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DETERMINANTS OF BONE STRENGTH AND PREDICTORS OF HIP FRACTURE AMONG FINNISH ADULTS

Results from the Health 2000 Survey and the Mini-Finland Health Survey

Maarit Kauppi

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To my precious family

ABSTRACT

Maarit Kauppi

Determinants of bone strength and predictors of hip fracture among Finnish adults. Results from the Health 2000 Survey and the Mini-Finland Health Survey

University of Turku, Faculty of Medicine, Department of Clinical Medicine, Internal Medicine; Doctoral Programme of Clinical Investigation, University of Turku; National Institute for Health and Welfare, Turku, Finland. Annales Universitatis Turkuensis. Medica – Odontologica, Turku, Finland 2015.

The objective of this thesis was to identify the determinants of bone strength and predictors of hip fracture in representative samples of Finnish adults. A secondary objective was to construct a simple multifactorial model for hip fracture prediction over a 10-year follow-up period.

The study was based on the Health 2000 Survey conducted during 2000 to 2001 (men and women aged 30 years or over, n=6 035) and the Mini-Finland Health Survey conducted during 1978 to 1980 (women aged 45 years or over, n=2 039). Study subjects participated in health interviews and comprehensive health examination. In the Health 2000 Survey, bone strength was assessed by means of calcaneal quantitative ultrasound (QUS). The follow-up information about hip fractures was drawn from the National Hospital Discharge Register.

In this study, age, weight, height, serum 25-hydroxyvitamin D (S-25(OH)D), physical activity, smoking and alcohol consumption as well as menopause and eventual HRT in women were found to be associated with calcaneal broadband ultrasound attenuation (BUA) and speed of sound (SOS). Parity was associated with a decreased risk of hip fracture in postmenopausal women. Age, height, weight or waist circumference, quantitative ultrasound index (QUI), S-25(OH)D and fall-related factors, such as maximal walking speed, Parkinson's disease, and the number of prescribed CNS active medication were significant independent predictors of hip fracture. At the population level, the incremental value of QUS appeared to be minor in hip fracture prediction when the fall-related risk factors were taken into account.

A simple multifactorial model for hip fracture prediction presented in this study was based on readily available factors (age, gender, height, waist circumference, and fall-related factors). Prospective studies are needed to test this model in patient-based study populations.

Keywords: calcaneal quantitative ultrasound, QUI, S-25(OH)D, fall risk, maximal walking speed, hip fracture, risk assessment, elderly

TIIVISTELMÄ

Maarit Kauppi

Luun lujuutta määrittävät ja lonkkamurtumia ennustavat tekijät suomalaisilla aikuisilla. Tuloksia Terveys 2000- ja Mini-Suomi -terveystutkimuksista

Turun yliopisto, lääketieteellinen tiedekunta, kliininen laitos, sisätautioppi; Turun yliopiston kliininen tohtoriohjelma; Terveyden ja hyvinvoinnin laitos, Turku, Finland. Annales Universitatis Turkuensis. Medica – Odontologica, Turku, Finland 2015.

Tämän väitöskirjan tavoitteena oli tunnistaa luun lujuutta määrittäviä ja lonkkamurtumien ilmaantuvuutta ennustavia tekijöitä suomalaisia aikuisia edustavissa aineistoissa. Lisäksi tavoitteena oli muodostaa yksinkertainen malli, jolla voitaisiin ennustaa lonkkamurtumia yli 10 vuoden seurantajakson aikana.

Väitöstutkimus koostui kahdesta suomalaista aikuisväestöä edustavasta aineistosta, Terveys 2000 –tutkimukseen vuosina 2000-2001 osallistuneista 30 vuotta täyttäneistä miehistä ja naisista (n=6 035) sekä Mini-Suomi –terveystutkimukseen vuosina 1978-1980 osallistuneista 45 vuotta täyttäneistä naisista (n=2 039). Tutkittavien terveyttä ja toimintakykyä selvitettiin terveyshaastatteluiden ja monipuolisen terveystarkastuksen avulla. Terveys 2000 –tutkimukseen osallistuneilta henkilöiltä arvioitiin luun lujuutta kantaluun ultraäänimittauksen (QUS) avulla. Tiedot seurannan aikaisista lonkkamurtumista saatiin valtakunnallisesta HILMO-rekisteristä.

Tutkimuksessa todettiin, että ikä, paino, pituus, seerumin 25-hydroksi-D-vitamiini (S-25(OH)D), fyysinen aktiivisuus, tupakointi ja alkoholin käyttö sekä menopaussi ja mahdollisen hormonikorvaushoidon kesto naisilla olivat yhteydessä ultraäänen vaimentumaan (BUA) ja nopeuteen (SOS) kantaluussa. Synnyttäneisyys oli yhteydessä pienempään lonkkamurtumariskiin postmenopausaalisilla naisilla. Ikä, pituus, paino tai vyötärön ympärys, kantaluun ultraääni-indeksi (QUI), S-25(OH)D sekä kaatumisalttiuteen liittyvät tekijät, kuten maksimaalinen kävelynopeus, Parkinsonin tauti ja keskushermostoon vaikuttavien lääkkeiden lukumäärä olivat lonkkamurtumia itsenäisesti ennustavia tekijöitä. Kun kaatumisen riskitekijät otettiin huomioon, kantaluun ultraäänimittaus toi väestötasolla lonkkamurtumariskin ennustamiseen vain vähäistä lisäarvoa.

Tässä tutkimuksessa esitetty yksinkertainen malli lonkkamurtumariskin arvioimiseksi perustui helposti saatavilla oleviin tekijöihin (ikä, sukupuoli, pituus, vyötärön ympärys, maksimaalinen kävelynopeus, Parkinsonin tauti, keskushermostoon vaikuttavien lääkkeiden lukumäärä). Mallin toimivuutta tulisi arvioida potilasaineistoihin perustuvissa pitkittäistutkimuksissa.

Avainsanat: kantaluun ultraäänimittaus, QUI, S-25(OH)D, kaatumisalttius, maksimaalinen kävelynopeus, lonkkamurtuma, riskin arviointi, ikääntyneet

CONTENTS

ABBREVIATIONS

ADL	Activities of Daily Living
BMD	Bone Mineral Density
BMI	Body Mass Index
BMU	Bone Multicellular Unit
BUA	Broadband Ultrasound Attenuation
CI	Confidence Interval
CNS	Central Nervous System
CRF	Clinical Risk Factor
CV	Coefficient of Variation
DM	Diabetes Mellitus
DXA	Dual-energy x-ray absorptiometry
FN	Femoral Neck
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
IADL	Instrumental Activities of Daily Living
IOF	International Osteoporosis Foundation
PD	Parkinson's Disease
QCT	Quantitative Computed Tomography
QUI	Quantitative Ultrasound Index
QUS	Quantitative Ultrasound
R^2	Coefficient of Determination
RA	Rheumatoid Arthritis

RR	Relative Risk
SD	Standard Deviation
SI	Stiffness Index
SLE	Systemic Lupus Erythematosus
SOS	Speed of Sound
VOS	Velocity of Sound
WHO	World Health Organisation

LIST OF ORIGINAL PUBLICATIONS

I Kauppi M, Impivaara O, Mäki J, Heliövaara M, Marniemi J, Montonen J, Jula A. Vitamin D status and common risk factors for bone fragility as determinants of quantitative ultrasound variables in a nationally representative population sample. Bone 2009, 45:119-124.

II Kauppi M, Heliövaara M, Impivaara O, Knekt P, Jula A. Parity and risk of hip fracture in postmenopausal women. Osteoporos Int 2011, 22:1765-1771.

III Kauppi M, Impivaara O, Mäki J, Heliövaara M, Jula A. Quantitative ultrasound measurements and vitamin D status in the assessment of hip fracture risk in a nationally representative population sample. Osteoporos Int 2013, 24:2611-2618.

IV Kauppi M, Stenholm S, Impivaara O, Mäki J, Heliövaara M, Jula A. Fall-related risk factors and heel quantitative ultrasound in the assessment of hip fracture risk: a 10-year follow-up of a nationally representative adult population sample. Osteoporos Int 2014, 25:1685-1695.

1 INTRODUCTION

Fragility fractures constitute a serious health problem in elderly populations, worldwide. Hip fractures, in particular, commonly result in excess mortality, impaired functional capacity and substantial health care costs [1-4]. In Finland, about 7 000 hip fractures occur annually. Some 6 000 of these are first hip fractures [5]. The risk of hip fracture increases with age in both genders. Over 95 percent of the victims are 50 years or older [6]. Women are more likely to sustain a hip fracture and the female to male incidence ratio appears to be about two to one [4,7].

The risk of fragility hip fracture varies widely among countries. The annual age-adjusted incidence of hip fracture has recently been reported to range from 58 to 574 fractures per 100 000 persons among women and from 35 to 290 fractures per 100 000 persons among men [8]. Incidence rates reported from the Scandinavian countries are among the highest. According to statistics from 2003 to 2008 on Finnish subjects aged 50 years or older the annual incidence of the first hip fracture was 470 fractures per 100 000 persons among women and 250 fractures per 100 000 persons among men [9].

The average age at the occurrence of hip fracture has increased over time. In Finland, a mean age of a hip fracture patient increased by seven years in women and by six years in men between the years 1970 and 2010 [10]. The age-adjusted incidence of hip fracture appears to be increasing in some countries, but levelling off or declining in others [4,10-13]. Nevertheless, even if the incidence declines, the number of hip fractures is likely to grow as a result of an increasing life expectancy and a larger number of elderly people in society [14,15].

Appropriate information on all major risk factors of hip fractures is essential for proper identification of subjects with a particularly high fracture risk and to refer these for a comprehensive clinical assessment and to receive preventive measures and care as required.

Bone mass (and therefore bone strength or fragility) is largely determined by heredity and a number of factors including age, various lifestyle factors such as nutrition, physical activity, smoking and alcohol consumption and by chronic disease conditions and medications [16]. Bone loss substantially accelerates in women as they pass the menopause [17]. Such factors, so-called clinical risk factors (CRF), can be used for the assessment of fracture risk. Bone mineral density measurements by means of dual energy X-ray absorptiometry (DXA) can serve the same purpose. Combinations of risk factors and density measurements are likely to improve the risk assessments [18].

Most hip fractures occur as a consequence of a fall [19]. One third of subjects aged 65 or over, and more than half of those aged 80 or over fall yearly [20,21]. Factors associated with poor mobility, impaired balance and poor vision predispose one to falls and therefore ultimately also to fractures [19,22-24].

Several risk factors increase fracture risk both by decreasing bone strength and increasing liability to fall. Typical examples of such factors include age, female gender, vitamin D deficiency, heavy alcohol intake, physical inactivity and certain diseases and medications [19,22,23].

Guidelines by the World Health Organization (WHO) and International Osteoporosis Foundation (IOF) propose that assessments of future fracture risk should be based on a 10-year probability of fracture [25]. Supported by the WHO, the Fracture Risk Assessment Tool (FRAX) has been developed for this purpose [26]. FRAX is based on age, gender, weight, height, smoking, alcohol intake, rheumatoid arthritis, use of systemic glucocorticoid therapy and a number of other potential causes of secondary osteoporosis. FRAX can be used with or without bone mineral density measurement. However, liability to fall is not taken into account by FRAX. Even if this algorithm may identify subjects at increased risk of fracture and help in clinical decisions, it is so far not known whether its application indeed will be able to prevent major fractures, such as hip fractures in Finnish men and women.

The majority of studies on the determinants and predictors of hip fractures have been carried out in women. In addition, the study populations of such studies have rarely been strictly representative of the general population and the follow-up periods have generally been rather short. We have had the opportunity to investigate these aspects of hip fracture in two rather large nationally representative study populations with fairly long follow-up periods.

In a nationwide survey covering large numbers of subjects living in dispersed and remote localities bone strength can hardly be expected to be assessed by means of DXA. Instead, quantitative calcaneal ultrasound (QUS) suits well for this purpose. The device is transportable and does not involve ionizing radiation, and above all, QUS has been shown to predict hip fractures comparably to DXA [27-29].

Prospective studies assessing calcaneal QUS together with clinical risk factors for hip fracture prediction are scarce [30]. Moreover, the impact of single risk factors or such factors in various combinations on the variation in hip fracture risk is uncertain. It seemed therefore pertinent to investigate the determinants of bone strength and the predictors of hip fracture by means of QUS in representative samples of Finnish men and women and, in particular, to construct a simple model for hip fracture prediction based on a limited number of readily available risk factors in a follow-up study extending up to 10 years.

2 REVIEW OF THE LITERATURE

The literature review of the present academic dissertation was based on searches performed through Medline database using search terms of relevant issues, such as bone physiology, determinants and measurement techniques of bone strength, osteoporosis, hip fracture incidence and risk factors of hip fracture. These searches were supplemented by manually reviewing bibliographies of eligible studies and relevant review articles. However, no systematic literature review was performed. The quality grading of the literature was based on an author's subjective assessment rather than on use of any quality assessment instruments [31].

2.1 Bone strength

2.1.1 Bone structure and physiology

The human skeleton consists of over 200 bones. They provide a rigid framework for locomotion that supports the body and maintains its shape. In addition, it protects vital organs and participates in mineral homeostasis. The skeleton is also a primary site of hemopoiesis [32].

Bones are made of proteins (mainly collagen) that are impregnated with crystals of calcium hydroxyapatite. This composite structure gives bone its contradictory properties of stiffness yet flexibility and lightness yet strength. The relative proportions of protein and mineral vary across anatomic sites according to the function a given bone usually performs [33].

According to their shapes bones can be divided into long (e.g., femur), short (e.g., tarsal bones), flat (e.g., hip bone, sternum) or irregular bones (e.g., vertebras) [32]. The outer layer of bone is composed of cortical (compact) bone, which is solid and dense. Cortical bone has an outer periosteal surface and inner endosteal surface. The interior of bone is filled with trabecular (cancellous) bone that is a spongelike network of plates and rods. The structure of trabecular bone makes the overall bone structure lighter and allows room for the blood vessels and marrow. Trabecular bone has also a much greater surface area and is metabolically more active than cortical bone. The relative proportion of cortical and trabecular bone is 80 to 20 percent of the total bone mass but varies greatly among different bones. For example, the proportion of trabecular bone ranges from 70 percent to 90 percent in vertebral bodies and in the heel and less than 10 percent in the midshafts of long bones such as the femoral shaft and radius. The neck of femur is 25 percent of trabecular bone, whereas the intertrochanteric region is about 50 percent to 75 percent trabecular bone [34].

Cortical and trabecular bone is normally formed in a lamellar way such that collagen fibrils are laid down in alternating orientations. This kind of structure

gives lamellar bone its significant strength. In nonlamellar or woven bone the collagen fibrils are laid down in a disorganized manner, and therefore woven bone is weaker than lamellar bone. Woven bone is formed during the formation of primary bone and may also be seen in some pathologic conditions [32].

Bone is a dynamic tissue and is constantly undergoing a change in response to environmental stimuli. These changes are performed throughout life in adaptive processes of modelling and remodelling. The cells engaged in these processes are osteoblasts (bone forming cells) and osteoclasts (bone resorbing cells), which compose bone multicellular units (BMU) [32]. Osteocytes ("bone maintainers") are involved in the remodelling process; e.g., by functioning as mechanosensory cells that sense and signal the need for adaptive processes [35]. They also comprise most of all bone cells in adult bone, and are the longest lived bone cells. In bone modelling, new bone is formed by osteoblasts without prior bone resorption. This process predominates during childhood and adolescence, and enables longitudinal and radial growth of bones as well as their adaptations in shape in response to physiologic stimuli and mechanical forces. During bone remodeling, bone formation is preceded by bone resorption performed by osteoclasts. By this process bone is renewed in order to maintain its strength and mineral homeostasis [32,36-38].

Normally, bone remodeling is balanced and only little changes in the total amount of bone occur. This is regulated by various physiologic and biomechanical factors. Systemic hormones (such as parathyroid hormone (PTH), calcitonin, thyroid hormone, insulin, growth hormone (GH), insulin-like growth factor-1 (IGF-1) hormone, cortisone and sex hormones), cytokines, vitamins and minerals as well as mechanical loading have important regulatory roles [32]. Estrogen has an antiresorptive effect on bone by reducing osteoclastic activity, but also an anabolic effect by increasing the proliferation, differentiation and function of osteoblasts. Androgens play an important role in bone formation. Testosterone is likely to have an anabolic effect on bone formation by itself, but has also beneficial effects on bone by its conversion to estrogen [17]. PTH together with vitamin D has a role in regulating of calcium homeostasis, and already very small decreases in serum calcium stimulate the secretion of parathyroid hormone, which in turn releases calcium in the circulation [34].

2.1.2 Age-related changes

During growth, the balance between the volume of bone being resorbed and formed in the BMU is positive and leads to the addition of bone in each remodeling event. After the longitudinal growth has ceased bone mass and density continues to increase until the twenties or early thirties when the peak bone mass is achieved. Peak bone mass is largely (60-80%) determined by genetic factors, but also other factors, such as physical activity and nutrition play an important role during the growth [38]. After reaching the peak bone mass the remodelling rate decreases. When age advances, the amount of bone formed in each BMU, in

each site remodeled declines. This is likely to result in net bone loss especially in perimenopausal and postmenopausal phases when, due to estrogen deficiency, bone remodeling rate increases in women. Also, in men bone remodelling is likely to increase slightly along with increasing age [39]. An increased remodelling rate leads to trabecular thinning (predominant in men) and disconnection of trabeculae (predominant in women), cortical thinning and porosity [40]. During their lifespans, women lose about 50 percent of their trabecular bone and 30 percent of their cortical bone. Corresponding figures for men are 30 percent and 20 percent, respectively [41]. Achieving the highest possible peak bone mass during the growth period is important in order to maintain sufficient bone mass to withstand these changes. Age-related bone loss is partly compensated by concurrent periosteal apposition. Even though this periosteal apposition does not increase the total amount of bone, it increases the bending resistance by enlarging the diameter of the bone as well as by redistributing bone tissue further from the central axis of the bone [39,40]. However, as a consequence of all age-related changes in bone material and structural properties, aging bones' ability to absorb energy when loaded decreases and bones become more fragile and susceptible to fracture.

2.1.3 Osteoporosis

A WHO study group defined osteoporosis as: "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture" [42]. According to a more recent definition from the NIH Consensus Development Panel on Osteoporosis, osteoporosis is: "a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture" [43]. Operationally osteoporosis is defined on the basis of a BMD measurement. According to the WHO criteria, osteoporosis is defined as: "a BMD that lies 2.5 SDs or more below the average value for young healthy women (a T-score of $\leqslant$ -2.5)" [42]. A T-score between -1 and -2.5 is thought to refer to osteopenia and a T-score of -1 or higher is considered as normal. T-score values of BMD were originally used in epidemiological studies to enable comparison among populations. It was only later when T-score values were applied to diagnostics of osteoporosis in clinical practice. Currently, the NHANES III female reference data is recommended to be used for T-score derivation occurring at the hip region for both women and men [44].

Osteoporosis is traditionally classified into primary and secondary osteoporosis [45]. Primary osteoporosis is thought to be related to the aging process, and can occur in both genders. However, it is often associated with hypogonadism that especially women experience after the menopause. Therefore, this condition is more common in women than in men (by a ratio of about 6 to 1). In secondary osteoporosis, the loss of bone mass results from a disease, medication or certain lifestyle factors. Important causes of secondary osteoporosis include: long-term use of systemic glucocorticoids, heavy alcohol use, smoking,

gastrointestinal disease, such as inflammatory bowel disease and celiac disease, hyperthyroidism, hyperparathyroidism and hypercalciuria. Also, diabetes and rheumatoid arthritis may result in osteoporosis [46,47].

2.1.4 Assessment of bone strength

Bone strength is determined by bone quantity; i.e., the amount of bone bulk, but also by structural and material properties of bone. Material properties include factors associated with bone mineral content and density, collagen composition as well as the number, size and localization of microdamage. Structural properties involve bone geometry and bone microarchitecture such as trabecular architecture, cortical thickness and porosity [33,48]. In clinical practice, bone strength is usually assessed by means of dual energy X-ray absorptiometry (DXA), quantitative computed tomography (QCT) and quantitative ultrasound (QUS) measurements.

DXA

BMD measured by means of dual energy X-ray absorptiometry (DXA) is regarded as the method of choice in diagnosing osteoporosis [44]. DXA can be used to assess both axial (e.g., proximal femur and lumbar spine) and appendicular skeleton (e.g., radius and calcaneus). It can also be used to assess bone mineral content of the whole skeleton [49,50]. The first generation of DXA scanners (e.g., Hologic QDR-1000 and Lunar DPX) used a pencil beam X-ray, whereas new generation systems (e.g., Hologic QDR-4500 and Lunar Expert-XL) use a fan-shaped X-ray beam. Because the X-ray has both high- and low-photon energies, two different types of tissue (mineralized and soft tissue) can be distinguished. Thus, a direct measurement of BMD without interference from soft tissue is possible. The result is an areal (g/cm^2) and not a volumetric (g/cm^3) BMD. This may lead to overestimation of BMD in large bones [49]. The accuracy of the DXA measurements for bone mineral content has been reported to be three to eight percent [51] and the precision (CV=coefficient of variation) is 0.6 to 1.9 percent [52,53]. The radiation dose for DXA measurement depends on device, measurement site and the scan mode used. The effective dose is generally low, ranging from 0.07 µSv used in peripheral scans with a pencil beam DXA [54] and up to nearly 60 µSv used in vertebral scan with fan-beam DXA [49,50].

BMD measured by means of DXA is assumed to account for 60 to 80 percent of bone strength. However, clinical implementation of BMD measurement has not been unproblematic. There are biological variations in the composition of bone. Differences also exist between the measurement techniques of DXA. Therefore T-scores measured at different sites and with different techniques are not commensurable [44]. The femoral neck is used as a reference site for the DXA measurement because of its high predictive value of hip fracture in many prospective studies [55,56]. There is a substantial overlap in BMD values among subjects who sustain a hip fracture and those who do not. DXA thus appears to be

predictive of hip fracture rather at the population than at the individual level [57,58].

QUS

Quantitative ultrasound measurement is based on mechanical ultrasound waves (frequency range from 20 kHz to 100 MHz) that pass through bone and cause bone material to vibrate on a micro-scale. This in turn, alters the shape, intensity and speed of a propagating wave [59]. Based on this, bone tissue can be characterized in terms of speed of sound (SOS, m/s) and broadband ultrasound attenuation (BUA, dB/MHz). In addition to SOS and BUA composite variables, such as stiffness index (SI) and quantitative ultrasound index (QUI) have been introduced. These variables are linearly weighted averages of SOS and BUA [60].

There are many different quantitative ultrasound devices on the market. Ultrasound devices can be divided into water-coupled (wet) or gel-coupled (dry) systems. Examples of wet systems are Achilles+ (Lunar Corp; Madison, WI, USA) and UBA 575+ (Walker Sonix Inc., Worcester, MA, USA), which is no longer available, provides a background for current systems. Dry systems include CUBA Clinical (McCue Plc; Winchester, UK) and Sahara Clinical Bone Sonometry (Hologic Inc., Bedford, MA, USA). The measurement sites may differ between the devices. However, in the clinical setting the most widely used quantitative ultrasound measurement site is calcaneus [61,62]. One reason for this is that calcaneus is mostly composed of trabecular bone, which is metabolically more active than cortical bone, and is thus more sensitive to the changes in bone density and structure. In addition, calcaneus is a weight-bearing bone having two nearly plane-parallel sides and is covered only by thin soft-tissue layers, which makes the measurement easier [63]. The short-term precision (CV) of QUS ranges between 2.5 to 6.0 percent for BUA, 3.1 to 5.5 percent for SOS and 3.3 to 3.5 percent for QUI [64,65].

Previous studies have shown QUS values to correlate reasonably well with BMD measured by means of DXA, the strongest associations being found in site-specific measurements (e.g., calcaneus) [66]. However, according to previous meta-analysis, QUI has been shown to have relatively low sensitivity and specificity as for identifying individuals determined osteoporotic by DXA measurement [67]. For example, at QUI T-score threshold level of -1.5, the summary estimate of sensitivity was 66% (95% CI=53-77 %) and the specificity was 74% (95% CI=66-81%). This may arise from the fact that these two techiques partly measure different properties of the bone. In addition to bone mineral density, QUS is influenced by structural properties of the bone. For example, QUS values differ depending on the orientation of the bone sample being measured, which suggests that QUS values mirror mechanical anisotropy of the bone. In addition, QUS has been shown to correlate with structural parameters measured by histomorphometry [63,68,69].

Although QUS is not a diagnostic method of osteoporosis comparable to dual energy X-ray absorptiometry, it has other assets. It is portable, less expensive than DXA and free of ionizing radiation. QUS has been shown to discriminate between the subjects with and without fractures, and to predict hip and other fragility fractures equally well as DXA [27-29,64,65,70,71]. However, the information about hip fracture prediction with QUS in men is rather scarce [29,72,73].

QCT

Quantitative computed tomography (QCT) uses a calibration standard to convert Hounsfield Units (HU) of the conventional CT image to bone mineral density values. It may be used to assess bone mineral density both in axial spine (multidetector CT) and in appendicular skeleton; e.g., forearm, tibia and calcaneus (high-resolution peripheral quantitative CT) [50,74,75]. Compared to other techniques, the main advantage in QCT measurement is its ability to measure true volumetric BMD (g/cm³). Thus, the result is not size-dependent. With QCT, it is also possible to assess trabecular and cortical bone separately. Moreover, it enables an assessment of bone microstructure [75,76]. The short-term precision (CV) of spinal, hip and peripheral QCT range between 0.9 to 4 percent. The in vivo accuracy lies between four to 15 percent. Radiation exposure of QCT protocols vary depending on the imaging site and technique used. The effective doses for multidetector CT measurements are of the order of <0.01-2.6 mSv, whereas approximate effective doses for high-resolution peripheral QCT scans may be as low as <0.005 mSv [50,75,77].

There is evidence that spinal QCT can be used to make decisions about the initiation of treatment, and it is also useful in monitoring changes in BMD over time and the response to treatment. In women, spinal and peripheral QCT measurements predict vertebral and hip fractures, respectively. However, evidence of such prediction is lacking in men. In addition, further prospective studies are needed to assess the ability of spinal QCT to predict hip fractures in both men and women [75,77]. One of the limitations of QCT is its relatively high radiation exposure compared to, for example, DXA. In addition, accessibility of general CT scanners is limited. Also, the reference data for QCT, particularly in men and children, are few. Therefore, QCT has been mainly used as a research tool and its clinical use has thus far been limited [77].

2.2 Hip fractures

2.2.1 Diagnosis and classification

Diagnosis of hip fracture is based on a clinical X-ray examination. Hip fractures can be classified into two main groups: intracapsular or femoral neck fractures and extracapsular fractures [78]. Extracapsular fractures include pertrochanteric

and subtrochanteric fractures. Figure 1 shows the locations and diagnostic codes (ICD-10) of these fractures of the proximal femur [79]. In Finland, the ICD-10 codes have been used since year 1996 following the ICD-8 and ICD-9 codes that were used during the years: 1987 to 1995 [80]. These codes are reported in the National Hospital Discharge Register. This register has been shown to be a reliable and accurate source of information about hospital admissions and discharges. The coverage with respect to hip fractures has been reported to be 98 percent [81,82].

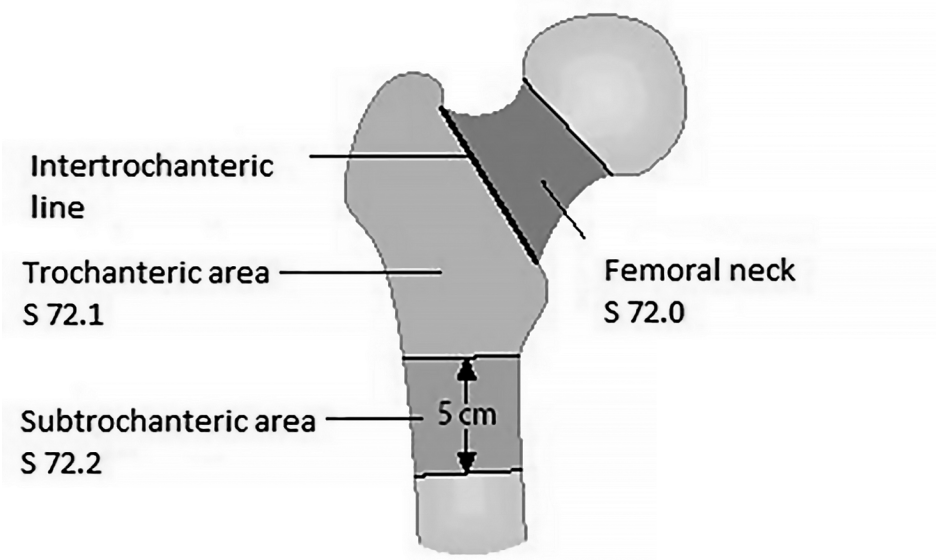

Figure 1. Classification and diagnostic codes (ICD-10) of fractures in the proximal femur (adapted and modified from previous report [9]).

2.2.2 Risk factors

The risk of hip fracture is determined not only by bone fragility but also by non-skeletal or fall-related factors, including those associated with the fall event, such as the impact force and hardness of landing surface [40,83]. Many of the risk factors interact in a complex manner and may be defined as multifactorial risk factors [19]. Figure 2 summarizes the most well-recognized risk factors of hip fracture related to bone-strength, fall risk or both.

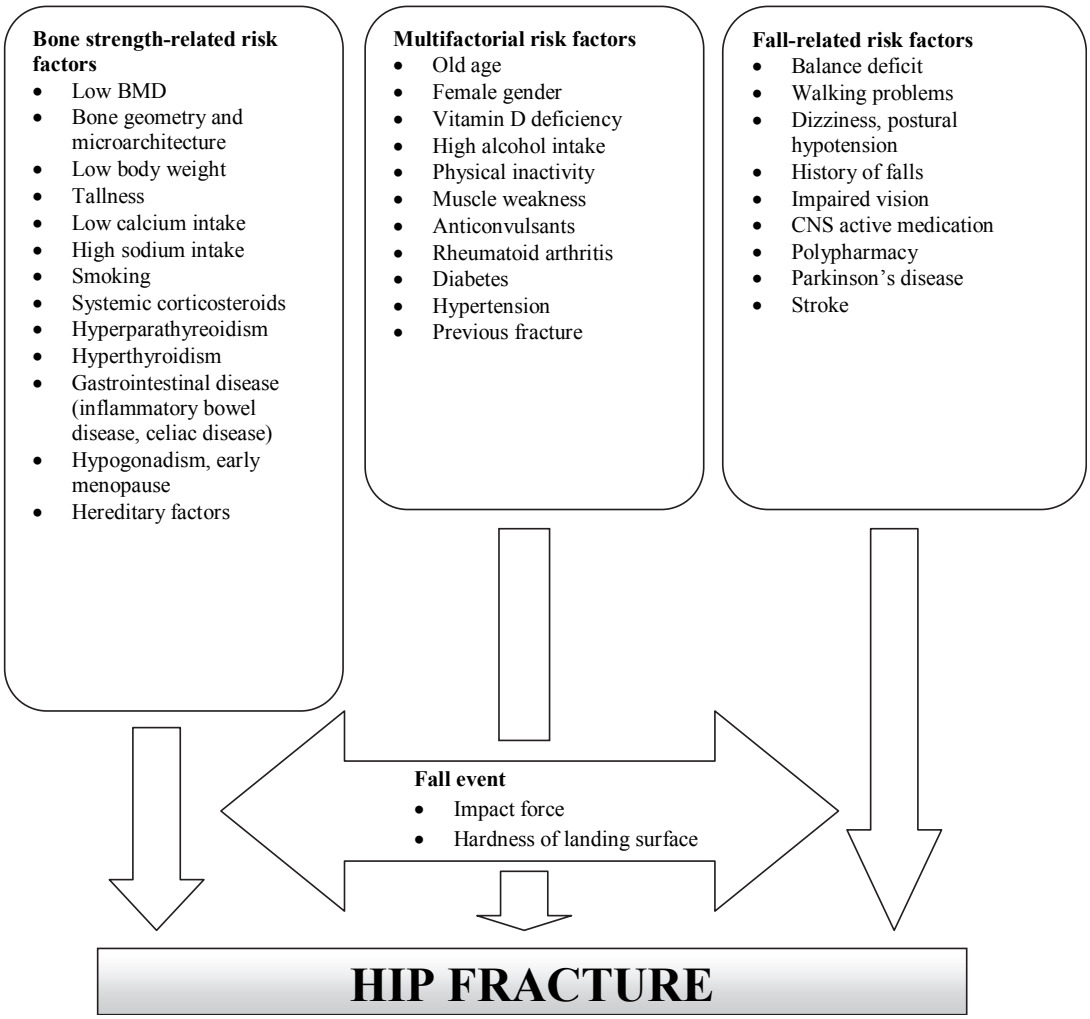

Figure 2. Risk factors of hip fracture. Adapted and modified from previous reports [16,19,22-24,40,83-86].

Bone strength-related risk factors

Bone strength is determined by its material properties, such as mineral content and density, and the structural properties, such as bone geometry and microarchitecture of bone [33,48]. BMD is the surrogate measure of bone strength most often assessed in clinical practice. Prospective studies have shown that at the population level, each SD reduction in femoral neck BMD measured with DXA approximately doubles the risk for hip or other osteoporotic fractures [55,56]. Similar increments in risk have been found for one SD reductions in calcaneal QUS variables assessed by different ultrasound devices. For example, the gradients of risk (RR/SD) of hip fracture have been estimated to be 1.69 and 1.96

for BUA and SOS, respectively [30]. QUS variables have also been suggested to measure some structural and qualitative properties in addition to BMD [63,68,69].

Excessive weight loss has been found to be harmful for bone health, and is associated with an increased risk of hip fracture especially in thin subjects [87,88]. An inverse association between body weight and hip fracture risk has been established in several prospective studies [89-92]. This is likely to be associated with a lower bone mineral density in subjects with low body mass, but it may also reflect underlying chronic conditions. In addition, an increased risk of hip fracture in these subjects may partly result from thinner fat padding protecting the hip in the occasion of a fall [93]. However, the association between body weight and fracture risk appears to be non-linear. Leanness is a risk factor of fracture rather than obesity as a protective factor [94]. Obesity may protect against some fractures, such as hip fractures, but be a risk factor for others (for example, ankle and humeral fractures) [95]. Also tallness has been found to be a predictor of hip fracture in several previous studies [19,23,92,96]. The increased risk of hip fracture in taller subjects is presumably a consequence of biomechanical factors, such as hip axis length (HAL) [23,97]. Hip fracture risk increases by 1.6– to 1.9–fold for each SD increase in HAL above the mean of the control population [97]. In addition, the femoral neck-shaft angle, femoral neck width and upper femoral neck area as geometrical characteristics may contribute to hip fracture risk [98]. Also, a greater impact during a fall may increase the risk of fracture in taller subjects compared to shorter subjects.

An adequate intake of calcium is an important factor for normal growth and development of the skeleton [99]. Calcium supplementation may increase bone mass during the growth period [100] and decrease bone loss in premenopausal women [101]. However, the results about the association between calcium supplementation and bone strength or fracture risk later in life are less clear-cut. Most of previous prospective cohort studies and RCTs have found no significant association between calcium supplementation alone and hip fracture risk, and even adverse effects have been reported [102-104]. It is likely that when the intake of calcium is at a sufficient level, supplementation may have only little effect on fracture risk. On the other hand, in order to obtain significant reductions in fracture risk, an adequate supply of vitamin D along with calcium may be needed, and the benefit of supplementation is likely to be evident mostly among subjects deficient of these nutrients [105]. According to previous evidence, a calcium intake of 1200 mg/d in combination with vitamin D (cholecalciferol) doses of 800 IU/d would reduce the hip fracture risk in elderly institutionalized women who are deficient in calcium and vitamin D [106,107].

High sodium intake increases calcium excretion in urine. This, in turn, may accelerate bone loss and osteoporosis [108]. A longitudinal study on postmenopausal women has shown that halving the sodium intake was associated with a significantly reduced rate of bone loss [109]. However, it is not known how

much this contributes to fracture risk because studies assessing sodium intake and fracture risk are lacking.

Active smoking has been established to be a significant risk factor for future hip fracture in several prospective cohort studies [91,92,110,111]. Lower BMD in smokers compared to non-smokers explains a part of a higher fracture risk. However, there are BMD-independent factors that contribute to fracture risk. These potentially include certain lifestyle factors related to smoking habit, such as low physical activity, that may increase the risk of falls. In addition, smoking may induce changes in microarchitecture of bone not captured by BMD measurement [112].

Long-term systemic glucocorticoid use is an important risk factor for secondary osteoporosis and hip fracture. The association between glucocorticoid use and bone loss or fracture risk has been shown to be dose-dependent with more pronounced effects seen with daily doses of at least five mg (of prednisolone or equivalent) [113,114]. Other chronic conditions associated with decreased bone strength and increased hip fracture risk include hyperparathyroidism [115], gastrointestinal diseases, such as inflammatory bowel disease [116], untreated celiac disease [117] and hyperthyroidism [118].

Estrogen deficiency is mainly responsible for the age-related bone loss in postmenopausal women but also in older men [17]. Amenorrhea related to endocrine abnormalities (e.g., anorexia nervosa, athletic amenorrhea) and early menopause as well as a short fertile period increases the risk of osteoporotic fractures [119-121]. On the other hand, HRT may prevent adverse effects of menopause on the skeleton and decrease fracture risk in postmenopausal women [122,123]. The previously found association between increased parity and decreased risk of hip fracture [124,125] is likely to reflect beneficial effects of longer estrogen exposure period on bone structure and strength.

The risk of hip and other osteoporotic fracture is higher among those whose parent has suffered a hip fracture [126-128]. Heritable factors, including genetic and environmental factors have been estimated to determine 50 to 85 percent of the variance in BMD depending of the skeletal site [126,127]. In addition, there is a heritable contribution from femoral neck geometry [129], regulation of bone remodelling, S-25(OH)D and PTH concentrations [130,131], age at menopause [132] and muscle strength [133], all of which are likely to contribute to bone fragility and hip fracture risk.

Fall-related risk factors

Falls are common among older subjects. One third of people aged 65 years or older and over half of those aged 80 years or older fall every year [20,21]. Although only a few percent of these falls lead to fracture, most of hip fractures occur as a consequence of the fall [19]. Impaired neuromuscular functions, such as decreased muscle strength, walking difficulties and impaired balance are among the most important predictors of falls and fractures [24,128,134-137].

Walking speed is a good indicator of muscle strength, balance and other sensorimotor functions [138,139]. There are different test protocols to measure walking speed. The most often used distances are 2.4 meters [140,141], 4 meters [142,143] and 6.0 or 6.1 meters [135,144]. Also, a 10-meter walking course has often been used in Finland [145,146]. Either usual or maximal walking speed can be measured [147,148]. There is no established optimal threshold value of walking speed for fracture prediction but a usual walking speed of 1.0 m/s have been used to predict several future adverse health outcomes in elderly subjects [147].

Chronic conditions such as Parkinson's disease or stroke affect postural control and balance through neuromuscular or sensory decline, and are likely to increase risk of falls and hip fractures [23,149]. Similarly, certain central nervous system active (CNS) medication, especially benzodiazepines, antidepressants and antipsychotics have been shown to be independently associated with increased risk of falls and fractures in older subjects [85,150-156]. Polypharmacy with such medications, in particular, has been shown to be harmful [86,151]. In addition, dizziness or postural hypotension [157,158], prior history of falls [159-161] and impaired vision [162-164] have been shown to be associated with increased risk of falls, injurious accidents and hip fractures.

Multifactorial risk factors

Many risk factors for hip fracture act through decreasing bone strength and quality as well as by increasing liability to fall. Age is one example of this kind of multifactorial risk factor. The risk of hip fracture has been estimated to increase 13-fold between the ages of 60 and 80. Only a four-fold increase of this can be explained by decreases in bone mineral density [9]. The rest is associated with increased liability to fall, and perhaps with other age-related aspects of health and functional capacity that are not necessarily captured by routine measurements.

Most of hip fractures occur in postmenopausal women. This arises partly from the postmenopausal estrogen deficit, which predisposes to an increased risk of bone fragility. Also, peak bone mass and size attained during the growth period remains smaller in women compared to men, thus leaving women with less reserve to withstand age-related losses in bone strength [17]. In addition, the incidence of falls and fall-related injuries in old age has is higher among women compared to men [165].

An adequate supply of vitamin D from diet or from the synthesis in the skin is essential for preserving calcium homeostasis and bone health. Vitamin D (cholecalciferol, D_3 and ergocalciferol, D_2) is metabolized by the liver to 25-hydroxyvitamin D (S-25(OH)D) and subsequently in the kidneys to its active form, 1,25-dihydroxyvitamin D (1,25(OH)2D). The production of this active form of vitamin D is regulated by plasma parathyroid hormone (PTH) and serum calcium and phosphorus levels [166,167]. S-25(OH)D is usually used to determine a subject's vitamin D status. Although there is no consensus on optimal levels of serum 25-hydroxyvitamin D, concentrations between 50 and 80 nmol/l

have been suggested to be sufficient with regard to bone health [167,168]. This is based on S-25(OH)D concentrations at which measured PTH levels begin to level off [169,170].

In addition to its actions on bone, vitamin D is proposed to have beneficial effects on muscle strength, balance control and physical function [171]. These effects, in turn, are likely to decrease the risk of falling and fracture. However, the results concerning the association of BMD and hip fracture risk with vitamin D status have been inconsistent [172-179]. Case-control studies and cohort studies have often found lower levels of S-25(OH)D in hip fracture cases compared to controls or inverse relation between vitamin D status and fracture risk. Randomized controlled trials (RCT), however, have often showed no significant difference in BMD or hip fracture risk between those randomised to supplementation and controls [172,177]. There is growing evidence that vitamin D supplementation would be more efficient in reducing hip fracture risk if combined with calcium [105,176,178,180]. Vitamin D supplementation appears to be beneficial for bone health mainly among those with low S-25(OH)D levels [181]. In women, the relationship between S-25(OH)D and fracture risk has been suggested to be dependent on race or ethnicity. In white women, a significant negative association between S-25(OH)D and fracture risk has been found, whereas no significant association or even higher fracture risk in higher S-25(OH)D values have been reported in Black, Asian, Hispanic or Native American women [182].

Alcohol abuse is detrimental for bone health [183,184]. It may increase the risk of falls and is associated with increased fracture risk [92,156,185,186]. In contrast, several studies have found moderate alcohol use to be associated with higher bone density [187-189], and the results on the association between moderate alcohol use and hip fracture risk are controversial [22,186,190,191].

Many prospective cohort studies have shown an inverse association between physical activity and hip fracture risk in men and women [92,111,192-195]. Physical inactivity tends to be associated with reduced bone strength [196,197], muscle strength and motor coordination [198], all of which are likely to increase fracture risk. Raising the level of physical activity during the lifespan has been found to be associated with a decreased fracture risk [194,199]. Similarly, decreasing the level of physical activity increases hip fracture risk later in life [200].

The association between physical activity and fracture risk may be confounded by health status and the genetic inheritance of qualification for a physically active lifestyle [195]. Subjects with a better health and muscular function are more likely to choose a physically active lifestyle. Yet, some previous studies have found a beneficial effect of leisure-time physical activity with respect to hip fracture risk even independently of health status and function [192,200]. However, because there is a lack of randomized controlled trials evaluating the causality between

physical activity and hip fractures, the potential confounding cannot be ruled out [195,201].

Handgrip strength is a good indicator of overall muscle strength and also predicts physical disability and mobility limitation [202,203]. In addition, maintenance of handgrip strength over perimenopausal transition appears to be associated with lower bone loss [204], and low handgrip strength predicts hip fractures in elderly men and women [135,205]. Mechanical loading that muscle induces on an adjacent bone has an important role in determining bone mass and strength [206]. Moreover, appendicular muscle mass correlates with bone cortical thickness also at sites not adjacent to mechanical loading [207]. This finding suggests that there are some additional paracrine and endocrine interactions between bone and muscle tissue by which they coordinate their masses [208].

The use of antiepileptic drugs, such as phenytoin, phenobarbital and carbamazepin associate with an accelerated rate of bone loss and consequent bone fragility [209,210]. In addition, prospective studies show an increased risk of falls and hip fractures among postmenopausal women and elderly men using antiepileptic drugs independent of BMD [152,211].

The increased risk of fractures that are related to rheumatoid arthritis (RA) [212,213] is partly attributed to the effects of glucocorticoid treatment. However, an increased fracture risk exists also in RA patients not using oral glucocorticoids. RA is associated with joint inflammation, consequent joint destruction and periarticular bone loss. In addition, chronic systemic inflammation in RA may result in increased risk of systemic bone loss [212,214]. Also, nonsteroidal anti-inflammatory drugs (NSAID), commonly used to treat RA, may contribute to fracture risk [215,216]. Moreover, RA is associated with an increased risk of falling, which is at least partly due to joint pain, impaired muscle strength, fatigue, postural instability and consequently reduced functioning [217-220].

Subjects with type 1 diabetes have generally decreased BMD, whereas those with type 2 diabetes have often normal or high BMD [221]. However, the risk of hip fracture has been found to be higher in subjects with either type 1 or type 2 diabetes, compared to subjects without this disease [23,128,221,222]. It is suggested that hyperglycemia, elevated oxidative stress and hypercysteinemia, which are often associated with diabetes, may disturb collagen cross-link formation that impair bone properties independently of BMD [223]. Also, peripheral neuropathy, a common complication associated with long-lasting diabetes, is likely to increase risk of falling and risk of fracture [224].

Hypertension associates with increased calcium excretion in urine and consequent bone mineral loss in some [225,226] but not in all [227,228] studies. Large case-control and prospective studies have found a higher risk for hip and other osteoporotic fractures in hypertensive subjects [84,229,230]. A recent study based on the Dubbo Osteoporosis Epidemiology Study proposed the association between hypertension and fracture risk to be independent of BMD [231]. Hypertension may damage brain structures controlling gait control and balance,

which in turn may predispose to falls [232,233] and consequent fractures. However, more information is needed about the association of hypertension and hip fracture risk. For example, the contribution of antihypertensive medication to this association is inconclusive. Certain groups of antihypertensive drugs, such as thiazide diuretics and beta-blockers, increase BMD and decrease the risk of hip fractures [234,235]. On the other hand, some studies have found negative [236,237] or no association [238,239] between antihypertensives and bone strength. An increased risk of falling and fall-related injuries among users of antihypertensive drugs demonstarted in some studies [152,153,240] is likely to be due to the acute effects of medication on postural blood pressure causing orthostatic hypotension. On the other hand, antihypertensive medication may decrease the risk of fall in the long run by improving blood pressure control and preventing orthostatic hypotension [241]. However, the role of individual classes of hypertensive medication with respect to fall risk has not been explicitly determined [240].

Several earlier studies have shown previous fragility fracture to be a significant predictor of future osteoporotic fractures, including hip fractures [22,128,159,160,242,243]. A minor part of this association has been explained by low BMD the proportion of which has been shown to decrease with age. The mechanism for the BMD-independent increase in fracture risk is not fully understood but is likely to be associated with coexisting morbidity increasing the risk of fall [160,242].

2.3 Prediction of hip fracture

Because several independent risk factors for hip fracture have been identified, the challenge is to develop methods for accurate identification of subjects at increased risk for hip fracture who might benefit from preventive or therapeutic measures. For this, it is essential to determine those factors and combinations of them which contribute the most to the risk. Measures of bone strength and fall-related factors have independent effects on fracture risk, and combining such factors and other so-called clinical risk factors (CRF) improves the detection of subjects at increased risk of various fragility fractures, including hip fractures [24,144,159,160,244]. Within a given level of BMD, women with a greater number of clinical risk factors are at increased risk of sustaining a hip fracture. Correspondingly, within a category of number of CRF, lower BMD has been found to be associated with higher rates of hip fracture [128].

The World Health Organization (WHO) and the International Osteoporosis Foundation (IOF) have recommended that the risk of fracture should be expressed as a short-term absolute risk (for example, 10-years) [25]. Assessment tools using this approach have been established, of which the WHO Fracture Risk Assessment Tool (FRAX) [26], QFracture algorithm [245] and Garvan Fracture Risk

Calculator [246] are supposedly the most commonly used tools for assessing fracture risk. Table 1 shows a summary of these fracture risk assessment tools.

The FRAX algorithm, developed in conjunction with the World Health Organization, was published in 2008. It calculates the 10-year probability of hip and other major osteoporotic fractures, such as spine, wrist and humerus [18], and can be applied to subjects aged 40 to 90 years. The FRAX tool is available online as well as in simplified paper version. The model of FRAX is based on data of a series of meta-analyses derived from nine population-based cohorts from around the world, and has been validated in 11 independent cohorts [244]. Variables included in the FRAX algorithm are age, weight, height, and dichotomized risk factors, such as prior fragility fracture, parental history of hip fracture, current tobacco smoking, the use of long-term glucocorticoids, rheumatoid arthritis, alcohol consumption and other causes of secondary osteoporosis, such as type I diabetes, osteogenesis imperfecta, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition or malabsorption and chronic liver disease. The algorithm can be used either with or without BMD measurement (femoral neck). Both risk of fracture and risk of death are taken into account while computing the fracture probability [26].

FRAX has been criticized for it does not take into account the risk of falling or variables, such as vitamin D status or calcium deficiency in fracture prediction. It also lacks a dose-response relationship for alleged risk factors, such as use of glucocorticoids, smoking or alcohol intake, and does not take into account racial and ethnic differences that may influence the risk [247-249]. In addition, the cohorts, are not truly representative of the general populations. For instance, practically all of the subjects in the validation cohorts have been women [244]. However, some recent studies have suggested a similar ability of FRAX to predict hip fractures in men compared to women [250,251].

QFracture algorithm, first published in 2009, was designed to estimate an absolute risk of osteoporotic fracture and hip fracture in primary care [252]. This algorithm is based on a large database of routinely collected data from 357 general practices in the United Kingdom (2 357 895 patients aged 30-85 in the development cohort) and is validated by data from 178 practices (1 275 917 patients aged 30-85 in the validation cohort). The QFracture algorithm allows fracture risk estimation from one to 10 years in subjects aged 30 to 99 years. Variables used are readily available in patients' healthcare records or that patients themselves probably know without the need for clinical measurements or laboratory tests. These include age, gender, BMI, smoking, alcohol use, history of falls, parental history of osteoporotic fracture, type 2 diabetes, cardiovascular disease, asthma, cancer, rheumatoid arthritis, chronic liver or kidney disease, gastrointestinal malabsorption, use of tricyclic antidepressants or corticosteroids, use of HRT and endocrine disorders. QFracture was updated in 2012 when further developments were performed according to the recommendations made by the National Institute for Health and Clinical Excellence (NICE). These included

extending the age range to patients older than 85 years and including additional variables such as previous fragility fracture, ethnic group, epilepsy and use of anticonvulsants, care home residency, additional inflammatory arthropaties, chronic obstructive airway disease, type 1 diabetes, Parkinson's disease and dementia. There were 3 142 673 patients in the development cohort and 1 583 373 patients in the validation cohort of the updated algorithm. The updated algorithm has been shown to explain 71.7% of the variation in hip fracture risk in women and 70.4 percent in men [245]. It thus shows improved performance compared to the 2009 algorithm. Compared to FRAX, QFracture is at least as effective in identifying patients with an increased risk for hip fracture [252].

The Garvan Fracture Risk Calculator was developed in 2007 using data collected in the Dubbo Osteoporosis Epidemiology Study conducted by the Bone and Mineral Research Program of Sydney's Garvan Institute of Medical Research [246]. The Garvan Fracture Risk Calculator integrates the femoral neck BMD T-score information with four clinical risk factors; i.e., age, gender, number of falls in the past year and number of fractures since age 50 years. This tool allows 5- and 10-year probability calculation for hip and other types of fractures, including for example spine, wrist, humerus, pelvis, rib, sternum and distal femur. Elderly subjects, aged 60 to 96 years can be assessed. The Garvan tool has shown moderate and similar discriminative ability compared to FRAX tool both in older men and women [253-255]. However, because the number of risk factors included in the Garvan tool is limited, it may underestimate fracture risk in patients with many clinical risk factors. Another limitation of this tool is that it is available only for subjects aged 60 years or older. In addition, it is based only on the Australian population [256].

Table 1. Summary of the most commonly used fracture risk assessment tools.

	FRAX [26,244]	QFracture [245,252]	Garvan [246]
Year of publishing	2008	2009 (updated in 2012)	2007
Development and validation cohorts	Development: 9 prospective population-based cohorts (n=46 350)* Validation: 11 prospective population-based cohorts (n=230 486)**	Development: database from 357 general practices in the UK (n=2 357 895 in 2009; n=3 142 673 in 2012) Validation: database from 178 practices in the UK (n=1 275 917 in 2009; n=1 583 373 in 2012)	Development: Dubbo Osteoporosis Epidemiology Study (DOES) cohort (n=2216) Validation: internal validation by the bootstrap method
Target group	Subjects aged 40-90 years	Subjects aged 30-99 years	Subjects aged 60-96 years
Variables included	Age, gender, weight, height, prior fragility fracture, parental history of hip fracture, current tobacco smoking, alcohol consumption, ever use of long-term glucocorticoids, RA, causes of secondary osteoporosis (type 1 DM, osteogenesis imperfecta, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease), BMD (optional)	Age, gender, BMI, history of falls, history of fragility fracture, parental history of osteoporotic fracture, ethnicity, smoking, alcohol use, type 1 or type 2 DM, cardiovascular disease, asthma or COPD, dementia, PD, cancer, RA or SLE, epilepsy, chronic liver or kidney disease, gastrointestinal malabsorption, endocrine disorders, use of anticonvulsants, antidepressants or corticosteroids, care home residency, HRT	Age, gender, number of falls in the past year, number of fractures since age 50 years, FN BMD T-score (optional)
Risk scores	10-year probability of hip or other osteoporotic fractures (clinical spine, humeral, forearm)	1- to 10-year probability of hip and other osteoporotic fractures (wrist, vertebral, proximal humerus)	5- and 10-year probability of hip and other types of fractures (spine, wrist, humerus, pelvis, rib, sternum and distal femur)

*The Rotterdam Study, EVOS/EPOS, CaMos, Rochester cohort, Sheffield cohort, DOES, Hiroshima cohort, two cohorts from Gothenburg

**THIN, SOF, York, Geelong I and II, OPUS, PERF, EPIDOS, Miyama, SEMOF, WHI

RA=rheumatoid arthritis, DM=diabetes mellitus, PD=Parkinson's disease, SLE=systemic lupus erythematosus, HRT=hormone replacement therapy, FN=femoral neck

The development and validation cohorts of these fracture risk assessment tools as well as study populations of previous prospective studies assessing bone strength together with clinical risk factors for hip fracture prediction have rarely been representative of the general population. The majority of these studies have been carried out in women. Table 2 summarizes the characteristics and main results of the prospective studies assessing bone strength combined with clinical risk factors for prediction of hip fracture. Some of these studies had relatively large study populations. The number of participants ranged between 225 and 12064. However, none of these studies were based on a truly representative sample of the general population. Only four of these studies included also men in their study populations [72,73,135,243]. The mean follow-up times ranged from 33 months up to 14 years, but extended over five years only in seven studies [128,135,137,243,257-259]. Eight of the studies assessed QUS for its prediction of hip fracture [72,73,137,144,159-161,257]. Six of these studies [137,144,159,160,257,259] included fall-related risk factors, such as walking speed and muscle strength in the final analyses. Only two prospective studies used the Sahara device as a QUS measurement method [137,161]. One study [243] estimated the proportion of hip fractures that may have been hypothetically reduced by elimination of certain risk factors. According to this analysis, approximately 57 percent of hip fracture cases in women and 37 percent in men were attributable to the presence of low BMD, postural instability and/or quadriceps weakness, a history of falls and prior fracture. None of these studies assessed how much of the variation in hip fracture risk could be explained by single risk factors or different combinations of them.

Against this background, it seemed necessary to study the determinants of bone strength assessed by means of QUS, and the predictors of hip fracture in representative samples of the Finnish adult population. In particular, it seemed pertinent to construct a simple model for hip fracture prediction based on a limited number of readily available risk factors in a follow-up study extending up to 10 years.

Table 2. Prospective studies for hip fracture risk assessment with bone strength measurement (DXA or QUS) and clinical risk factors (CRF) combined.

Name/place of study [ref.]	Participants	Follow-up time (mean) /no. of hip fract.	Source of hip fracture information	Bone strength measurement device /parameter	Studied CRFs	Main findings
*EPIDOS/ France [24]	7575 women aged 75+ yrs (mean 80.5 yrs) living in five French areas, recruited from population-based listings, such as voter-registration or health-insurance membership rolls	1.9 yrs/ 154	Self-report, confirmation through radiographs	DPX-Plus (Lunar)/ FN BMD	Age, center, self-reported physical disability and motion difficulty, chair stand test, foot tapping test, walking speed, tandem stands, tandem walk, calf circumference, walking outdoors, leaving neighborhood, cleaning house, leisure physical activity, handgrip and quadriceps strength, corrected visual function, medication use	Adjusted for age, center and each other, gait speed (RR=1.3, 95% CI=1.1-1.6), score tandem walk (RR=1.2, 95% CI=1.0-1.5), visual acuity (lowest quartile) (RR=2.0, 95% CI=1.1-3.7) and FN BMD (RR=1.8, 95% CI=1.5–2.2) were significant predictors of hip fracture. Fall-related factors and BMD had similar discriminant values, but their combined assessment improved the prediction of hip fracture.
*EPIDOS/ France [144]	5895 women aged 75+ yrs (mean 80.5 yrs) living in five French areas, recruited from population-based listings, such as voter-registration or health-insurance membership rolls	33 months/ 170	Self-report, confirmation through radiographs	Lunar Achilles (Lunar Corporation, Madison WI) /BUA; DPX-Plus (Lunar)/ FN BMD	Age, gait speed	Adjusted for age, FN BMD and each other, BUA (RR=1.4, 95% CI=1.2-1.7) and gait speed (RR=1.5, 95% CI=1.3-1.7) were significant predictors of hip fracture. Taking age into account, the sensitivity of BMD at the 50% cutoff was sig. higher compared to BUA (85% vs. 74%), but not compared to gait speed (79%).

EPISEM/ France & Switzerland [159]	12064 women aged 70-100 yrs pooled from two prospective cohort studies, EPIDOS and SEMOF (SEMOF: a cohort of 7062 Swiss women 70+ yrs recruited from official state register to attend a prospective multi-centre study comparing three QUS devices in the assessment of hip fracture)	3.2 yrs/ 307	Self-report or family member report, conf. from medical records	Lunar Achilles (GE-Lunar Corp) /SI	Age, height, weight, BMI, prior fracture, history of fall, prior estrogen treatment, chair test, DM, sedentary lifestyle	Adjusted for each other SI, age, BMI, prior fracture, history of fall, prior exposure to estrogen, chair test, and DM were significant risk factors of hip fracture. Compared to SI values of ≥77.6 adjusted HRs for SI values of 59.1-77.6 and ≤59.1 were 2.1 (95% CI=1.3-3.3) and 4.5 (95% CI= 2.8-7.1), respectively. Combining CRF to SI appears to correctly identify more women at low risk than either alone.
EPISEM/ France & Switzerland [160]	12064 women aged 70-100 yrs pooled from two prospective cohort studies (EPIDOS, SEMOF)	3.2 yrs/ 307	Self-report or family member report, conf. from medical records	Lunar Achilles (GE-Lunar Corp) /SI	Age, height, weight, BMI, prior fracture, prior fall, estrogen treatment, chair test, DM, education, physical activity, smoking, use of glucocorticoids, early menopause, surgical menopause, thyroid hormone treatment, parity	Adjusted for each other SI, age, BMI, prior fracture, chair test, history of fall, smoking and DM were significant and independent predictors of hip fracture. SI alone showed higher GR than CRF alone, and combination of SI and CRF had higher GR than either alone.
ECOSAP/ Spain [161]	5146 women aged 65+ yrs (mean 72.3 yrs), a non-randomized sample of consecutive cases recruited from 58 primary care centers throughout Spain	2.8 yrs/ 54	Self-report, X-ray, radiological or surgical reports	Sahara (Hologic, Waltham, MA, USA)/ QUI	Age, weight, height, BMI, age at menarche and menopause, parity, history of falls, prevalent fractures, family history of fractures, smoking, alcohol use, calcium intake, physical activity, sensory problems, medical history, medication use	Adjusted for age, history of falls, prevalent fractures, family history of fractures and calcium intake, HRs for 1 SD decreases were 1.56 (95% CI=1.13-2.16) for BUA, 1.21 (95% CI=0.95-1.56) for SOS and 1.40 (95% CI=1.01-1.95) for QUI. Other significant predictors of hip fracture were age, family history of fracture and calcium intake.

MOF/UK [257]	1289 women aged 70+ yrs (mean 77.9 yrs) recruited from an age-sex register of a general practice, including those in residential accommodation	3 yrs/ 37, 5.5 yrs/ 63	General practice and hospital records	UBA 1001 (111-P, Walker Sonix)/ BUA	Age, previous fracture, height, weight, kyphosis, physical activity, smoking, walking speed, handgrip strength, chair stand, trunk maneuver, frequency of climbing stairs, timed 10 foot taps, disability (ADL), fall history, tandem stands, mobility, reported health, medical problems, drug and dietary supplement use, dietary calcium intake, foot problems, circulation, cognitive impairment (CAPE)	Adjusted for age, handgrip strength, poor health, cognitive impairment, walking speed and each other, weight (p =0.0156), trunk maneuver (p=0.0075), epilepsy (p=0.0084), kyphosis (p=0.0058), poor circulation (p=0.0019) and short-term steroid use (p=0.01) were independent predictors of hip fracture within 3 years. Within 5.5 years independent risk factors were weight (p=0.0035), reported poor health (p=0.0374), epilepsy (p=0.0081) and age (p=0.0065).
MrOS Study/ US [135]	5902 men aged 65+ yrs, living in six US communities, cohort was designed to be representative of community-dwelling, ambulatory men aged 65+ yrs	5.3 yrs/ 77	Self-report, confirmed by physician review or radiological records	Hologic 4500 DXA/ FN BMD	Age, clinic, BMI, history of heart attack or stroke, handgrip strength, walking speed, chair test, narrow walk, leg power	Adjusted for age, clinic, FN BMD, BMI, history of heart attack and stroke, chair test, leg power, narrow walk and walking speed were significantly associated with hip fracture risk. When all variables of physical performance were entered to the model, only chair test remained significant.
*/**DOES/ Australia [243]	960 women and 689 men aged 60+ yrs (mean 70.6 yrs) recruited from the whole population of city of Dubbo, Australia	12 yrs (md)/ 115	Radiologists' reports	LUNAR DPX-L densitometer (GE-LUNAR Corp., Madison, WI, USA)/ FN BMD	Age, gender, quadriceps strength, body sway, history of falls, history of fracture	Adjusted for FN BMD, history of fracture, fall during the previous 12 months, quadriceps weakness, and postural instability were each associated with increased risk of hip fracture in men and women. The combination of these risk factors accounted for 57% of hip fractures in women and 37% in men.

*SOF/ US [22]	9516 women aged 65+ yrs (mean 72 yrs) recruited through lists such as voter-registration	4.1 yrs/ 192	Self-report, confirmed by review of radiographs	1) OsteoAnalyzer (SiemensOsteon , Wahiawa, Hawaii)/ calcaneal BMD 2) QDR 1000 (Hologic, Waltham, MA)/ FN BMD (performed for 7786 women)	Age, height, weight, BMI, waist and hip circumference, knee height, education, hair color, ethnic origin, medication and supplement use, health status, medical history, reproductive history, smoking, alcohol use, history of maternal hip fracture, self-rated health, caffeine intake, calcium intake, walking for exercise, on feet ≤4 h/day, ADL, IADL, chair test, muscle strength, walking speed, tandem stands and tandem walk, cognitive function, visual acuity and contrast sensitivity, depth perception, blood pressure, pulse	Many of the studied risk factors were independent predictors of hip fracture (including calcaneal BMD, age, inability to perform chair test, previous fracture, poor depth perception). Women with multiple risk factors and low BMD had an especially high risk of hip fracture.
*SOF/ US [128]	6787 women aged 66+ yrs (mean 73.3 yrs) recruited from four US clinical centers through lists such as voter-registration	10.1 yrs/ 602	Self-report, confirmed by review of radiological reports	QDR 1000 (Hologic, Waltham, MA)/ total hip BMD	Age, height, weight, BMI, body composition, wrist and waist circumference, medication and supplement use, health status, medical history, reproductive history, functional status (ADL, IADL), tobacco and alcohol use, history of fracture, maternal hip fracture, history of falls, depression, social support, neuromuscular function (incl. digit symbol test, walking speed, quadriceps strength,chair stand etc), cognitive function, depth perception	Adjusted for each other, BMD, older age, history of fracture after age 50, maternal history of hip fracture after age 50, greater height at age 25, impaired cognition, slower walking speed, nulliparity, type 2 DM and depth perception each independently predicted a 1.17- to 1.84-fold increase in hip fracture risk.

The Netherlands [72]	578 women and 132 men aged 70+ (mean 82.2) years recruited from homes or apartment houses for the elderly in Amsterdam area	2.8 yrs (md)/ 31	Self-report confirmed by physician	CUBA Clinical instrument (McCue Ultrasonics, Winchester, UK)/ BUA, SOS	Age, gender, weight, history of falls and fractures, physical activity, use of walking aid, immobility, living in a home (vs. apartment) for the elderly	Adjusted for age and gender, RR for 1 SD decrease in BUA was 2.3 (95% CI=1.4-3.7) and in SOS 1.6 (95% CI=1.1-2.3). Other significant predictors were older age, low weight and immobility.
*Rochester/ US [258]	225 women aged 37-94 years (md 68 yrs), an age-stratified random sample of women aged 30 yrs or over using the medical records linkage system of the Rochester Epidemiology Project	14.0 yrs/ 28	Self-report confirmed by medical records	Dual photon absorptiometry/ FN BMD, BMC	Age, weight, height, BMI, smoking, alcohol consumption, physical activity, medical history, 7-day dietary record, balance, heel-to-toe walking test, muscle strength, serum and urine calcium, serum phosphorus, creatinine, alkaline phosphatase, immunoreactive PTH, osteocalcin (OC), estrone, estradiol, testosterone, androstenedione, sex-hormone binding globulin (SHBG), urinary creatinine, hydroxyproline, glomerular filtration rate (GFR)	Significant age-adjusted predictors of proximal femur fractures were: FN BMD (HR=1.96, 95% CI=1.10-3.49]), trochanteric BMD (HR=2.23, 95% CI=1.19-4.20), estradiol index (estradiol/SHBG) (HR=1.55, 95% CI=1.06-2.27), testosterone index (testosterone/SHBG) (HR=1.64, 95% CI=1.10-2.43) and SHBG (HR=1.40, 95% CI=1.10-1.77). In a multivariable model including age, bone density, free estradiol index, dietary protein and 24-h urine calcium, FN BMD (HR=2.51, 95% CI=1.81-3.47) and free estradiol index (HR=1.50, 95% CI=1.10-2.05) were significant predictors of hip fracture.
EPIC-Norfolk/ UK [73]	8328 women and 6471 men aged 42-82 years, recruited from general practices	1.9 yrs/ 31	Diagnostic codes from East Norfolk health authority database	CUBA sonometer (McCue Ultrasonics, Winchester, UK)/ BUA, VOS	Age, gender, height, BMI, weight, medical history (incl. fractures), smoking,	Adjusted for age, gender, weight, height, smoking and history of fractures, BUA (HR=2.22, 95% CI=1.28-3.82) and VOS (HR=1.99, 95% CI=1.32-3.00) were significant predictors of hip fracture.

Finland [137]	1222 women aged 70-73 (mean 72 yrs) living independently in Oulu area, recruited through the National Population Register of Finland	5 yrs/ 53	Hospital discharge register, confirmed from patient records	1) Osteometer DTX 200 (Osteometer Meditech Roedovre, DK)/radial BMD; 2) Sahara (Hologic Bedford, MA) /BUA, SOS, QUI	Age, weight, height, BMI, alcohol use, smoking, coffee consumption, lifetime leisure-time physical activity, calcium intake, functional mobility (TUG), medical history, medication, participation in activities during the lifespan	High BMI (OR=0.87, 95% CI= 0.80-0.95) and low functional mobility (TUG ≥11 vs. <11 s.) (OR=3.51, 95% CI=1.76-6.98) were significantly and independently associated with hip fracture risk.
The Netherlands [259]	348 women 70+ yrs (mean 80.3 yrs) recruited from apartments and homes for the elderly in Amsterdam and its vicinity	5 yrs/ 16	Self-report, confirmed by physician	Norland XR-26 /FN BMD, troch BMD	Age, weight, height, BMI, yrs since menopause, residence, postmenopausal fracture history, alcohol use, smoking, mobility (5-point walking score), medication, S-25(OH)D, S-1.25(OH)D, sex hormone binding globulin (SHBG), serum intact PTH, osteocalcin, alkaline phosphatase, phosphate, albumin, calcium, creatinine, hydroxyproline, type I collagen crosslinked N-telopeptide (NTx), ca excretion	Adjusted for weight, age (RR=1.6, 95% CI=1.1-2.5), BMI (RR=1.9, 95% CI=1.1-3.3), fracture history (RR=4.2, 95% CI=1.5-11.6), FN BMD (RR=2.6, 95% CI=1.2-5.7) and troch BMD (RR=3.0, 95% CI=1.4-6.6) were significantly associated with hip fracture risk. After backwards Cox regression analysis fracture history, BMI and mobility were most strongly associated with hip fracture risk.

Bone strength parameters referring to DXA measurement: BMD (bone mineral density); BMC (bone mineral content)
Bone strength parameters referring to QUS measurement: BUA (broadband ultrasound attenutation); SI (stiffness index); QUI (quantitative ultrasound index); SOS (speed of sound); VOS (velocity of sound)
*Cohorts included in development or validation cohorts of the FRAX tool
**Cohort included in development cohort of the Garvan Fracture Risk Calculator

3 AIMS OF THE STUDY

The objective of this study was to identify determinants of bone strength and predictors of hip fracture in representative samples of Finnish adults.

The specific aims were:

1. To identify determinants of the estimated bone strength assessed by means of calcaneal quantitative ultrasound
2. To determine the bone strength-related risk factors of hip fracture
3. To ascertain the fall-related risk factors of hip fracture
4. To construct a simple multifactorial model for hip fracture prediction

4 STUDY POPULATIONS AND METHODS

4.1 Study populations

4.1.1 Studies I, III and IV

Studies I, III and IV were based on the Health 2000 Survey, a comprehensive nationwide health survey conducted in Finland during 2000-2001 (Figures 3 and 5) [260]. A stratified two-stage cluster sample comprised subjects aged 30 years or over living in mainland Finland (community and institutions). The study frame was regionally stratified according to five university hospital regions, each with approximately one million habitants. From each of these university hospital regions 16 health care districts were sampled as clusters (80 health center districts out of the total of 249 districts in mainland Finland). The 15 largest health center districts in the country were all selected in the sample with probability of 1, and the remaining 65 health center districts by systematic probability proportional to the size method. From these 80 health center districts a sample of 8 028 persons was selected by systematic random sampling (Figure 3). In order to include a sufficient number of elderly persons, subjects aged 80 or over were oversampled (2:1) relative to their proportion in the population.

The structured health interview elicited information about participants' health status, illnesses, use of health care services, functional capacity, health behavioral factors and sociodemographic factors. The participation rate of the health interview was 87% (n=6 986) of the original study sample. A comprehensive health examination performed in a health center after the health interview included assessment of functional capacity, symptom interview and clinical examinations performed by a physician. Measurements of blood pressure, heart rate, resting ECG, basic anthropometrics and heel bone quantitative ultrasound were performed. Also, fasting blood samples for serum glucose and 25-hydroxyvitamin D analyses were taken. The participation rate of the comprehensive health examination was 79% (n=6 354). Questionnaires elicited information about different aspects of subjects' functional capacity, quality of life, common symptoms, leisure time activities, lifestyle factors, living environment, psychological experiences and job perceptions. A detailed description of the study design, data collection methods and health and functional status of population of this health Survey has been reported elsewhere [260].

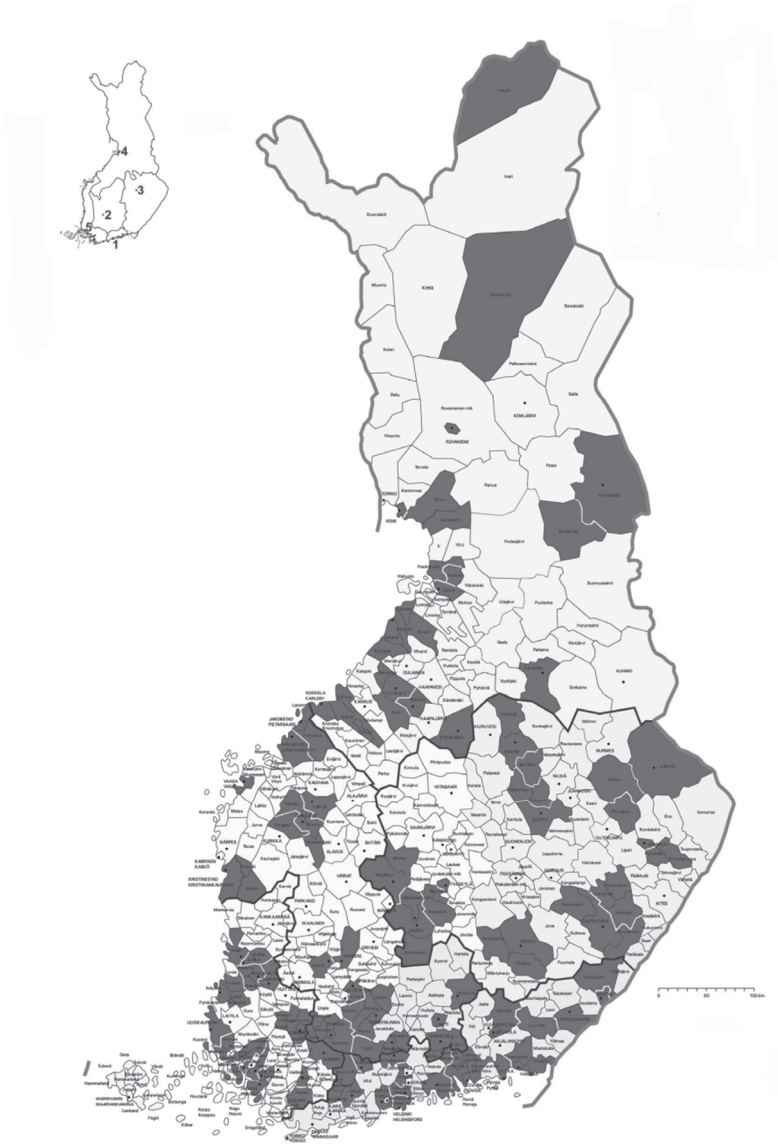

Figure 3. Study areas of the Health 2000 Survey.

4.1.2 Study II

Study II was based on the Mini-Finland Health Examination Survey, which was a comprehensive health survey implemented during 1978-1980 (Figures 4 and 6) [261]. The study population was a stratified two-stage cluster sample drawn from the national population register to represent Finnish adults aged 30 years or older. Firstly, forty representative strata were selected out of clusters of one or more neighboring municipalities. One cluster was then picked at random to represent each stratum. Secondly, a sample of 8 000 subjects (3 637 men and 4 363 women) was randomly drawn from the population register by systematic sampling (Figure 4).

The study included a health interview, which elicited information about participants' health, functional capacity, medications, use of health care services and aspects of health behavior. Altogether 7 703 subjects (over 96% of the whole sample) participated in the health interview. A basic health examination was carried out 1-6 weeks after the interview and included interviews on symptoms, several examinations, such as blood pressure and pulse measurements, ECG and spirometry. Also, blood and urine samples were taken and a joint function test evaluating musculoskeletal impairment was performed. Altogether 7 217 subjects (90% of the whole sample) participated in the health examination. Details of the study design and implementation of this health survey has been reported elsewhere [261].

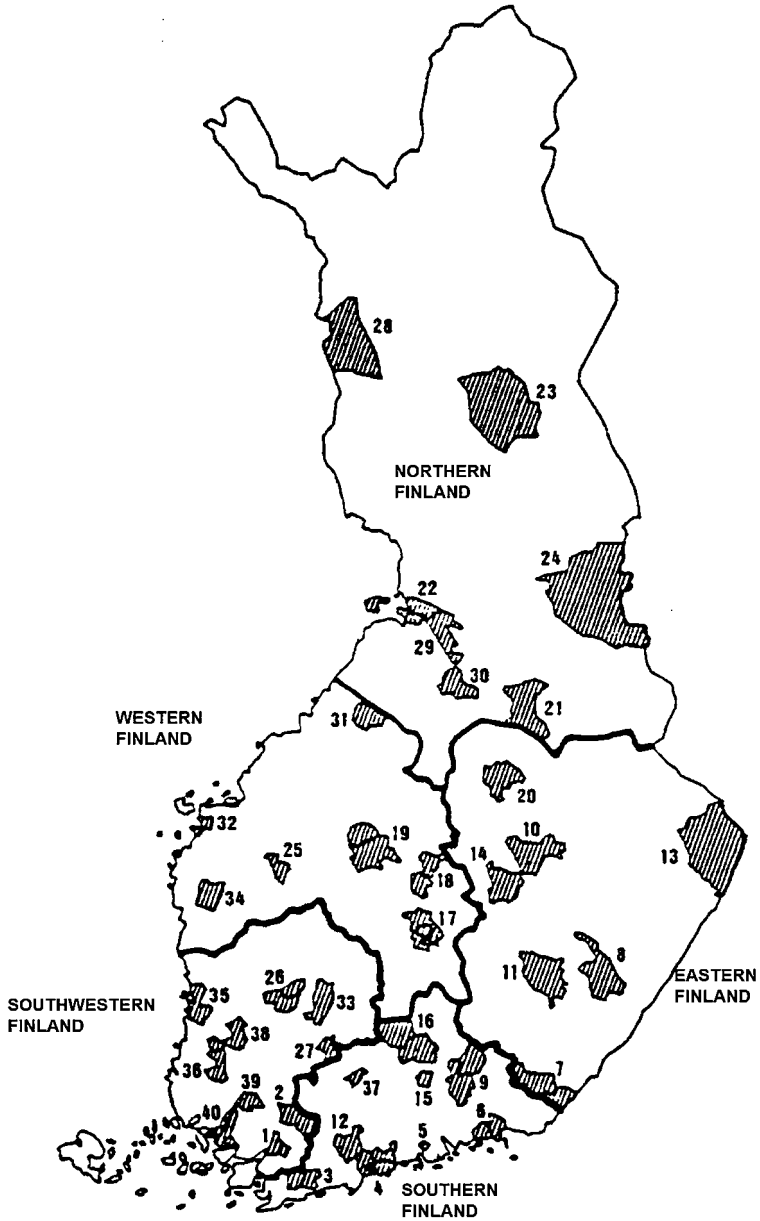

Figure 4. Study areas of the Mini-Finland Health Examination Survey.

The Health 2000 Survey and the Mini-Finland Health Survey were both conducted in accordance with the ethical principles of the Declaration of Helsinki [262]. The Health 2000 Survey was approved by the Ethics Committee for epidemiology and public health in the hospital district of Helsinki and Uusimaa, Finland. All participants gave their written informed consent. The flow of studies (I, III, IV) based on the Health 2000 data is shown in Figure 5. The flow of study II, based on the Mini-Finland survey, is shown in Figure 6. The data and the inclusion criteria used in the original publications are shown in Table 3.

Table 3. Study designs, populations and inclusion criteria of participants in the original studies

Study	Survey	Design	Age (years)	Participants	Inclusion criteria
I	The Health 2000 Survey	Cross-sectional	30-97 (mean 52.0)	n=6035 (75%), 2736 men and 3299 women	-Participated in a health examination (proper) -Information on QUS measurements and vitamin D status available
II	The Mini-Finland Health Survey	Prospective (mean follow-up period of 13 years)	45-95 (mean 63.2)	n=2028 (80%), all postmenopausal women	-Participated in an interview and health examination -Information on parity and age at the last menstrual period available -No previous hip fractures
III	The Health 2000 Survey	Prospective (mean follow-up period of 8.4 years)	50-98 (mean 62.9)	n=3305 (75%), 1433 men, 1872 women	-Participated in a health examination (proper) -Information on QUS measurements and vitamin D status available -No high-energy hip fracture
IV	The Health 2000 Survey	Prospective (mean follow-up period of 9.8 years)	55-97 (mean 66.4)	n=2300 (80%), 969 men, 1331 women	-Participated in a health examination (proper) -Information on QUS measurements, vitamin D status, maximal walking speed and handgrip strength available -No high-energy hip fracture -No previous hip fractures

Note: Percentages in parentheses indicate the proportion of individuals in each category of the original study sample.

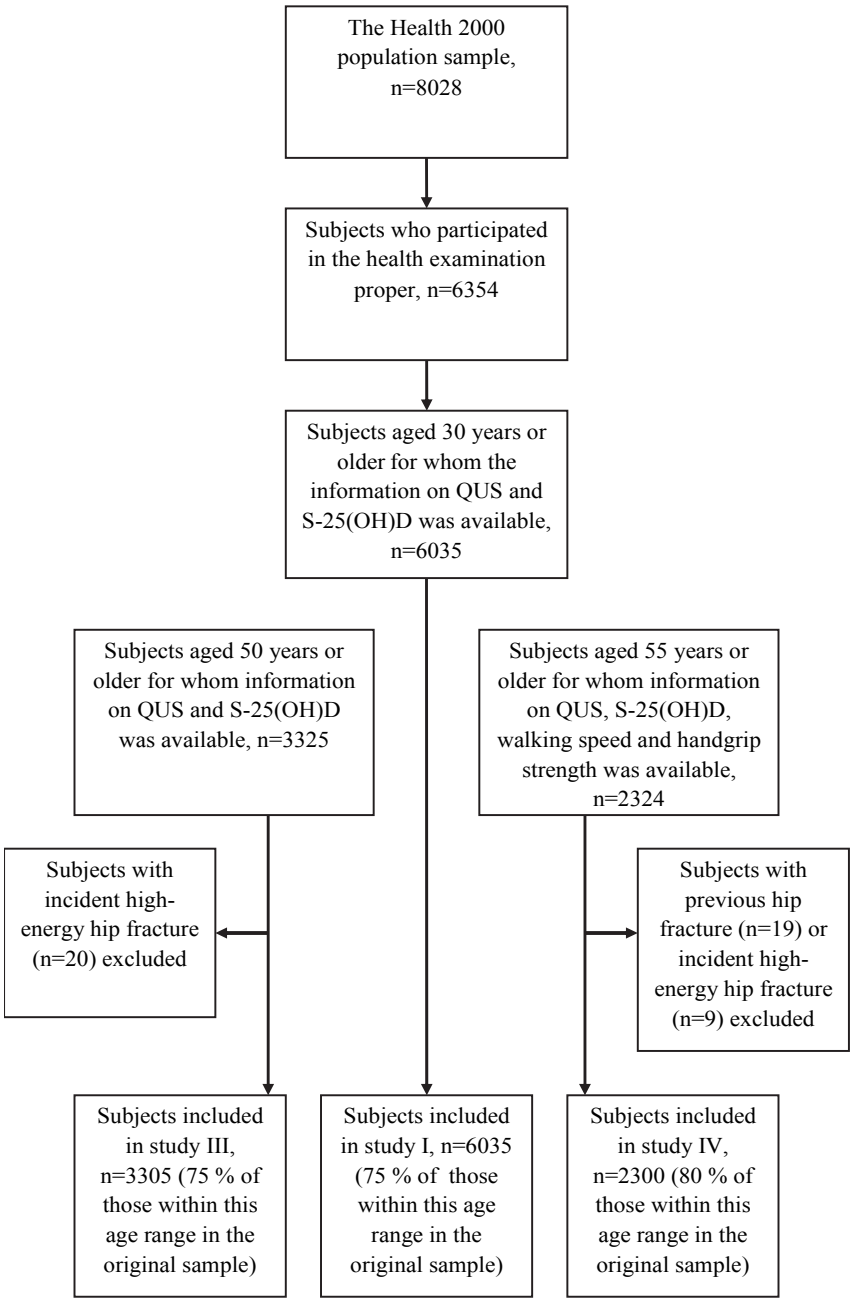

Figure 5. A flowchart for studies I, III and IV based on the Health 2000 data.

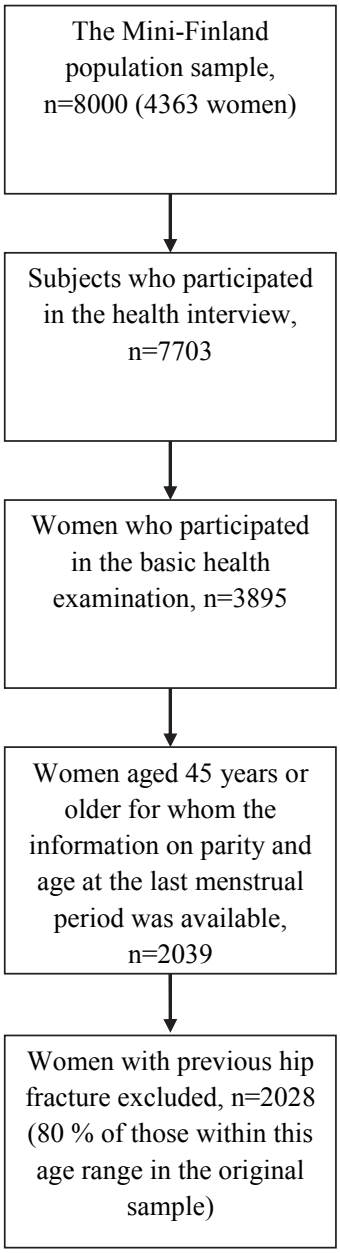

Figure 6. A flowchart for study II based on the Mini-Finland survey.

4.2 Methods

Hip fractures (Studies II, III and IV)
The follow-up information about hip fractures was drawn from the National Hospital Discharge Register, which has been shown to be an accurate and reliable source of information with 98% coverage and 98% sensitivity with respect to hip fracture diagnoses [82]. The patients admitted to the hospital for primary treatment of hip fractures (Studies III and IV: codes 72.0-72.2 as primary or secondary diagnoses according to ICD-10; Study II: code 820 according to ICD-8 and ICD-9) were identified. High-energy fractures; i.e., those following falls exceeding one meter from one level to another or traffic accidents or causalities alike were defined according to the external cause codes from the Hospital Discharge Register and were excluded (Studies III and IV).

QUS (Studies I, III and IV)
Quantitative ultrasound measurements were performed by trained examination nurses. A Hologic Sahara device (Hologic Bedford, MA, USA) was used to record broadband ultrasound attenuation (BUA, dB/MHz) and speed of sound (SOS, m/s) transmitted in a medio-lateral direction across the calcaneum. Both SOS and BUA are higher in healthy than in osteoporotic calcaneal bone. The measurement was performed on the right foot except in case of two repeated error messages, in which case re-measurement was performed on the left foot. A Sahara device was always kept at room temperature when used, and temperature changes did not pose problems in connection with transits to different examination locations. There were five devices, one for each of the five districts. Each of them was checked for performance quality daily before the first participant using the phantom provided by the manufacturer. Other quality measures used to monitor the quality of the examination included repeat and parallel measurements on field team staff, on subjects in same examination group and parallel measurements between groups (ten voluntary participants). The reliability coefficient for repeat measurements (n=193) covering all field teams was 0.91 for BUA and 0.92 for SOS. The QUS values were compared with BMD measured by DXA (Norland XR-26) in 105 volunteers with bone densities distributed throughout the clinical relevant range [263]. The correlation coefficients ranged for SOS from 0.53 (with BMD at the femoral neck) to 0.57 (with BMD at the lumbar spine) and for BUA from 0.46 and 0.56, respectively ($p<0.0001$ for all correlations). Furthermore, a strong correlation ($r=0.72$) was found between calcaneal BUA and bone mineral density (BMD) measured by peripheral DXA (PIXI) at the same site [66]. A composite variable, the quantitative ultrasound index (QUI) [264], was calculated from the values of BUA and SOS.

S-25(OH)D (Studies I-IV)
Venous blood samples were taken from arm vein after a minimum four hour fasting. The serum specimens were immediately (no later than 90 min from sampling) frozen to -20˚C on site. The samples were transferred from the field storage points to final storage in boxes packed in dry ice no later than 1-2 weeks after sampling. For the final storage, the samples were kept in -20˚C (the Mini-Finland) or -70˚C (the Health 2000) until analysed and were protected from light when processed. S-25(OH)D was measured by radioimmunoassay (the Health 2000: Incstar, Stillwater, MN, USA/ the Mini-Finland: Diasorin). In the Health 2000 Survey (studies I, III, and IV) the intra-assay coefficient of variation (CV) was 3.5% and the interassay CV was 6.9% at the concentration of 36 nmol/l. The limit of detection was 3.8 nmol/l. In the Mini-Finland survey (study II) the interassay coefficient of variation was 7.8% at the mean level of 47.3 nmol/l (n=167) and 9.12% at the level of 131.3 nmol/l (n=135).

Anthropometry and body composition (Studies I-IV)
Weight and height were measured with light clothing without shoes, height to the nearest 0.5 cm and weight to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Waist circumference was determined as the mid-point between the lowest rib and the iliac crest. Circumference measurements were recorded to an accuracy of 0.5 cm. Body fat was estimated (in kilograms and percentage) with an impedance meter (InBody 3.0, Biospace Seoul, Korea). This instrument measured the resistance of the arms, trunk and legs at frequencies 5, 50, 250, and 500 kHz and makes use of eight tactile electrodes of which two are in contact with the palm and thumb of each hand and two with the anterior and posterior aspects of the sole of each foot.

Smoking, alcohol consumption and physical activity (Studies I-IV)
Smoking reported in a health interview was classified into three categories: never-smokers, former smokers (those who had quit smoking at least one month prior to the survey) and current smokers (studies I, III and IV). In Study II, the category of current smokers was further classified into current smokers of cigars, pipe or fewer than 20 cigarettes a day, and current smokers of 20 cigarettes or more a day.

Alcohol use was estimated on the basis of the reported average consumption during the past month and expressed as absolute ethanol in grams/week (g/wk). In studies I and III, this was classified into the following three categories: no use, moderate use and heavy use. The limit of heavy use was set at 280 g/wk in men and 140 g/wk in women [265]. In study II, alcohol use was classified into four categories: no use, use of 1-49, 50-249 and >249 g/wk, respectively. In study IV, the following classification was used: no use, use of 1-84 g/wk and use of >84 g/wk. The limit of 84 g/wk was based on the guidelines used in Italy and in the United States recommending no more than 7 units of alcohol per week for elderly

men and women [266]. This limit has also been suggested by the Finnish Ministry of Social Affairs and Health.

A questionnaire elicited information on leisure-time physical activity that was classified into three categories: active (regular physical activity, for example jogging, cycling or swimming), moderately active (physical activity along with other activities, for example, fishing or gardening) and sedentary (no actual physical activity).

Walking speed (Study IV)

Walking speed was measured with a stopwatch over a distance of 6.1 meters [267]. Subjects were asked to walk the distance as quickly as they could, starting from their normal, standing posture behind the start line and continuing at full speed beyond the end line. Walking aids were allowed when necessary. The reliability of this test was good (intraclass correlation coefficient, ICC=0.77, n=163) [268].

Handgrip strength (Study IV)

Handgrip strength was measured in Newtons from the dominant hand with a hand-held dynamometer (Good Strength, IGS01, Metitur Oy, Jyväskylä). The subjects were asked to grip the handle as hard as possible for 3-5 seconds. The test was repeated after 30 seconds and the maximum result was recorded. If the difference between the two measurements was greater than 10%, a third test was done again 30 seconds later. Intraclass correlation coefficient of this test was 0.95 (n=265) [268].

Chronic conditions (Study IV)

Information on Parkinson's disease and stroke was based on the structured sets of questions and on the diagnostic assessments by the field physicians in connection with the clinical examination. In addition, information drawn from the National Hospital Discharge register was used to assess the occurrence of stroke [268]. Subjects were considered hypertensive if they were entitled to special reimbursement for hypertension medication, had a mean systolic blood pressure $\geqslant$140 mmHg or mean diastolic blood pressure $\geqslant$90mmHg or had been diagnosed with hypertension and were receiving antihypertensive medication. Subjects were considered to have diabetes if their fasting plasma glucose level was $\geqslant$7.0 nmol/l or if they were using insulin or oral antidiabetic medication.

CNS active medication and liability to fall (Study IV)

Faintness or dizziness as recent symptoms were inquired about and classified into one of the following three categories: not at all, quite little and to some extent or more. The number of falls during the previous 12 months while walking was classified into two categories: 0-1 and 2 or more falls. Reported information about central nervous system (CNS) active medication (such as opioids, anticonvulsants,

antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants or psycholeptics and psychoanaleptics in combination) was classified into one of three categories according to the number of such drugs in current use: 0, 1-2 and 3 or more drugs.

Self-rated health and level of education (*Study II)*
Self-rated health was classified according to a three-point scale: good, moderate or poor. The level of education (Study II) was classified according to the total years of education as follows: <8 years (less than primary school), 8-12 years (primary school plus lower or higher level secondary education) and >12 years (higher education, mostly studies or degrees at university level).

Reproductive history and use of hormone replacement therapy (HRT) (Studies I and II)
Women were asked about their reproductive history and were considered postmenopausal after an absence of menses for 12 months. Years since menopause were calculated from the last (physiological) menstruation onwards. The use and eventual years of HRT were also asked about. The number of children was asked about, and parity was classified into three categories: nulliparous (no births), parous with one to two births and parous with three or more births.

Follow-up (Studies II, III and IV)
In Study II, the follow-up period started at the beginning of 1978 and continued until the end of year 1994, until the hospitalisation due to the first hip fracture, or until the date of death, whichever came first. Mean follow-up period was 13 years (26 200 person-years). In Studies III and IV the follow-up period started at the beginning of 2000 and continued until the end of follow-up period, until the hospitalization due to a hip fracture or until the date of death, whichever came first. In Study III, the follow-up period continued until the end of 2009, and resulted in a mean follow-up period of 8.4 years (27 757 person-years). In Study IV, the follow-up period continued until the end of 2011, with a mean follow-up of 9.8 years (22 540 person-years).

4.3 Statistical methods

All statistical analyses were performed with the SAS software (version 9.1/9.3; SAS Institute Inc., Cary, NC, USA) and SUDAAN, which takes into account the sampling design including the oversampling of those aged 80 years or over (Research Triangle Institute, Release 10.0.1). Data of baseline characteristics of the study population are reported as mean values (SD/SE) and/or percentages. A p value of less than 0.05 was considered statistically significant.

Study I

Pearson's correlation was calculated between the QUS (BUA and SOS) variables and determinants of bone fragility. The analysis of covariance was used to compare the age-adjusted ultrasound results according to smoking status, alcohol use and physical activity. Multiple linear regression analysis was performed in order to assess independent roles of S-25(OH)D, age, measures of body built, lifestyle factors and menopausal status in women as determinant of QUS variables.

Study II

Cross-sectional associations between the alleged risk factors of hip fracture and parity were analyzed with multivariate logistic regression. Cox's proportional hazards models were used to estimate the strength of association between parity and the risk of hip fracture during the follow-up. The full model excluding the first 5 or 10 years of follow-up from the analysis was also performed in order to explore the stability of the proportional hazards.

Studies III and IV

Comparisons between men and women and between subjects with and without an incident hip fracture were performed using Student's t test for continuous variables and chi-square test for categorical variables. Cox's proportional hazards models were used to estimate predictors of hip fracture. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) were calculated. For continuous variables, HRs were computed for an increment of one standard deviation (SD). Only factors that proved significant predictors of hip fracture in the gender and age adjusted models were included in the fully adjusted model. The predictive power of the models including various combinations of risk factors was further assessed by means of coefficients of determination (R^2) [269]. In Study IV, alongside with the R^2 assessments, the net reclassification improvement (NRI) method [270] was used to quantify the changes in classification of subjects to low or high risk categories of fracture risk after additions of different variables to the model. A 3% fracture risk was used as a threshold for these risk categories. This threshold is the 10-year hip fracture probability above which the treatment of osteoporosis is suggested to become cost-effective in the USA according to the National Osteoporosis Foundation (NOF) Guide Committee [271].

5 RESULTS

5.1 Characteristics of the study subjects

Study I
The study population consisted of 6 035 participants (55% women) of the Health 2000 Survey for whom the information on QUS measurements and vitamin D status was available (75% of the original sample). The mean age of men and women was 50.9 and 53.0 years, respectively. The mean values of BUA and SOS were 81.8 dB/MHz and 1556 m/s in men and 75.1 dB/MHz and 1550 m/s in women, respectively. Vitamin D status was similar in men and women (45.1 in men *vs.* 45.2 nmol/l in women). Half of the women were postmenopausal. Characteristics of the study population are shown in detail in Study I, Table 1.

Study II
The study population consisted of 2 028 women aged 45 years or over at baseline who had participated in the Mini-Finland Health Survey and for whom the information on parity and age at the last menstrual period was available (80% of the participating women aged 45 years or over). The mean age of women at baseline was 63.2 years. The mean S-25(OH)D concentration was 38.3 nmol/l. The number of women who had never given birth (nulliparous) was 395. The number of women with one to two births was 737, and 881 women had at least three births. During a mean follow-up of 13 years (26 200 person-years), 133 of the women sustained their first hip fracture at the mean age of 79.7 years.

Study III
Subjects aged 50 years or over at baseline for whom information on QUS measurement was available formed the study population of study III. After the exclusion of victims of high-energy-based hip fractures (n=20), the study population consisted of 3 305 subjects (75% of those within this age range in the original sample) of which 57 percent were women. The mean age of subjects at baseline was 62.9 years. The mean values of BUA, SOS and QUI were 76.2 dB/MHz, 1546 m/s and 93.9, respectively. The mean S-25(OH)D concentration was 46.8 nmol/l. Characteristics of the study population are shown in detail in Study III, Table 1. During a mean follow-up of 8.4 years (27 757 person-years) 95 of the subjects sustained a hip fracture at the mean age of 79.4 years. Of these, 89 were considered first hip fractures.

Study IV
Subjects aged 55 years or over at baseline who participated in the health examination and for whom information on walking speed, handgrip strength, QUS

measurement and S-25(OH)D was available formed the study population of study IV. After the exclusion of all subjects with previous hip fracture (n=19) and those with emerging high-energy-based hip fractures (n=9) the study population consisted of 2 300 subjects (80% of those aged 55 or over in the original sample) of which 58% were women. The mean age of subjects at baseline was 66.4 years. The mean value of QUI was 93.1 and the mean S-25(OH)D concentration 47.6 nmol/l. Handgrip strength among study population was on average 315.1 N. The mean value of maximal walking speed was 1.5 m/s. The prevalence of Parkinson's disease was 0.45 percent, and 7.7 percent of subjects had suffered from stroke. Almost three-quarters of subjects suffered from hypertension, and almost 10 percent were diabetics. The baseline characteristics of the study population are shown in Table 1 of Study IV. During the mean follow-up of 9.8 years (22 540 person-years), 96 (3.6%) of the subjects sustained a first hip fracture at the mean age of 80.7 years. Fracture of the femoral neck was the most common type of hip fracture representing 65 percent of all first hip fractures.

5.2 Determinants of QUS (Study I)

Higher age was associated with lower values of SOS and BUA in women. S-25(OH)D and height correlated positively with both QUS variables, and weight, BMI and fat mass were positively associated with BUA. On the other hand, BMI, fat percentage and fat mass correlated negatively with SOS in women.

Higher concentrations of S-25(OH)D were associated with significantly higher values of SOS and BUA also in multiple linear regression modelling including all significant bivariate correlates of QUS variables as covariates (Study I, Table 3). These associations appeared to be linear over the S-25(OH)D distribution (7-134 nmol/l) (*p* values of the squared term of S-25(OH)D in the adjusted models were non-significant). Mean values of SOS adjusted for age, height, weight and lifestyle factors were 1550 and 1554 m/s in the lowest and in the highest quintiles of S-25(OH)D, respectively. Corresponding figures for BUA were 74.1 and 77.2 dB/MHz. Other significant and independent determinants of BUA and SOS in women were age, height and postmenopausal status, all of which were negatively associated with the QUS variables. Weight was an independent determinant of BUA. The studied lifestyle factors, alcohol consumption, smoking and physical activity, were also significant and independent determinants of the QUS variables, except smoking and physical activity for BUA. In postmenopausal women analysed separately, S-25(OH)D, weight and years on HRT showed an independent positive contribution to both SOS and BUA. Age and smoking, on the other hand, were negative determinants of both QUS variables studied.

In men, age was negatively associated with SOS. S-25(OH)D, weight and BMI were significant positive correlates of BUA and SOS, whereas height, fat percentage and fat correlated positively with BUA.

According to the results of a multiple linear regression model, S-25(OH)D was significantly associated with SOS and BUA in men, when all other significant bivariate correlates of QUS variables were adjusted for. Similarly to women, this association appeared to be linear over the S-25(OH)D distribution (5-134 nmol/l) also in men. The adjusted mean values of SOS were 1551 and 1560 m/s in the lowest and in the highest quintile of S-25(OH)D, respectively. Corresponding values in BUA were 80.0 and 83.4 dB/MHz. Other independent and significant determinants of QUS variables were age and height and these were negatively associated with SOS and weight, which was positively associated with both SOS and BUA. Alcohol consumption, smoking and physical activity were significant and independent determinants of both QUS variables in men.

5.3 Risk factors of hip fracture (Studies II-IV)

Studies II-IV assessed age, gender, anthropometry, parity, QUI, S-25(OH)D, walking speed, handgrip strength, lifestyle factors, number of falls, chronic conditions and medication for their prediction for hip fracture. Table 4 summarizes independent risk factors for hip fracture according to the studies.

Table 4. Independent risk factors for hip fracture (x-marked) according to studies II-IV.

Variables	Study II[a]	Study III[b]	Study IV[c]
Age	x	x	x
Gender		x	
Weight		x	
Height		x	x
Waist circumference			x
S-25(OH)D	x	x	
Smoking	x		
Alcohol consumption	x		
Physical activity	x		
Parity	x		
QUI		x	x
Walking speed			x
Parkinson's disease			x
CNS active medication			x

[a] Adjusted for the variables in the column (x-marked) and for BMI, age at the last menstrual period, level of education and self-rated health
[b] Adjusted for the variables in the column (x-marked)
[c] Adjusted for the variables in the column (x-marked) and for gender and handgrip strength

Age and gender (Studies II-IV)

Increasing age was a strong independent predictor of hip fracture in all follow-up studies. In Study II, including women aged 45 years or over at the baseline, one SD increment in age (9.2 years) was associated with over a threefold increase in hip fracture risk when adjusted for BMI, reproductive factors, vitamin D status, lifestyle factors, level of education and self-rated health (Study II, Table III). Similarly in Study III including both men and women, aged 50 years or older, one SD increase in age (9.8 years) was associated with a 3.5-fold risk of hip fracture (Study III, Table 3). Also in Study IV, including men and women aged 55 years or older, one SD increase in age (8.2 years) was associated with over a two-fold risk of hip fracture (Study IV, Table 3).

Age was a significant predictor of hip fracture also in a separate analysis among subjects aged 75 years or over (n=528, Study IV). According to this

analysis one SD increase in age (3.6 years) was associated with almost a 1.5-fold risk of hip fracture when gender was taken into account (HR=1.44, 95% CI=1.18-1.76).

Female gender appeared to be significantly and independently associated with hip fracture risk in Study III (HR=2.39, 95% CI=1.15-4.96) after adjusting for age, height, weight, S-25(OH)D and QUI. However, no significant association between gender and hip fracture risk was found in Study IV, either in the age-adjusted model or in the model further adjusted for height, waist circumference, QUI, handgrip strength, walking speed, Parkinson's disease and number of CNS active medication (Study IV, Table 3).

QUS (Studies III and IV)

Bone strength was assessed by means of calcaneal quantitative ultrasound. On the basis of measured BUA and SOS values, QUI was estimated. This was used in the final risk assessment models. Adjusted for gender, age, height, weight and S-25(OH)D, one SD increment in QUI (21.7) was associated with a 40 percent lower risk of hip fracture in Study III (Table 3). Conversely, a decrease of one SD in QUI was associated with a 67 percent increase in risk (HR=1.67, 95% CI=1.16-2.34). Similarly, one SD increment in BUA (19.5 dB/MHz) was associated with a 38 percent lower risk (95% CI=0.46-0.84) and one SD increment in SOS (35.3 m/s) was associated with a 39 percent lower risk (95% CI=0.42-0.87) for hip fracture. In Study IV, with the follow-up time extending up to 11 years, QUI was also a significant predictor of hip fracture. Adjusted for gender, age, height, waist circumference and fall-related factors, such as walking speed, handgrip strength, number of CNS active medication and Parkinson's disease, one SD increment in QUI (21.7) was associated with a 28 percent lower risk for subsequent hip fracture (HR=0.72, 95% CI= 0.53-0.98).

The quintiles of QUI were further examined to assess if there would be a certain cut-off value with respect to hip fracture risk. Adjusted for gender, age, height and weight, QUI values of less than 74.3 appeared to be associated with a doubled risk for hip fracture (HR=2.14, 95% CI=1.21-3.78) compared to values greater than or equal to 74.3 (Study III). QUI did not quite reach statistical significance in the age and gender adjusted analysis (HR=0.74, 95% CI=0.53-1.01) performed among subjects aged 75 years or over (Study IV). However, the cumulative hazards of hip fracture, adjusted for gender, height and waist circumference, showed a substantial divergence between the quintiles of QUI after this age (Study IV, Figure 1 a). Yet, when the hazards were further adjusted for fall-related factors (maximal walking speed, Parkinson's disease and the number of prescribed CNS active medication), they were markedly smaller and less divergent between the quintiles (Study IV, Figure 1 b).

S-25(OH)D (Studies II-IV)

S-25(OH)D was an independent and significant predictor of hip fracture in Studies II and III. In Study II, one SD increment in S-25(OH)D (18.3 nmol/l) adjusted for age, BMI, reproductive factors, lifestyle factors, education and self-rated health, was associated with a 21 percent lower risk of hip fracture (RR=0.79, 95% CI=0.64-0.98) among postmenopausal women. In Study III, including both men and women aged 50 years or over, one SD increment in S-25(OH)D (17.5 nmol/l) was associated with a 31 percent lower risk (HR=0.69, 95% CI=0.55-0.87) when adjusted for gender, age, height, weight and QUI. According to the analysis of quintiles of S-25(OH)D, the values less than 60.0 nmol/l indicated a significantly higher risk of hip fracture (HR=2.53, 95% CI=1.17-5.46) compared to values greater than or equal to 60.0 nmol/l (Study III). In Study IV, S-25(OH)D did not quite reach statistical significance in the model adjusted for age and gender (HR=0.85, 95% CI=0.70-1.03).

Anthropometry (Studies II-IV)

Higher body weight was associated with a lower risk of hip fracture in Study III when adjusted for gender, age, height, S-25(OH)D and QUI (HR=0.73, 95% CI=0.54-0.99). However, in Studies II and IV BMI or weight did not quite reach statistical significance (Study II, Table 3; Study IV, Table 3). On the other hand, waist circumference appeared to be an independent predictor of hip fracture in Study IV. One SD increment in waist circumference (12.4 cm) was associated with a 29 percent lower risk for hip fracture (HR=0.71, 95% CI=0.55-0.92).

Tall stature was a risk factor of subsequent hip fracture. In Study III, the risk was increased by 82 percent per 9.5 cm increment in height (HR=1.82, 95% CI=1.43-2.32) when adjusted for gender, age, weight, S-25(OH)D and QUI. Similarly, in Study IV an increment of 9.4 cm in height was associated with 74 percent higher risk of subsequent hip fracture (HR=1.74, 95% CI=1.23-2.46) in the model adjusted for gender, age, waist circumference, QUI and fall-related factors such as, handgrip strength, walking speed, Parkinson's disease and number of CNS active medication.

Smoking, alcohol consumption and physical activity (Studies II-IV)

In Study II, smoking, alcohol consumption and physical activity were significantly associated with hip fracture risk (Study II, Table 3). Current smoking of at least 20 cigarettes a day was especially harmful (RR=9.26, 95% CI=3.85-22.25). Alcohol consumption of at least 249 g of ethanol/week was associated with almost fivefold higher risk of hip fracture compared to those not using alcohol (RR=4.78, 95% CI=1.02-22.38). Those women who were moderately physically active had 36 percent lower risk of fracture (RR=0.64, 95% CI=0.42-0.97) compared to sedentary women. In Studies III and IV, none of the studied lifestyle factors were significant predictors of hip fracture (Study III, Table 3; Study IV, Table 3).

Handgrip strength and walking speed (Study IV)
Handgrip strength and maximal walking speed were examined for their prediction of hip fractures in Study IV. Both of these variables differed between subjects with and without an incident hip fracture (p values of <0.0001 for both). Also, in the gender- and age-adjusted models, a one SD increase in both handgrip strength (121.8 N) and maximal walking speed (0.40 m/s) was significantly associated with hip fracture risk (Study IV, Table 3). However, when further adjustments were made for height, waist circumference, QUI, Parkinson's disease, number of CNS active medications and each other, only maximal walking speed proved to be an independent and significant predictor of hip fracture. According to this model, one SD increase in walking speed (0.40 m/s) was associated with a 30 percent lower risk of hip fracture (HR=0.70, 95% CI=0.54-0.92).

Chronic conditions (Study IV)
Contribution of chronic conditions, such as Parkinson's disease, stroke, hypertension, and diabetes, to hip fracture risk was assessed in Study IV. Of these, only Parkinson's disease appeared to have an independent and significant association with hip fracture risk. Subjects with Parkinson's disease had a sevenfold risk of hip fracture compared to those free of this disease (HR=7.08, 95% CI=2.19-22.93) when adjusted for gender, age, height, waist circumference, QUI, handgrip strength, walking speed and number of CNS active medication.

CNS active medication and liability to fall (*Study IV*)
The number of prescribed CNS active medication (opioids, anticonvulsants, antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants or psycholeptics and psychoanaleptics in combination) differed between subjects with and without an incident hip fracture (p=0.03) (Study IV, Table 2). According to the model that included gender and other significant predictors, such as age, height, waist circumference, QUI, handgrip strength, walking speed and Parkinson's disease, subjects using three or more CNS active medications had almost a threefold risk of hip fracture (HR=2.82, 95% CI=1.03-7.77) compared to those who did not use such medication.

There was a tendency towards increased risk of hip fracture along with increasing degree of faintness or dizziness as recent symptoms. Also, a higher number of falls during the previous 12 months tended to be associated with increased hip fracture risk. However, these associations did not reach statistical significance in gender- and age-adjusted models (Study IV, Table 3).

Parity (Study II)
Study II assessed parity for its prediction of hip fracture in postmenopausal women over a mean follow-up of 13 years. Adjusted for age, parity showed an inverse association with hip fracture risk (RR=0.74, 95% CI=0.61-0.90) per increment of one SD (2.4 births). This association appeared, however, to diverge

from linearity and thereby parity was classified into three categories: nulliparous, parous with 1-2 births and parous with three or more births. Adjusted for age, BMI, age at the last menstrual period, S-25(OH)D, smoking, alcohol consumption, physical activity, education and self-rated health the risk of hip fracture were significantly lower in women with three or more births (RR=0.50, 95% CI=0.32-0.79) compared to nulliparous women. The risk tended to be lower also among women with one to two births compared to nulliparous women although the difference was not statistically significant (RR=0.85, 95% CI=0.55-1.32).

A statistically significant interaction was found between parity and age at the last menstrual period (p=0.03). Only those women with three or more births and who were more than 50 years of age at their last menstrual period had a significantly decreased risk for hip fracture compared to nulliparous women. The same did not hold true among women with three or more births who were 50 years or younger on that occasion (Study II, Table 4).

5.4 Multivariate prediction of hip fracture (Studies III and IV)

The predictive power of models with various combinations of risk factors was assessed by means of coefficients of determination (R^2). In Study III, R^2 indicated that age alone explained 66 percent of the variation in the observed hip fracture risk. When gender, height and weight were added to the model, R^2 increased to 72 percent. The addition of QUI improved this figure by four percentage units (a 6% relative increase) and the addition of S-25(OH)D by three percentage units (a 4% relative increase) (Study III, Table 4). The model, including all of these variables, explained 78 percent of the variation in hip fracture risk.

According to the results of separate analyses in Study III on subjects 75 years or over performed, absolute R^2 values were clearly lower compared to younger subjects. The model, including age, gender, height and weight explained 10 percent of the variation in the observed hip fracture risk. Adding QUI or S-25(OH)D to this model improved the coefficient of determination by seven percentage units (a 70% relative increase). The addition of both of these improved the predictive power of this model by 13 percentage units (130% relative increase).

In Study IV, including men and women aged 55 years or over, the model that included age, gender, height and waist circumference explained 59 percent of the variation in the observed hip fracture risk. This figure was improved by an increment of four percentage units (a 7% relative increase) when walking speed was added to the model. Adding QUI to the model improved its predictive power by 3 percentage units (a 5% relative increase). The model, including all of these variables added by Parkinson's disease and CNS active medication, explained

68% of the variation in hip fracture risk. Without QUI the predictive power of this model was 66% (Study IV, Table 4).

The additional analyses of net reclassification improvement (NRI) performed using a three percent risk threshold showed a significantly improved performance of the model, which included age, gender, height and waist circumference when either Parkinson's disease (NRI=3.3%, p=0.04), use of CNS active medication (NRI=6.0%, p=0.01) or QUI (NRI=6.4%, p=0.03) was added. No significant change was found in NRI when walking speed was separately added to that model (NRI=3.4%, p=0.15). However, walking speed along with Parkinson's disease and CNS active medication significantly improved the discriminative ability of the same model (NRI=8.4%, p=0.01). Further addition of QUI into that model including all other significant predictors resulted in no significant improvement (NRI=0.4%, p=0.84).

6 DISCUSSION

6.1 Determinants of QUS (Study I)

In this thesis bone strength was assessed by means of a calcaneal QUS measurement performed with the Hologic Sahara device (Hologic, Bedford, MA, USA). No previous study has identified determinants of calcaneal QUS in a representative Finnish adult population sample. Here, several risk factors of bone fragility previously found to be associated with BMD, assessed by means of DXA, were also found to be determinants of calcaneal QUS.

QUS values in men and women were inversely associated with age. This is in accordance with a number of previous studies that show a decreased level of BMD and QUS along with increasing age [272-277]. These changes appeared to be linear in men. In women, the slope was steeper after the age of about 50 years. This is not unexpected because the decline in ovarian function and the resultant decrease in estrogen levels are likely to affect bone strength in the postmenopausal phase [17,277-280]. This finding is also reflected in the negative association found between postmenopausal status and QUS variables.

Vitamin D status was a significant and independent determinant of SOS and BUA in both men and women. This finding is in accordance with previous studies that show the importance of adequate vitamin D status for bone health [281-283]. There is no consensus on what would be the optimal S-25(OH)D concentration. Based on S-25(OH)D concentrations at which measured PTH levels begin to level off [169,170], concentrations between 50 and 80 nmol/l have been considered sufficient for bone health [167,168]. In the present study, no specific threshold value was found. Instead, the associations with SOS and BUA appeared to be rather linear over the entire S-25(OH)D distribution.

We found an inverse association between fat mass and S-25(OH)D in spite of higher intakes of vitamin D in those with higher body fat mass (Study I, Figure 1). This agrees with previous case-control and population-based studies [284-287]. More recent studies have similarly found decreased S-25(OH)D levels in obese subjects [288,289]. These findings may be explained by a decreased bioavailability of vitamin D due to increased storage in the adipose tissue, sedentary lifestyle and genetic changes in vitamin D metabolism in obese subjects [286,289,290].

The positive association between weight and QUS variables was an expected finding in agreement with several previous studies that showed higher QUS or BMD values in heavier subjects [276,277,291,292]. The association between height and QUS values was found to be negative in the multiple linear regression model adjusted for age, weight, S-25(OH)D and lifestyle factors. This finding is contradictory to that of Welch et al. [277] who found a positive association

between height and BUA. The discrepant result in the present study might result from fairly slender bones in tall subjects. The studied lifestyle factors, physical activity, smoking and alcohol consumption appeared to be significant determinants of QUS variables with the exception of smoking and physical activity for BUA in women. Previous cross-sectional studies have found that physical activity is positively associated with QUS variables in both genders, whereas the associations between smoking or alcohol use and QUS have been less consistent [275,276,278,293-295]. Several previous studies have established a negative association between smoking and BMD [296-298]. The non-significant association between smoking and BUA in women probably resulted from the small number of smokers among them.

6.2 Risk factors of hip fracture (Studies II-IV)

Bone strength-related factors

Several prospective studies show that calcaneal QUS variables measured by means of various devices can predict hip fractures in elderly men and women [30,72,73,144,159-161]. Likewise, in the present study, QUS was a significant predictor of hip fracture even when adjusted for multiple potential predictors of hip fracture, such as S-25(OH)D, lifestyle factors, comorbidity and fall-related risk factors (III, IV). The hazard ratio of 1.67 per one SD decrease in QUI was comparable to a gradient of risk of 1.99 for the QUI reported in a recent meta-analysis [30]. However, there is a considerable heterogeneity existing among studies for the association of QUS variables and hip fracture risk, largely due to technological differences between the different devices [64]. Only one prospective study, thus far, has assessed different QUS devices for hip fracture prediction in an elderly population [264]. According to the results of that study, two calcaneal QUS devices (Achilles+ and Sahara) showed a similar hip fracture prediction in all assessed variables (BUA, SOS, QUI/SI). Obviously, more information is needed to guage the performance of different QUS devices concerning fracture risk prediction. In addition, methods for standardization or cross-calibration among brands of QUS devices should be developed.

The results presented here showed a higher risk of hip fracture in subjects with QUI values below 74.3 (III). This value was higher compared to the results of a previous study based on a large dataset from three case-control studies in which the threshold of QUI measured with Sahara device was at 63.2 [299]. The differences in these threshold values may be partly explained by differences in the age-range and designs of the studies. The study population of the present study (III) included both men and women aged 50 years or over while that of Hans et al. [299] included only women aged 65 years or over.

In a separate analysis of a subpopulation aged 75 years or older (IV), QUI did not quite reach statistical significance (HR=0.74, 95% CI=0.53-1.01) for an

association with hip fracture risk. Previous studies assessing BMD measured by means of DXA for prediction of fractures have similarly found smaller risk gradients along with an increasing age [56,300,301]. Here, an increasing divergence in cumulative hazards of hip fracture adjusted for gender, height and waist circumference was seen between the quintiles of QUI after the age of 75 years (Study IV, Figure 1 a). After further adjustment for fall-related factors, such as walking speed, Parkinson's disease, and CNS active medication the hazards diminished and became less divergent (Study IV, Figure1 b). This is likely to indicate a gradual shift of focus in hip fracture prediction from bone strength to fall risk related factors in the oldest subjects.

In agreement with the results of several previous prospective studies [89-93], a higher weight was associated with a decreased risk for hip fracture in this study (III). Higher weight is associated with higher skeletal load, which is likely to increase bone strength. Also, higher fat mass and a longer waist circumference, a surrogate marker for abdominal fat [302], were associated with lower hip fracture risk (IV). Adipose tissue becomes a major source of estrogen in postmenopausal women [303]. Therefore, a higher amount of adipose tissue may be associated with a higher amount of estrogen which in turn, affects bone turnover. In addition, a thicker adipose tissue layer has a protective effect in case of a fall. On the other hand, low BMI, weight loss in particular, may be an indicator of overall poor health which contribute to fracture risk. However, the association between obesity and fracture risk is not unambiguous. It has been suggested that neuromuscular performance rather than body mass is an explanatory factor of bone strength [304]. Also, several studies have found that a substantial proportion of osteoporotic fractures, including hip fractures, occurs in obese postmenopausal women and older men [95]. Moreover, it has been suggested that obesity is a risk factor for some fractures, such as ankle and humeral fractures, but protective against some fractures, such as hip fracture [95].

In agreement with the results of several previous studies [19,23,92,96], tallness was a significant predictor of hip fracture in this study. Suggested mechanisms by which tallness affects hip fracture risk include a greater impact in falling as well as geometrical characteristics of the femoral neck that affects bone strength [23,97,98].

Previous studies have shown adverse effects of active smoking with respect to hip fracture risk [91,92,110,111]. In the present study heavy smoking (≥20 cigarettes/day) was significantly associated with increased risk of hip fracture among postmenopausal women aged 45 years or over (II). However, in Studies III and IV, including both men and women aged 50 years or over, smoking did not reach statistical significance. In these studies smoking was classified into categories of never-smokers, former smokers and current smokers and the impact of heavy smoking may have not been captured. On the other hand, the number of heavy smokers is likely to be low, especially among elderly women.

Similarly to several previous studies [124,125] a lower risk of hip fracture was found along with increasing parity. Compared to nulliparous women the risk was significantly lower among women who had given three or more births (II). Among these women, the risk was lowest in women who were older than 50 years at their last menstrual period. These findings are likely to reflect the beneficial effects of long-term estrogen exposure on bone health and fracture risk [121].

Fall-related factors (IV)

Maximal walking speed was a significant and independent predictor of incident hip fracture in the present study (IV). This agrees with the results of previous prospective studies using elderly men and women cohorts [24,128,134,135]. Walking is a complex motor skill and the automaticity of which is likely to diminish along with increasing age [305]. Walking speed is, in older subjects, a useful indicator of muscle strength, balance and other sensorimotor functions [138,139], which will ultimately affect fall risk and subsequent risk of fracture. Here, maximal walking speed of around 1.5 m/s was optimal for hip fracture prediction. This is clearly higher than the threshold value of 1.0 m/s used in previous studies assessing walking speed for the prediction of several adverse health outcomes [147]. This difference may be at least partly explained by actually different outcomes in these studies. Nevertheless, the population of the current study was younger than those in previous studies. In addition, previous studies mostly assessed habitual walking speed, whereas the present study dealt with maximal walking speed.

Other significant fall-related risk factors in this study were Parkinson's disease and use of CNS active medication. These findings are in accordance with those of previous studies [23,85,128,149,150,154,155]. In the present study, over a sevenfold risk of hip fracture was found in subjects with Parkinson's disease compared to those free from this disease. However, the number of patients with Parkinson's disease was small (n=11) and the results should therefore be interpreted with caution.

Elderly subjects are prone to suffer from adverse effects of medication. This is related to physiological changes, which along with increasing age, affect absorption, distribution, metabolism and excretion of medicines. In addition, polypharmacy is more common in old age. Both, the total number and certain specific medications increases the risk of falls [151]. Here, subjects who used at least three prescribed CNS active medicines (such as opioids, anticonvulsants, anxiolytics, hypnotics, and sedatives, antidepressants and psycholeptics) had an increased risk of hip fracture compared to those who were not receiving such medication.

Multifactorial risk factors (II,III,IV)

An older age is a well-established risk factor for hip fracture. Old age is associated with decreased bone strength, but predicts hip fractures even independently of

BMD [6,9]. It appears that later in life factors associated with functional capacity gain more significance with respect to hip fracture prediction. In the present study, age was a significant and independent predictor of hip fracture even when adjusted for QUI and fall-related risk factors, such as walking speed, Parkinson's disease and CNS active medication (IV).

Elderly women are especially prone to hip fracture because they have generally lower peak bone mass and smaller bones compared to men, and because their estrogen deficiency causes a rapid lose of bone mass after menopause [17]. Here, women had over twice the risk of hip fracture compared to men when adjusted for age, body build, S-25(OH)D and QUI.

Similarly to some earlier prospective studies [173,174,179], S-25(OH)D was also in the present study an independent and significant predictor of hip fracture in men and women (II, III). According to the analysis of quintiles of S-25(OH)D values of less than 60.0 nmol/l indicated a significantly higher risk for hip fracture (HR=2.53, 95% CI=1.17-5.46) compared to values greater than or equal to 60.0 nmol/l (III). This is comparable to S-25(OH)D levels that range between 50 and 80 nmol/l, which were previously considered optimal for bone health [167,168]. On the other hand, S-25(OH)D did not quite reach statistical significance in the age- and gender-adjusted model (HR=0.85, 95% CI=0.70-1.03) in Study IV with somewhat longer follow-up period compared to Study III. Because S-25(OH)D was measured only at baseline, the changes in vitamin D status during the follow-up of Study IV were more likely than in Study III, which may diminish its association with fracture risk.

Previous studies have shown contradictory results on the association between vitamin D supplementation and fracture risk. Randomized controlled trials have often found no significant difference in BMD or hip fracture risk between subjects randomized to receive vitamin D supplementation and subjects in the control group [172,177]. On the other hand, observational studies have commonly shown significantly lower S-25(OH)D levels among subjects with hip fracture compared to controls [172]. Reasons for these contradictory results are not known. However, it is possible that the lack of a statistically significant association between vitamin D supplementation and fracture risk in RCTs has been related to insufficient statistical power because of too short follow-up times, inadequate number of recorded fractures, inappropriate vitamin doses or because the intervention has been targeted to a population that was not deficient in vitamin D [172,181]. On the other hand, it is likely that vitamin D supplementation would have been more efficient if combined with calcium [105,178,180]. Moreover, observational studies may suffer from uncontrolled confounding, such as physical activity with exposure to sunlight, comorbidity and frailty, which all mask an association [172].

Here (I), moderate hypovitaminosis or vitamin D deficiency (S-25(OH)D<37.5 nmol/l) was found in almost half of the study population aged 30 years or over studied during years 2000 and 2001. Comparable results have been found in a

more recent study that assessed vitamin D status in Finnish subjects aged 45 to 74 years in 2007 [306]. In order to ensure an adequate vitamin D status in the Finnish population, the recommended level of vitamin D intake has been recently raised in the updated Finnish Nutrition Recommendation [307] up to 10 µg (400 IU) per day for adults and children aged two years or older and 20 µg (800 IU) per day for subjects aged 75 years or older. There is an ongoing debate on what would be an optimal S-25(OH)D level with respect to skeletal and extra-skeletal health, and disagreement persists regarding the recommendations of vitamin D intake. For example, the US IOM (Institute of Medicine) recommends vitamin D doses of 20 µg (800 IU) in older adults (>70 years) in order to achieve S-25(OH)D levels of 50 nmol/l [308]. On the other hand, the US Endocrine society proposes daily doses of at least 38 to 50 µg (1500-2000 IU) in the same age group in order to achieve a target level of 75 nmol/l, and even higher intakes in some cases of vitamin D deficiency [309]. However, high doses of vitamin D may not be beneficial with respect to bone health and fall risk, and may even have adverse effects on bone health [181,310,311]. Adverse effects have been found to occur especially along with extremely high intermittently administered doses. Based on the results of these and other previous RCTs and observational studies [312], it may not be advisable to recommend high S-25(OH)D concentrations for the entire population. Rather, it is essential to identify subjects who are most likely to be vitamin D deficient (e.g., elderly subjects, institutionalized or homebound and subjects with malabsorption) and target the interventions of vitamin D supplementation, accordingly. In these cases, monitoring of serum 25(OH)D may be required.

An additional challenge with respect to determination and monitoring an optimal S-25(OH)D level is brought by the fact that results of S-25(OH)D measurements performed with different assays in different laboratories are not comparable [313-315]. Previous studies show that the capability of different assays to discriminate between low, moderate and high values is relatively good [314]. However, the definition of vitamin D status in absolute terms may be more complicated without standardization and careful cross-calibration between the values from different laboratories. This should be taken into account when comparing the results of different studies from different laboratories.

Previous studies have shown an inverse association between physical activity and hip fracture risk in men and women [92,111,192-195]. In the present study, a tendency towards higher risk was observed in sedentary subjects (II, III, IV). However, in the models adjusted for age and gender, physical activity did not quite reach statistical significance.

Previous fragility fracture is a significant predictor of future hip fracture [22,128,159,160,242,243]. Here, previous hip fracture did not show a significant contribution to hip fracture risk among men and women aged 50 years or older (III). This is likely to be related to the lack of statistical power since the proportion of subjects with previous fragility fracture was low (0.8%).

Socio-economic status has been suggested to contribute to hip fracture risk, even independently of known risk factors of osteoporosis [222,316,317]. In the present study (II), socio-economic status assessed by means of the level of education was not independently associated with hip fracture risk. This may partly be related to low number of those with high education (>12 years of education), but also to that other, more proximal risk factors of hip fracture, such as lifestyle may have explained the association [318].

6.3 Multivariate prediction of hip fracture (Studies III and IV)

A large number of risk factors for hip fracture have been identified, and the current challenge is to develop practical methods that could accurately identify subjects who are at an increased risk. Old age is a well-known powerful predictor of hip fracture. Identifying factors that significantly contribute to fracture risk along and beyond age is important. Here, age explained up to 66 percent of the variation in the fracture risk (III). The additions of QUI and S-25(OH)D or QUI and the fall-related risk factors (maximal walking speed, Parkinson's disease and number of prescribed CNS active medicines) clearly increased the predictive power of the model, which included age, gender and measures of body build (III, IV). This agrees with the results of previous prospective studies that show that combining bone strength-related factors with fall-related factors improves the prediction of hip fracture [24,144,159,160]. In the present study, improvements in the predictive power of the model that included age, gender, height and waist circumference were similar after the addition of QUI, walking speed, Parkinson's disease or CNS active medication. On the other hand, when QUI was added to the model that included age, gender, height, waist circumference and the fall-related factors only minor further improvement in the predictive power was seen. No significant improvement in discriminative ability (NRI) of the model was seen after this addition (IV). This finding suggests that a simple model including age, gender and measures of body built combined with the fall-related factors is at least as efficient in hip fracture prediction as a more complex model with measured bone strength-related factors. This parallels previous views that being prone to fall rather than bone fragility would be the principal determinant of fracture [248,319].

Recently, guidelines by WHO and IOF [25] have proposed a targeted approach in which assessment of future fracture risk would be based on 10-year probability of fracture. Based on this, fracture risk prediction tools, such as FRAX, QFracture and Garvan Fracture Risk Calculator have been developed [26,245,246]. FRAX has been recommended to be used for the assessment of fracture risk in clinical practice in many countries, including Finland [320]. However, information about the applicability of FRAX in the general Finnish population is lacking. In addition, no information is available about the threshold value of FRAX on which the

treatment would become cost-effective in Finland. One recent study assessed the calibration of the Finnish FRAX model in the OSTPRE (the Kuopio Osteoporosis Risk Factor and Prevention) study, a population-based cohort study of postmenopausal women from the Kuopio region of Finland [321]. In that study, the relationship between the FRAX probability of hip fracture and the 10-year period prevalence was examined by quintiles of fracture probability. The goodness-of-fit across these quintiles and predictive performance of FRAX model were evaluated. The authors of that study concluded that the Finnish FRAX tool provided appropriate discrimination for hip fracture risk. However, there was a lack of fit for absolute probabilities. The expected numbers of hip fractures based on FRAX models were significantly higher than self-reported (observed/expected ratio 0.46; 95% CI 0.33-0.63) and tended to be larger than observed ones (observed/expected ratio 0.83; 95% CI 0.65-1.04). The difference was evident especially in the highest risk quintile.

In the present study we performed analyses using the variables that were available to us to construct a model corresponding to the FRAX model as closely as possible. These variables included: gender, age, weight, height, current smoking, current use of systemic glucocorticoids, rheumatoid arthritis, insulin-dependent diabetes, Crohn's disease, colitis ulcerosa, and celiac disease, liver disease assessed by means of gamma-glutamyl transferase measurement, premature (<45 years) menopause in women and alcohol use of three or more units daily. No significant associations were observed between these variables and hip fracture risk in age- and gender-adjusted analyses (data not shown). This was not an unexpected finding because our study population was derived from a nationally representative population sample in which diseases associated with an increased risk of osteoporosis are rare compared with selected clinical study populations.

One of the known limitations of the FRAX tool is that it does not include falls as a risk factor [249]. The incorporation of fall risk to FRAX model has been argued to be problematic because information on falls has been scarce in cohorts used to derive and validate FRAX. However, there is evidence that falls [322,323] and fall-related fractures [324] can be prevented by interventions. This supports the idea of including fall-related risk factors in the fracture risk assessment, suggested by some authors [325].

In the present study the models for hip fracture risk prediction were derived from the representative population sample of Finnish men and women with a follow-up period extending up to 10 years. The predictive performance (R^2) of the models based on a few readily available risk factors, such as age, gender, measures of body build, bone strength-related factors and fall-related factors, was closely comparable with those reported from a previous prospective study based on the QFracture data covering a wide variety of predictors [245,326]. In the present study, the models including all significant predictors derived from the study data explained 68 to 78 percent of the variation in the hip fracture risk. The validation

study of the QFracture tool, using the same statistical method has reported R^2 values around 70 percent. Applied to the same data, the FRAX algorithm explained approximately 55 percent of the variation in the hip fracture risk [245]. Obviously, such studies cannot be directly compared. However, the results of the present study suggests that a simple model including readily available variables may perform equally well in fracture risk prediction compared to more complex models.

6.4 Strengths and limitations

The strength of the present study is that it was based on two nationally representative health surveys with an exceptionally high participating rate [260,261]. In the Health 2000 Survey, the essential information on health and functional capacity was obtained from more than 93 percent of the subjects, and 79 percent of the original sample participated in the health examination proper. In the Mini-Finland Survey, 96 percent of the sample participated in the health interview, and 90 percent in the health examination. The information about incident hip fractures was drawn from the National Hospital Discharge register, which is a reliable source of information with a nationwide coverage. The coverage of this register with respect to hip fractures is reported to be 98 percent. Also, the accuracy and sensitivity of the registered hip fracture diagnoses have been shown to be good (98%) [82].

One limitation of the current study was that the risk factors in Studies II, III and IV were measured only at baseline, and no information on the later changes of these factors was available. During a follow-up period extending up to 13 years changes are plausible in lifestyles, physical performance, health status and medication (II). Moreover, subjects living in residential care units were not included in our study population because QUS measurements were not included in home health examination conducted on subjects not attending the health examination proper (5% of the original sample). However, this is likely to diminish rather than give rise to the observed associations.

In Study II, parity was assessed for its prediction of hip fracture in postmenopausal women. In this context, it would have been useful to assess the role of lifetime estrogen exposure. However, no such information was at our disposal. Neither were we able to assess whether the association between parity and fracture risk was mediated by potential effects of parity on BMD. Moreover, we did not know whether nulliparity was intentional or due to a fertility problem.

The predictive performance of the simple model constructed in the present study appeared to be fairly good. However, its performance may have been maximized because it was constructed and tested on the same data. In order to test the predictive power of the model, it should be evaluated in a separate adult population.

A major limitation of the present study was the small number of hip fracture cases. Thus, in the analyses concerning rare risk factors statistical power was obviously low. For the same reason the analyses could not be made separately on men and women.

7 CONCLUSIONS

Older age, tallness, smoking and postmenopausal status in women were negatively associated with the QUS variables (SOS, BUA) whereas higher weight, higher concentration of S-25(OH)D and physical activity as well as years on HRT in postmenopausal women showed positive association with these variables. A lower level of alcohol consumption was associated with lower QUS values in women and with higher values of QUS in men.

Age, height, weight, waist circumference, QUI, S-25(OH)D and fall-related risk factors, such as maximal walking speed, Parkinson's disease and the number of prescribed CNS active medicines were independent predictors of hip fracture. In addition, nulliparity was significantly associated with hip fracture risk among postmenopausal women. Among subjects aged 75 years or over age, maximal walking speed and the use of three or more prescribed CNS active medicines were independent predictors of hip fracture.

Old age was the strongest predictor of the hip fracture explaining up to 66 percent of the variation in hip fracture risk. The additions of QUI, S-25(OH)D and the fall-related factors (maximal walking speed, Parkinson's disease and number of prescribed CNS active medicines) increased the predictive power of the model including age, gender and measures of body built. On the other hand, when QUI was added to the model, which included age, gender, height, waist circumference and the fall-related factors, only a minor further improvement in predictive performance was noticed.

The incremental value of QUI in the prediction of hip fracture risk was small. Moreover, because there are no established diagnostic threshold values for QUS, it cannot be used as a diagnostic method for osteoporosis. In addition, the issues concerning standardization and cross-calibration among different QUS devices are yet to be resolved. Therefore, calcaneal QUS examination cannot be recommended for the assessment of hip fracture risk in an unselected adult population.

The assessment of fall-related risk factors for hip fracture prediction appears to be essential in elderly subjects, in particular among those aged 75 years or over. The liability to fall can be assessed by the measurement of maximal walking speed and evaluations of the central nervous system for chronic diseases and medications affecting mobility and postural balance. The results of the present study suggest that a maximal walking speed of around 1.5 m/s would be optimal for hip fracture prediction. This threshold differs clearly from 1.0 m/s that has been used in previous studies as a threshold of habitual walking speed for the prediction of adverse health outcomes. However, further studies in larger elderly study populations are needed in order to determine the threshold value of maximal walking speed for identifying subjects at increased risk of hip fracture.

Lower level of S-25(OH)D was associated with a higher hip fracture risk. The optimal level of S-25(OH)D appeared to be equal to or greater than 60.0 nmol/l. However, the role of vitamin D status in hip fracture risk prediction appeared to be modest. Measurements of vitamin D thus can not be recommended for the assessment of hip fracture risk in unselected adult populations.

This study presents a simple multifactorial model for the assessment of hip fracture risk among Finnish adults aged 50 years or over. Prospective studies are needed to test this model in patient-based study populations.

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