures (p-values of log rank tests: Hip Fx p=0.012; Neck Fx p=0.002; Troch Fx p=0.578).
Fig. 10. Probability of hip fracture (left) and cervical fracture (right) among subjects with different baseline physical activity levels adjusted by age and BMI at baseline.

5.2 Relationship between ultrasound velocity, femoral aBMD, and femoral geometry (II)

The women with aBMD_{TF} T-score \leq -2.5 were thinner than the women with aBMD_{TF} values at osteopenic (p=0.047) or normal range (p=0.001). Similarly, the women whose aBMD_{TF} was at normal range had significantly higher BMI compared to the women with osteoporotic (p=0.007) or osteopenic (p=0.018) aBMD_{TF} values.

V_{LF} decreased significantly with subjects’ age (r=-0.21, p=0.019). Also, mean $V_{LF}$ was significantly lower in women with osteoporotic aBMD_{TF} than in women whose aBMD was at normal range (3475 m/s vs. 3631 m/s, p=0.008, Fig. 11). The area under the ROC curve was 0.73 (p=0.007) for $V_{LF}$ when discriminating women with osteoporotic aBMD$_{TF}$ from women with normal T-score.
A number of significant but weak correlations were found between $V_{LF}$ and DXA parameters as well as between $V_{LF}$ and radiographic measurements. The strongest correlation was found between $V_{LF}$ and aBMD$_{WARD}$ ($r=0.35$, $p<0.001$). With geometrical measurements the strongest correlation with $V_{LF}$ was observed with medial FSC$_1$ ($r=0.26$, $p=0.004$). Regression analysis showed that aBMD$_{WARD}$ and medial FSC$_1$ were significant predictors for $V_{LF}$. The coefficient of determination for the model was 16% ($p<0.001$, Table 5).

Table 5. Significant independent predictors of $V_{LF}$ in stepwise linear regression analysis.

<table>
<thead>
<tr>
<th>Velocity parameter</th>
<th>Predictor</th>
<th>β</th>
<th>95% CI</th>
<th>$p^1$</th>
<th>Regression model</th>
<th>$R^2$</th>
<th>$p^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{LF}$</td>
<td>BMD$_{WARD}$</td>
<td>410.7</td>
<td>178.2 - 643.3</td>
<td>0.001</td>
<td>0.157</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medial FSC$_1$</td>
<td>25.1</td>
<td>2.2 - 48.1</td>
<td>0.032</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Variables for the stepwise regression procedures were medial and lateral FSC$_1$, FSC$_2$, FSD$_1$, FSD$_2$, FND, femoral neck BMD, trochanteric BMD, intertrochanteric BMD, Ward’s triangle BMD, and total upper femur BMD. No age or BMI adjustments were used. β regression coefficient, CI confidence interval for β, $R^2$ coefficient of determination, $^1$ p-value for β, and $^2$ p-value for $R^2$. 

Fig. 11. On the left, the $V_{LF}$ values of the women with osteoporotic, osteopenic and normal aBMD$_{TF}$. Circles denote statistical outliers. On the right, the sensitivity and specificity of $V_{LF}$ in the discrimination of women with osteoporotic aBMD$_{TF}$ and women with normal aBMD$_{TF}$ T-score.
In study III, 81 women (17%) out of 490 sustained a fracture prior to bone measurements (1997–2006) and 61 women (12%) after the measurements (2006–2010). During the whole follow-up period (1997–2010), 174 fractures occurred in 130 subjects (27%). Corresponding figures for subjects with hip fractures were 9 (1.8%) before and 11 (2.2%) after the measurements, totaling 20 subjects (4.1%) with a hip fracture.

The women who sustained a fracture after the measurements (2006–2010) were older than those without fractures (p=0.005, Table 6). The women with a fracture before bone measurements (1997–2006) had a lower VLF compared to the women without fractures (p<0.05). Also, the women who sustained a fracture had lower aBMDFN when compared to the NF group (p<0.05) except when comparing the Hip Fx 1997–2006 group to the NF group.

Table 6. Characteristics of women with different fracture status in different time periods (n=490).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NF n=360</th>
<th>Fx 1997–2010 n=130</th>
<th>Hip Fx 1997–2010 n=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>79.9 (1.2)</td>
<td>80.0 (1.2)</td>
<td>80.0 (1.3)</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>67.7 (11.3)</td>
<td>67.8 (12.2)</td>
<td>69.8 (15.7)</td>
</tr>
<tr>
<td>Height [cm]</td>
<td>155.2 (5.4)</td>
<td>155.6 (5.8)</td>
<td>158.9 (7.2)</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>28.1 (4.5)</td>
<td>28.0 (4.7)</td>
<td>27.4 (4.6)</td>
</tr>
<tr>
<td>VLF [m/s]</td>
<td>3583 (193)</td>
<td>3547 (200)</td>
<td>3515 (245)</td>
</tr>
<tr>
<td>aBMDFN [g/cm²]</td>
<td>0.654 (0.102)</td>
<td>0.606 (0.083)</td>
<td>0.589 (0.102)</td>
</tr>
</tbody>
</table>

Values are Mean (SD). NF non-fractured group, FX fracture group, Hip Fx hip fracture group, VLF low-frequency ultrasound velocity, aBMDFN femoral neck areal BMD. * p<0.05 when compared to NF group

Low VLF was not significantly associated with previous fractures (1997–2006, OR=1.6, 95% CI 0.9–2.6) or with the fractures sustained after the measurements
However, the women with low $V_{LF}$ had a three-fold risk of having a hip fracture compared to those with moderate or high $V_{LF}$ (OR=3.0, 95% CI 1.2–7.6, Table 7). Also, low $V_{LF}$ was associated with increased risk of hip fractures before the measurements (1997–2006) (OR=6.3, 95% CI 1.5–25.5) compared to the women with moderate or high $V_{LF}$.

Decreased aBMD$\text{FN}$ increased the risk of fracture at all follow-up periods compared to women with femoral neck T-score$>-2.5$ (ORs between 1.8 and 2.4, $p<0.02$). Similarly, osteoporotic aBMD$\text{FN}$ was associated with increased risk of hip fracture (OR=3.4, 95% CI 1.4–8.6) during the whole follow-up period (1997–2010) compared to women with aBMD$\text{FN}$ T-score$>-2.5$. In addition, low aBMD$\text{FN}$ predicted hip fractures after the measurements (2006–2010) with a hazard ratio (HR) of 4.8 (95% CI 1.4–16.6) compared to the women with normal or osteopenic aBMD$\text{FN}$.

Table 7. Age- and BMI-adjusted association of low tibial $V_{LF}$ and osteoporotic aBMD$\text{FN}$ with fractures during a 13-year follow-up period in older women.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Fx (n=130)</th>
<th>Hip Fx (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>$V_{LF}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate or high (25-100%) (referent)</td>
<td>364</td>
<td>1.2 (0.8-1.9)</td>
</tr>
<tr>
<td>Low (0-25%)</td>
<td>126</td>
<td>2.4 (1.6-3.8)</td>
</tr>
<tr>
<td>aBMD$\text{FN}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-score &gt; -2.5 (referent)</td>
<td>355</td>
<td>1.2 (0.8-1.9)</td>
</tr>
<tr>
<td>T-score ≤ -2.5</td>
<td>135</td>
<td>2.4 (1.6-3.8)</td>
</tr>
</tbody>
</table>

According to logistic regression analysis including risk factors observed in study I, impaired functional mobility and low physical activity increased and moderate coffee consumption decreased the risk of hip fracture in the subpopulation in study III (full model $p=0.002$, $R^2=0.127$, 0). When $V_{LF}$ was added to the analysis, the model included $V_{LF}$, low physical activity, and impaired functional mobility ($p=0.001$, $R^2=0.137$, 0), $V_{LF}$ being the strongest independent factor for hip fracture (OR=3.3, 95% CI 1.2–9.0). Femoral neck aBMD did not reach statistical significance when included in the regression analyses.
Table 8. Logistic regression models without and with VLF for having a hip fracture in a population-based sample of older women.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>OR</th>
<th>95% CI for OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle-related risk factors1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TUG ≥ 11s vs. less (referent)</td>
<td>3.4</td>
<td>1.2 - 9.9</td>
<td>0.026</td>
</tr>
<tr>
<td>Low PA vs. moderate to high (referent)</td>
<td>2.8</td>
<td>1.0 - 7.5</td>
<td>0.046</td>
</tr>
<tr>
<td>Coffee consumption &gt; 3 cups/day vs. less (referent)</td>
<td>0.3</td>
<td>0.1 - 1.0</td>
<td>0.051</td>
</tr>
<tr>
<td>Lifestyle-related risk factors and VLF2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low VLF (0-25%) vs. Moderate or high (25-100%) (referent)</td>
<td>3.3</td>
<td>1.2 - 9.0</td>
<td>0.018</td>
</tr>
<tr>
<td>Low PA vs. moderate to high (referent)</td>
<td>3.1</td>
<td>1.1 - 8.5</td>
<td>0.028</td>
</tr>
<tr>
<td>TUG ≥ 11s vs. less (referent)</td>
<td>3.1</td>
<td>1.0 - 8.9</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Odds ratios (OR) are calculated compared to the NF group. TUG “Timed Up & Go” test, PA physical activity, CI confidence interval. The number of subjects in the analyses was Hip Fx n=18, NF n=296.

1 Age, BMI, TUG, PA, hypertension, coffee consumption, and smoking were included in the analysis to form the best model, 2 The best model after including VLF in the analysis, * p-value for the full model.

In study IV, 24 women have had low- or moderate-energy fractures in adult age, whereas there were 53 women in NF group (Fig. 7). The women in the Fx group were older (70.6 vs. 62.6 years, p=0.010) and had a higher BMI (27.7 vs. 25.6 kg/m², p=0.044) compared to the women in NF group. There were no differences in calcium or vitamin D intakes, use of bone medications, occurrence of bone affecting diseases or physical activity between the NF, Fx and OF groups. The majority of the fractures (59%) were in an upper extremity, especially in the radius (47%).

Decreased VLF value on radius increased the risk of low-energy fracture. (OR=2.1, 95% CI 1.2–3.5, Table 9). The discriminative ability for the tibia VLF was lost after adjustment for age and BMI (OR=1.2, 95% CI 0.9–1.7). For pQCT and DXA results similar OR values varying between 1.4 and 2.2 were found. The most significant predictor of low-energy fracture was tibial ScBMD (OR=2.2, 95% CI 1.1–4.3). Recorded areas under the ROC curve (AUCs) varied between 0.74 and 0.81 (p<0.001) for all modalities and measurement sites (Table 9). The tibial vBMD yielded the highest AUC (0.81, 95% CI 0.71–0.90). However, there were no significant differences between AUCs.
Table 9. Age- and BMI-adjusted association between the imaging modalities used and the risk of low-energy fracture in postmenopausal women.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>OR (95% CI)</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radius</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(V_{lf})</td>
<td>2.1 (1.2 - 3.5)(^b)</td>
<td>0.80 (0.71 - 0.90)(^a)</td>
</tr>
<tr>
<td>vBMD</td>
<td>1.3 (0.9 - 1.8)</td>
<td>0.76 (0.65 - 0.86)(^a)</td>
</tr>
<tr>
<td>CBMD</td>
<td>1.5 (1.0 - 2.3)(^c)</td>
<td>0.79 (0.69 - 0.89)(^a)</td>
</tr>
<tr>
<td>ScBMD</td>
<td>1.1 (0.8 - 1.7)</td>
<td>0.74 (0.63 - 0.85)(^a)</td>
</tr>
<tr>
<td>CTh</td>
<td>1.5 (1.1 - 2.2)(^c)</td>
<td>0.78 (0.68 - 0.89)(^a)</td>
</tr>
<tr>
<td><strong>Tibia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(V_{lf})</td>
<td>1.2 (0.9 - 1.7)</td>
<td>0.77 (0.67 - 0.88)(^a)</td>
</tr>
<tr>
<td>vBMD</td>
<td>1.9 (1.1 - 3.1)(^c)</td>
<td>0.81 (0.71 - 0.90)(^a)</td>
</tr>
<tr>
<td>CBMD</td>
<td>1.4 (1.0 - 1.8)(^c)</td>
<td>0.80 (0.71 - 0.90)(^a)</td>
</tr>
<tr>
<td>ScBMD</td>
<td>2.2 (1.1 - 4.3)(^c)</td>
<td>0.79 (0.68 - 0.89)(^a)</td>
</tr>
<tr>
<td>CTh</td>
<td>1.6 (1.0 - 2.6)</td>
<td>0.77 (0.67 - 0.88)(^a)</td>
</tr>
<tr>
<td><strong>DXA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aBMD(_{ab})</td>
<td>1.6 (1.0 - 2.6)(^c)</td>
<td>0.76 (0.67 - 0.89)(^a)</td>
</tr>
<tr>
<td>aBMD(_{L2-L4})</td>
<td>1.4 (0.9 - 2.0)</td>
<td>0.79 (0.68 - 0.89)(^a)</td>
</tr>
<tr>
<td>aBMD(_{FN})</td>
<td>1.5 (0.8 - 2.8)</td>
<td>0.75 (0.65 - 0.86)(^a)</td>
</tr>
<tr>
<td>aBMD(_{TF})</td>
<td>1.7 (0.9 - 3.4)</td>
<td>0.77 (0.67 - 0.88)(^a)</td>
</tr>
</tbody>
</table>

Reference category is non-fractured. OR odds ratio, AUC area under curve, CI confidence interval, \(V_{lf}\) low-frequency ultrasound velocity, vBMD volumetric total bone mineral density, CBMD volumetric cortical BMD, ScBMD volumetric subcortical BMD, CTh cortical thickness, aBMD areal BMD, WB whole body, L2-L4 lumbar vertebrae 2-4, FN femoral neck, TF total proximal femur. \(^a\) \(p<0.001\), \(^b\) \(p<0.01\), \(^c\) \(p<0.05\).
6 Discussion

Osteoporotic fractures are a significant public health problem. BMD cannot predict the fracture risk comprehensively by itself (Schuit et al. 2004), and a wide set of different risk factors have thus been adopted as part of fracture risk assessment. In addition, new methods to measure bone status are constantly being developed.

This study used a relatively large population-based sample of older women to study the risk factors of different hip fracture types. We also used the same population to estimate the ability of a novel low-frequency ultrasound method to assess proximal femur geometry and BMD as well as the risk of osteoporotic fracture. Finally, the upgraded low-frequency device with improved measurement precision was used in a smaller group of postmenopausal women to investigate fracture discrimination ability.

6.1 The effect of lifestyle-related factors on hip fracture risk (I)

Previous studies have indicated that the etiologies between hip fracture types differ (Kannus et al. 1996, Mautalen et al. 1996, Vega et al. 1991). In study I, we assessed the differences between the clinical risk factors of cervical and trochanteric hip fractures.

Our findings based on 49 cervical and 31 trochanteric fractures showed that women with high physical activity at baseline had a lower risk of future hip fractures (especially the risk of cervical fractures) than women with moderate or low activity. A similar dose-response relationship has earlier been reported in both male (Michaëlsson et al. 2007) and female populations (Feskanich et al. 2002). We found no association between trochanteric fractures and physical activity. This might indicate an association between physical activity and femoral geometry. Bone geometry seems to have more effect on the risk of cervical fracture, whereas BMD is more strongly related to trochanteric fracture risk (Pulkkinen et al. 2004). Since mechanical loading (i.e., physical activity) is a major determinant of the structure-related strength of the femoral neck (Nikander et al. 2009), lower physical activity and related structural weakening of the femoral neck may thus expose to cervical fractures.

Impaired functional mobility, assessed using the TUG-test, was an independent predictor of both hip fracture types. A similar conclusion was made by Zhu et al. (2011). The result of the TUG test reflects mobility and
neuromuscular function and is shown to correlate with the risk of fall (Shumway-Cook et al. 2000). In addition to TUG test, functional mobility and neuromuscular function can be assessed with different methods, such as walking speed, tandem walk, and repeated chair rise (Cummings et al. 1995, Dargent-Molina et al. 1996, Fox et al. 2000). Poor performance in these tests was associated with increased risk of fracture. In a study by Fox et al. (2000), walking speed was associated with both hip fracture types, but the ability to complete five chair stands was not associated with either.

In our study, higher BMI was a protective factor against both fracture types. This is in line with earlier findings (De Laet et al. 2005). There are at least three mechanisms why higher BMI is favorable in terms of osteoporotic fractures. Firstly, higher body mass induces higher stress especially on weight-bearing bones, which affects the bone strength (Hla et al. 1996). Also after the menopause the mesenchymal cells of the adipose tissue become a major source of estrogen (Simpson et al. 1999). Thus, a greater amount of adipose tissue increases the amount of estrogen affecting bone turnover. Additionally, during a fall, a thicker soft tissue layer absorbs more energy and reduces the forces affecting e.g., proximal femur (Robinovitch et al. 1991). On the other hand, high BMI is related to several co-morbidities (Sirola et al. 2012). In a recent study by Armstrong et al. (2011), lower BMI was found to increase the risk of cervical fracture more compared to pertrochanteric fracture. In our study no such effect was observed.

Old age is a significant and well-established risk factor of osteoporotic fracture. After the menopause the incidence of hip fracture increases, being over seven-fold among women aged over 70 compared to women in their 50s (Banks et al. 2009). Many studies also indicate that older age increases the risk of trochanteric fracture more compared to cervical fracture (Fox et al. 2000, Mautalen et al. 1996). This was also observed in the current study.

Based on our results, arterial hypertension decreases the risk of cervical hip fractures. This finding is somewhat controversial. Based on earlier studies hypertension increases the risk of falling due to reduced baroreflex sensitivity or hypotension (Harrington et al. 2000) and also decreases bone strength by affecting calcium metabolism (Cappuccio et al. 2000). Hence, an increase in the risk of hip fractures might be expected. However, the use of thiazide diuretics as a medication of hypertension has been reported to have positive effects in terms of bone strength (Schoofs et al. 2003) by reducing urinary calcium excretion and helping to maintain calcium balance (Adams et al. 1999) and by inhibiting bone
resorption by means of inducing metabolic alkalosis (Peh et al. 1993). Recently, a transient increase in hip fracture risk after the initiation of thiazine medication was reported (Berry et al. 2012).

We observed that moderate coffee consumption of more than 3 cups per day was a protective factor in the case of cervical fractures. However, when the threshold was raised to 5 cups per day this protective effect was lost (data not shown). In earlier studies, excessive coffee drinking has associated with an increased risk of hip fracture (Cummings et al. 1995, Jokinen et al. 2010). This may be due to negative calcium balance caused by caffeine (Higdon & Frei 2006). However, moderate coffee consumption has also been shown to have some health benefits (Higdon & Frei 2006), which together with our finding support moderate coffee consumption.

Previous studies have indicated the adverse effect of smoking in terms of fracture risk in both women and men (Baron et al. 2001, Jutberger et al. 2010, Kanis et al. 2005). The fracture risk is increased due to direct toxic effects of nicotine on the bones, reduction of calcium absorption, transient increases in cortisol levels after smoking, lower BMI, and an increased risk of falling in smokers, as well as lower estrogen levels and earlier menopause (Law & Hackshaw 1997). In a recent study, current smoking was associated with worse trabecular mechanical performance in hip fracture patients (Rodrigues et al. 2012). At the same time, smoking did not have an effect on aBMD. Thus, the relationship between smoking and trochanteric fractures may be explained by the high content of trabecular bone in trochanteric region. However, the small number of daily smokers limits the statistical power of our finding.

There were 459 non-participants (27.3%) in the original study cohort who, based on hospital discharge register and Cause of Death Register, had higher hip fragility (9.8% vs. 6.3%) and mortality (50.8% vs. 25.1%) during the follow-up period compared to the participants. Thus the results may not be suitable for generalization to institutionalized or very frail women.

6.2 Relationship between ultrasound velocity, femoral aBMD, and femoral geometry (II)

In study II, we measured $V_{LF}$ on mid-tibia and compared it to proximal femur aBMD and, for the first time, femoral geometry. Although tibia is an easily accessible site for axial transmission ultrasound measurements, it is not considered as a site prone to an osteoporotic fracture. The fracture risks of the hip
and lumbar spine are best assessed at site-matched locations (Bouxsein et al. 2002, Clowes et al. 2005, Marshall et al. 1996). However, the aim of these peripheral measurements, as Glüer (2008) stated, is to measure accurately bone quality at the peripheral sites and hope that they will appropriately reflect the bone status at the main osteoporotic fracture sites.

Tibial $V_{LF}$ showed only weak or modest correlations when estimating proximal femur status. The correlations between AT ultrasound velocity and central skeleton BMD have been reported in numerous studies. However, the correlations have at best been only modest, varying between 0.21 and 0.54 (Damilakis et al. 2003, Prevrhal et al. 2001). A similar correlation was also reported in vitro by Bouxsein et al. (1999). In general, $V_{FAS}$ on radius has yielded higher correlations to central BMD parameters compared to tibial $V_{FAS}$. One reason for this might be that the tibia is a weight-bearing bone and thus osteoporotic changes may not appear as soon as in non-weight-bearing sites, such as radius or phalanx (Knapp et al. 2001). It should also be remembered that $V_{FAS}$ reflects multiple factors affecting bone strength, such as cortical thickness and elastic properties (Muller et al. 2008, Raum et al. 2005). In any case, the correlations observed suggest that AT ultrasound measurements in radius and tibia may have diagnostic value.

The decline in $V_{FAS}$ in bone during aging is well established (Muraki et al. 2002, Orgee et al. 1996, Vega et al. 1998, Weiss et al. 2000b). Despite the narrow age range, we observed a weak negative correlation between tibial $V_{LF}$ and age. Recently, $V_{LF}$ was also shown to follow the typical age-related changes in bone (Kilappa et al. 2011). Thus, it is clear that osteoporotic changes in bone during aging can be observed using AT ultrasound. However, the assessment of osteoporotic status using QUS is not as straightforward as the assessment of fracture risk. Currently, no universally applicable diagnostic criteria exist for ultrasound measurements (cf. T-scores in DXA-measurements). One reasons for this is the number of different ultrasound modalities and measurement sites. Previous studies have indicated that the WHO T-score criteria for osteoporosis assessment used with DXA cannot be applied as such to SOS measurements (Hans & Kräg 2008, Knapp et al. 2004), and site-dependent T-scores for SOS measurement should also be used (Damilakis et al. 2003, Knapp et al. 2001, Njeh et al. 2001b). Clearly, there is a lack of valid reference data (T-scores) as well as standardized guidelines on how to interpret ultrasonic data and make diagnosis. Eventually, however, it all comes down to methods’ ability to predict fractures.
6.3 Discrimination of subjects with fractures (III, IV)

The results on the ability of axial transmission SOS to discriminate osteoporotic fractures have been inconsistent. A recent prospective study found no predictive ability to \( V_{FAS} \) of either radius or tibia in terms of osteoporotic fracture (Lee et al. 2010). On the other hand, multiple cross-sectional studies have shown low \( V_{FAS} \) to increase fracture risk (Table 2).

Fracture discrimination ability using Myriad SoundScan (\( f_c = 250 \) kHz) AT ultrasound device has been studied to some extent (Augat et al. 1998, Stegman et al. 1995). Augat et al. (1998) reported that decreased tibial \( V_{FAS} \) increases the risk of hip fracture (odds ratio, OR=1.4) compared to non-fracture control group. This is slightly lower compared to the Hip Fx OR for \( V_{FAS} \) observed in our present study. The corresponding OR for the hip aBMD varied between 3.0 and 3.8 in their study. Stegman et al. (1995) reported a low-energy appendicular fracture OR of 1.4 for the tibial \( V_{FAS} \). This observation is in agreement with the present results, where we found a similar trend in the retrospective part of the study.

Fracture discrimination ability of high-frequency AT ultrasound has been surveyed in many studies. Using the commercially available Omnisense (Sunlight, BeamMed Ltd, Petah Tikva, Israel) device, operating at a center frequency of 1.25 MHz, Hans et al. (2003) reported that 1 SD decrease in radial \( V_{FAS} \) was associated with a significant increase in hip fracture risk (age- and weight-adjusted OR=2.72). Estimated risk was similar compared to that observed with calcaneal transverse transmission QUS devices. The risk of hip fracture using the same device was also assessed by two other studies (Hans et al. 1999, Weiss et al. 2000a). Adjusted ORs reported varied between 1.9 and 2.4 for \( V_{FAS} \) measured on the radius and between 1.4 and 3.0 for other sites, AT measurement of calcaneus showing the highest risk estimation. Neither study assessed the \( V_{FAS} \) on tibia. Additionally, none of these three studies included DXA measurements as a reference method.

Clowes et al. (2005) reported higher ORs for central aDXA and distal forearm pQCT measurements compared to high-frequency ultrasound \( V_{FAS} \) measurements. In their study, \( V_{FAS} \) was unable to discriminate women with hip fractures from women who had not sustained hip fractures. Also in case of all osteoporotic fractures \( V_{FAS} \) performed significantly poorer compared to DXA and pQCT measurements. In our study radial \( V_{LF} \) yielded better or similar discrimination ability compared to pQCT and DXA measurements. One reason may be the fact that in our study the majority of the fractures were in an upper
limb, especially in the radius. However, in a study by Clowes et al. no better discrimination ability only for forearm fractures was observed. Thus, the difference may originate from difference in ultrasound frequency. The device used in the present study operated at a lower frequency (hence at longer wavelengths), implying greater penetration in the cortical layer and an enhanced ability to reflect cortical thickness.

Other studies have reported OR of fracture for $V_{FAS}$ on radius between 1.4 and 4.5 and for $V_{FAS}$ on tibia between 1.2 and 1.8 and for DXA-based aBMD on hip between 2.1 and 4.8 (Barkmann et al. 2000, Damilakis et al. 2003, Knapp et al. 2001, Knapp et al. 2002, Nguyen et al. 2004, Talmant et al. 2009). Of these studies, Nguyen et al. (2004) was the only one to report significant fracture discrimination ability for tibial $V_{FAS}$. We observed similar results in our study. Although low tibial $V_{LF}$ was associated with three-fold increase in hip fracture risk (III) it only yielded borderline significance after age and BMI adjustment in general fracture risk assessment in both populations (III, IV).

In general, AT ultrasound measurements of the radius seem to yield better fracture discrimination ability over tibial measurements. However, we observed comparable ORs for fracture with tibial pQCT measurements, especially for subcortical BMD. Similar observations have been made in high-resolution pQCT studies of distal tibia (Sornay-Rendu et al. 2007, Vico et al. 2008). In these studies the cortical thickness and total density of distal tibia were significantly lower in subjects with osteoporotic fractures compared to subjects with no fractures. Estimated risks (OR=1.8–2.1) similar to hip DXA (OR=2.0) were also reported (Sornay-Rendu et al. 2007). These observations indicate that tibia may also yield diagnostically valuable information. Upgraded array probe operates at the center frequency of 400 kHz which may be too high in terms of cortical thickness-wavelength ratio in tibia. With the older scanner setup poor precision may have decreased diagnostic sensitivity. However, further tuning of the excitation frequency could improve the discrimination ability of tibial $V_{LF}$.

Some of the above-mentioned fracture studies have reported that a combination of different measurement parameters may increase the discrimination ability and sensitivity and specificity (e.g., Hans et al. 1999). In our study, however, measured parameters were significantly correlated with each other, and thus, due to this collinearity of covariates, regression models were biased. Also, combining clinical risk factors and QUS parameters has shown to improve fracture prediction ability (Durosier et al. 2007, Hans et al. 2008,
Karjalainen et al. 2012). In our analyses low \( V_L \) remained a significant risk factor when included in the lifestyle-related risk factor model. However, it needs to be considered that the lifestyle-related risk factors were collected at baseline whereas QUS measurements were made at eight years from baseline. Thus, the results need to be confirmed in future prospective studies.

Direct comparison between the studies is difficult. The results are affected by differences between ultrasound techniques, measurement setups as well as fracture types. In addition, differences in study population have impact. Most fracture studies are case-control studies by nature, which may yield better fracture discrimination results compared to population-based studies. Still, our results were in line with earlier findings suggesting that axial transmission low-frequency ultrasound method has potential in fracture prediction. However, there is still a lack of extensive prospective studies to confirm the usability of AT ultrasound in assessment of osteoporotic fracture risk.

Different results for different hip fracture types have been published to some extent. With axial transmission ultrasound significantly lower tibial \( V_{TAS} \) was observed with subjects who had trochanteric fractures compared to subjects with cervical hip fractures (3786 vs. 3592 m/s) (Vega et al. 1998). Augat et al. (1998) reported that decreased tibial \( V_{TAS} \) increases the risk of trochanteric fracture (OR=1.7) whereas no difference in the risk of cervical fracture was observed. Similarly, a reduction in calcaneal transverse transmission QUS parameters increased the risk of trochanteric fracture (OR=2.5–3.5) significantly more compared to the risk of cervical fracture (OR=1.2–1.3) (Schott et al. 2005). Similar results were observed with DXA-based aBMD. In our studies, the number of hip fractures was too small for separate analysis of hip fracture types.

6.4 Limitations of the study

In study I, all of the data, excluding fracture data, was collected only at baseline and was not repeatedly collected during the follow-up. There may have been changes in the daily routines or lifestyles of the participants that have a major effect on fracture risk. Also, altered medical status or changed medication during the follow-up period may significantly affect the risk of fracture. This may also be the reason why we did not observe a difference in the risk of hip fractures between women who had received estrogen treatment or taken osteoporosis medication at baseline compared to women who did not receive estrogen treatment.
A major limitation in studies II and III was the imperfect ability of the mechanical scanning device to compensate for the effect of varying soft tissue thickness. As proposed by a large difference between the velocities of upward and downward scans, the soft tissue thickness was most likely to vary along the scanning range (Bossy et al. 2004). To compensate for the effect of varying soft tissue thickness, the $V_{LF}$ was calculated as a harmonic mean of upward and downward velocities. The method used follows loosely the bidirectional scanning procedure introduced by Bossy et al. (2004). However, the bulky scanning mechanism had limited flexibility in repositioning and maintaining its position relative to subject’s leg between and within consequent ultrasound scans. This presumably led to different physical conditions between consecutive scans and poor compensation of varying soft tissue thickness. It is expected that this random error on $V_{LF}$, due to imperfect compensation for the soft tissue thickness variation, explains most of the precision error reported ($CV_{RMS}$ between 2.2% and 3.2%). To overcome this limitation, the transducer setup was upgraded to the array probe after the measurements in studies II and III. Improved reproducibility ($CV_{RMS}$) of 0.5% has been reported after this (Kilappa et al. 2011).

In studies II and III, we did not have a site-matched reference measurement on the mid-tibia. This would have enabled comparison between different techniques and possibly given more insight concerning the ability of LF ultrasound to assess bone status. In the study by Kilappa et al. (2011), it was shown for the data set of study IV that a multivariate regression model, including a combination of site-matched pQCT vBMD and CTh data, did not significantly improve the prediction of $V_{LF}$ compared to vBMD alone. It was reported that CBMD was the best predictor, explaining up to 72.3% of the variability in $V_{LF}$.

The number of fractures in studies I, III, and IV was modest. Especially the number of hip fractures in studies I and III limited the statistical reliability of the results.

### 6.5 Future work

The results observed in this study suggest that the LF ultrasound method has potential in fracture prediction. However, in the case of retrospective studies, it is always possible that the changes observed in bone status are due to the fracture events and not vice versa. Further prospective studies with larger population are needed to assess the combined effect of clinical risk factors and LF ultrasound. In
future, we can expect that LF ultrasound may be used as a screening tool when assessing the need of DXA measurement as suggested earlier for heel QUS (Krieg et al. 2008).

The LF device is able to measure two distinct wave modes, namely the FAS wave and the slower guided wave (consistent with the fundamental antisymmetrical Lamb mode $A_0$) (Nicholson et al. 2002). Both modes have been shown to be sensitive to osteoporotic changes in bone (Moilanen et al. 2003, Moilanen et al. 2007, Nicholson et al. 2002). It remains to be seen if the combination of these two distinct wave modes will further improve fracture prediction ability of LF ultrasound.
7 Conclusions

The low-frequency ultrasound method showed promising results in bone characterization. In the discrimination of low femoral aBMD the tibial low-frequency ultrasound was shown to be satisfactory, although not optimal. In addition to bone strength, fracture risk was associated with many different lifestyle-related factors. Based on the results of this study it can be concluded that:

1. Impaired functional mobility and low BMI are risk factors for both cervical and trochanteric hip fractures. Low physical activity increased and arterial hypertension decreased the risk of cervical fractures, whereas smoking and advanced age predicted trochanteric hip fractures. (I)

2. The proximal femur geometry and BMD explained a significant portion of the variability in tibial low-frequency ultrasound velocity. (II)

3. The low-frequency ultrasound velocity showed promising results in hip fracture risk assessment using the scanning ultrasound device (III). Decreased low-frequency ultrasound velocity was a significant risk factor of hip fracture even when combined with lifestyle-related risk factors. Equivalent or better retrospective fracture discrimination ability was achieved compared to the widely used x-ray-based methods using the array ultrasound probe (IV).
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