Risk Assessment for Osteoporotic Fractures among Men and Women from a Prospective Population Study: The EPIC-Norfolk Study

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Declaration

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text and acknowledgment. Parts of the work described in this thesis have been published or presented elsewhere as indicated in the text and Appendices. The work presented in this thesis has not been previously submitted for a degree, diploma or other qualifications at any other university and is not being concurrently submitted for any degree.

This thesis was undertaken in the Department of Public Health and Primary Care in Cambridge under the supervision of Professor Kay-Tee Khaw. This dissertation does not exceed 60,000 words as stipulated by the School of Clinical Medicine.

Signed:
Date:

FOR MY BELOVED PARENTS

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Summary

Risk Assessment for Osteoporotic Fractures among Men and Women from a Prospective Population Study: The EPIC-Norfolk Study

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Osteoporotic fractures are a major and increasing clinical and public health concern internationally. Identification of individuals at high risk for fragility fractures may enable us to target preventive interventions more effectively. In this thesis, I aimed to evaluate novel risk factors for osteoporosis and develop a fracture risk assessment model among the middle-aged and older people. I used data from the European Prospective Investigation into Cancer (EPIC)-Norfolk study, which is a large population-based prospective study started in 1993. About 25,000 men and women were assessed at baseline and about 15,000 of them returned for a second examination 4 years later. All participants are followed up to the present for clinical events including fractures. My work is in two parts. For the first part, I examined the risk of fracture associated with some novel or less well studied risk factors. These risk factors included change in height over time, respiratory function, physical activity and body fat mass. We found that men and women with annual height loss >0.5 cm are at increased risk of hip and any fracture (relative risk=1.9 (95% CI 1.3-2.7) per cm/year height loss). One litre lower forced expiratory volume in 1 second (FEV1) was associated with a 2-fold risk of hip fracture in men and women. We also observed a non-linear association, independent of body mass index, between increasing body fat mass and lower fracture risk in women but not in men. I performed a systematic review and meta-analysis of studies evaluating the association between physical activity and hip fractures. Using a new validated questionnaire in EPIC-Norfolk, we observed varying relationships between physical activity in different domains of life and fracture risk in men and women. For the second part of the thesis, I

developed a biostatistical model to calculate 10-year risk of developing a fracture among EPIC-Norfolk study participants. This model incorporates clinical and radiological assessments known to be associated with fractures and can be extended to other risk factors assessed in other prospective cohorts. This helps clinicians to achieve a better estimate of the prospective risk of fracture in their patients. I applied this model to compare the predictive value of two different clinical assessment methods for osteoporosis, namely dual-energy X-ray absorptiometry (DXA) and quantitative ultrasound (QUS). We found that that the predictive power of QUS is comparable to, and independent of, predictive power of DXA. In summary, my studies have added to our knowledge about some novel and easy-to-use risk factors of osteoporosis and proposed a practical method to merge and utilise data from different risk factors for estimation of fracture risk in individuals.

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List of Abbreviations

95% CI	95% Confidence Interval
%BF	Percentage Body Fat
AUC	Area Under the ROC Curve
BMD	Bone Mineral Density
BMI	Body Mass Index
BUA	Broadband Ultrasound Attenuation
CaMos	Canadian Multi-centre Osteoporosis study
CRFs	Clinical Risk Factors
CV	Coefficient of Variation
CT	Computed Tomography
DXA	Dual-energy X-ray Absorptiometry
EPIC	European Prospective Investigation into Cancer
EPAQ2	EPIC Physical Activity Questionnaire version 2
FEV_1	Forced Expiratory Volume in 1 second
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
MET	Metabolic Equivalent
QCT	Quantitative Computed Tomography
QUS	Quantitative Ultrasound
RCT	Randomised Clinical Trial
ROC	Receiver Operating Characteristics
RR	Relative Risk
SD	Standard Deviation
SOS	Speed Of Sound

List of Publications from this Thesis

Peer-reviewed Journal Papers

Moayyeri A, Luben RN, Bingham S, Welch A, Wareham NJ, Khaw KT. Measured height loss predicts fractures in middle aged and older men and women: the EPIC-Norfolk prospective population study. Journal of Bone and Mineral Research 2008 Mar;23(3):425-32

Moayyeri A, Bingham S, Luben RN, Wareham NJ, Khaw KT. Respiratory function as a marker of bone health and fracture risk in an older population: the European Prospective Investigation into Cancer-Norfolk Study. Journal of Bone and Mineral Research 2009 May;24(5):956-63

Moayyeri A. The association between physical activity and osteoporotic fractures: A review of the evidence and implications for future research. Annals of Epidemiology 2008 Nov;18(11):827-35

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Moayyeri A, Kaptoge S, Dalzell N, Luben RN, Wareham NJ, Bingham S, Reeve J, Khaw KT. The effect of including quantitative ultrasound assessment in models for estimation of 10-year absolute risk of fracture. Bone 2009 Aug;45(2):180-4

Conference Presentations

32nd ASBMR Annual Meeting, Toronto, Canada, Oct 2010. The Non-Linear Association between Percentage Body Fat and Fracture Risk: The European Prospective Investigation into Cancer-Norfolk Study

37th European Symposium on Calcified Tissues, Glasgow, UK, Jun 2010. The association between body composition and bone health in EPIC-Norfolk study

ECCEO10 and IOF World Conference of Osteoporosis, Florence, Italy, May 2010. Association between different domains of physical activity and osteoporotic fractures

36th European Symposium on Calcified Tissues; Vienna, Austria, May 2009. Comparison of quantitative ultrasound and dual-energy X-ray absorptiometry for prediction of 10-year absolute risk of fracture among older men and women

ECCEO9 and IOF Meeting; Athena, Greece, Mar 2009. Quantitative ultrasound versus dual-energy X-ray absorptiometry for prediction of prospective fracture risk: the EPIC-Norfolk study

30th ASBMR Annual Meeting; Montreal, Canada, Sep 2008. Performance of QUS in comparison to DXA for prediction of prospective fractures among older men and women: the EPIC-Norfolk study

35th European Symposium on Calcified Tissues; Barcelona, Spain, May 2008. Absolute risk of fractures in middle-aged and older men and women: the European Prospective Investigation into Cancer-Norfolk study

ECCEO8; Istanbul, Turkey, Apr 2008. Estimation of absolute fracture risk among middle-aged and older men and women: the EPIC-Norfolk population cohort study

ISCD Annual Meeting; San Francisco, USA, Mar 2008. The effect of including QUS Assessment in fracture risk prediction models for older men and women: the EPIC-Norfolk cohort study

12th National Osteoporosis Society Conference.; Edinburgh, UK, Nov 2007. Respiratory function is associated with bone ultrasound measures and hip fracture: European prospective investigation into cancer-Norfolk population cohort study

Bone Research Society Annual Meeting; Aberdeen, UK, Jul 2007. Height loss predicts fractures in middle aged and older men and women: the EPIC-Norfolk prospective population study

Thesis Structure

The scope of this PhD thesis consisted of: 1) assessment of new risk factors for osteoporotic fractures given the data available in the EPIC-Norfolk study; and 2) development of a model for integrating established risk factors and estimation of 10-year absolute risk of fracture in this population. The thesis structure follows this scope. Chapter 1 is a literature search and a general introduction to the problem from different epidemiological aspects. To minimise repetition of methods in different Chapters, I have written out the common methods of the study in Chapter 2. Therefore, the Methods sections in the following Chapters contain only methods related to the specific objective of the Chapter. The rest of the thesis is structured around chapters written as papers, which answer specific research questions related to the scope of this PhD project. Chapters 3, 4, 6, and 7 are based on studies for search of novel or less-studied risk factors of fracture using EPIC-Norfolk data. Given the importance and complexity of physical activity as a risk factor, I carried out a systematic review of the literature and the results are presented in Chapter 5. In Chapter 8, I have reviewed the importance of absolute risk measures in epidemiology and potential applications of it in the field of bone research. Chapters 9, 10, and 11 are based on the model I developed for estimation of absolute fracture risk in EPIC-Norfolk. Each of these Chapters follows the same format: Abstract, Introduction, Methods, Results, and Discussion. Chapter 12 presents a general discussion placing the research findings in context and highlighting potential areas for further work. Most of the thesis is written in the first person plural to acknowledge co-authorship for the papers. However, I have been in charge for the entire projects of this thesis and I am fully responsible for the data, analyses, and results of this thesis.

Chapter 1: Introduction

In this Chapter, I firstly explain the current state of knowledge about the epidemiology and burden of osteoporosis and hip fractures in the world and the increasing need for development of preventive strategies in high-risk populations. A review of the established risk factors of osteoporotic fractures is presented alongside with a brief introduction of the risk factors evaluated in this thesis. Different methods for risk assessment of osteoporosis are described and discussed with an emphasis on the absolute risk estimation methods. I then explain the aims and objectives of different sections of this thesis.

1.1. Epidemiology and burden of osteoporosis

Osteoporosis is defined as a "systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk" [1]. Osteoporosis is a highly prevalent disease among the elderly. For the year 2000, there were an estimated 3.1 million new osteoporotic fractures in Europe [2]. The 2004 US Surgeon General's report has estimated that about 10 million Americans over the age of 50 years have osteoporosis, and around 1.5 million fragility fractures occur in these patients each year [3]. The report estimates that approximately one in two women and one in five men over the age of 50 will have an osteoporosis-related fracture in their remaining lifetime [3]. An analysis of the General Practice Research Database (GPRD, which includes 6% of the UK population) showed a similar figure in the UK [4]. The most common sites of fragility fractures are the hip, spine and distal forearm.

Approximately 98% of hip fractures occur among people aged 35 years and over, and the incidence of hip fracture in most populations increases exponentially with age (*Figure 1.1*) [5]. In 1990, an estimated 1.66 million hip fractures occurred worldwide, of which 1.19 million were in women [6]. The GPRD study estimated that the lifetime risk of hip fracture for 50-year-olds in the UK is 11.4% and 3.1% for women and men, respectively [4]. However, these figures might be underestimated given the changes in expected mortality rates [7]. Many vertebral fractures are asymptomatic, and there is disagreement about the radiographic definition of such fractures. It is estimated that only one-third of radiographically-diagnosed vertebral fractures come to medical attention [8]. The overall age-standardised incidence of vertebral fracture in the European Prospective Osteoporosis Study (EPOS) was 10.7 per 1,000 person-years in women and 5.7 per 1,000 person-years in men (*Figure 1.1*) [9]. It is estimated that 1.4 million clinical vertebral fractures and 1.6 wrist fractures occurred globally in 2000 [2]. Wrist fractures show a pattern of occurrence that differs from that of hip and

vertebral fractures. Most wrist fractures occur in women with 50% occurring in women aged over 65 years (*Figure 1.1*). Data from the GPRD study showed that the lifetime risk of wrist fracture in a 50-year-old British woman is 16.6%, falling to 10.4% by 70 years of age. The corresponding figures in men are 2.9% and 1.4%, respectively [4].

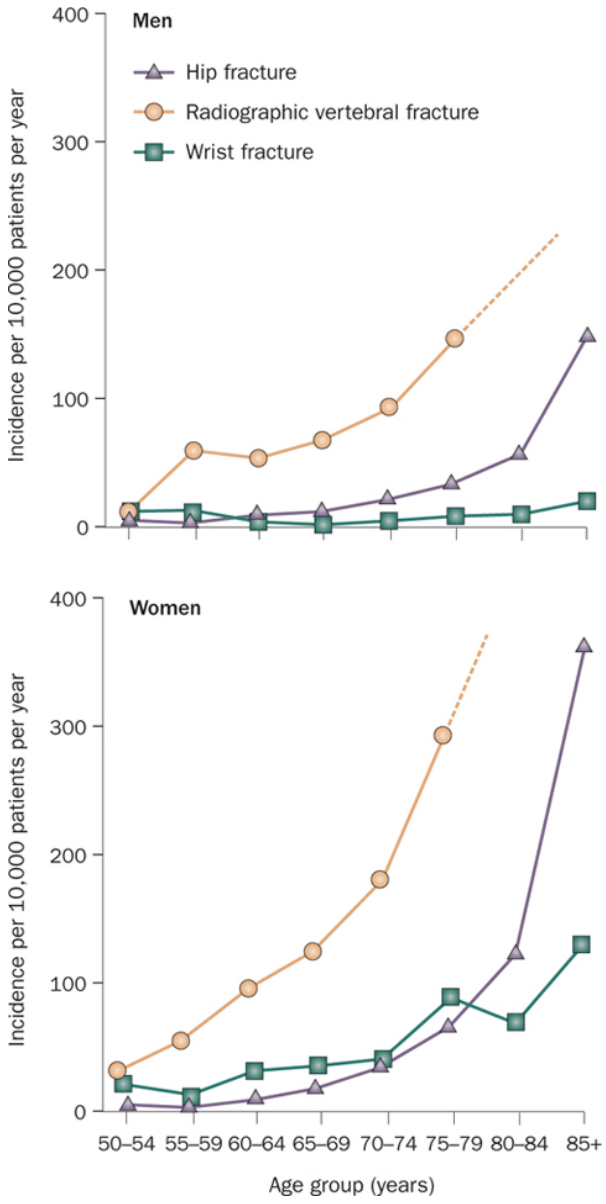

Figure 1.1: Age- and sex-specific incidence of hip, radiographic vertebral, and wrist fractures
Data derived from the European Prospective Osteoporosis Study [9] and General Practice Research Database [4]. Figure is reproduced from reference [10].

It should be noted that, while hip and vertebral fractures are associated with substantial burden associated with osteoporosis, the incidence of fractures in other sites is much higher and they impose a considerable burden on populations. These fractures are important as they occur at an earlier age compared to hip fracture, and their incidence rate exceeds that of hip fracture even in men and women aged >80 years (*Figure 1.2*) [11]. In the year 2000, 4.3 million out of 9 million osteoporotic fractures were at sites other than hip, spine and forearm [2].

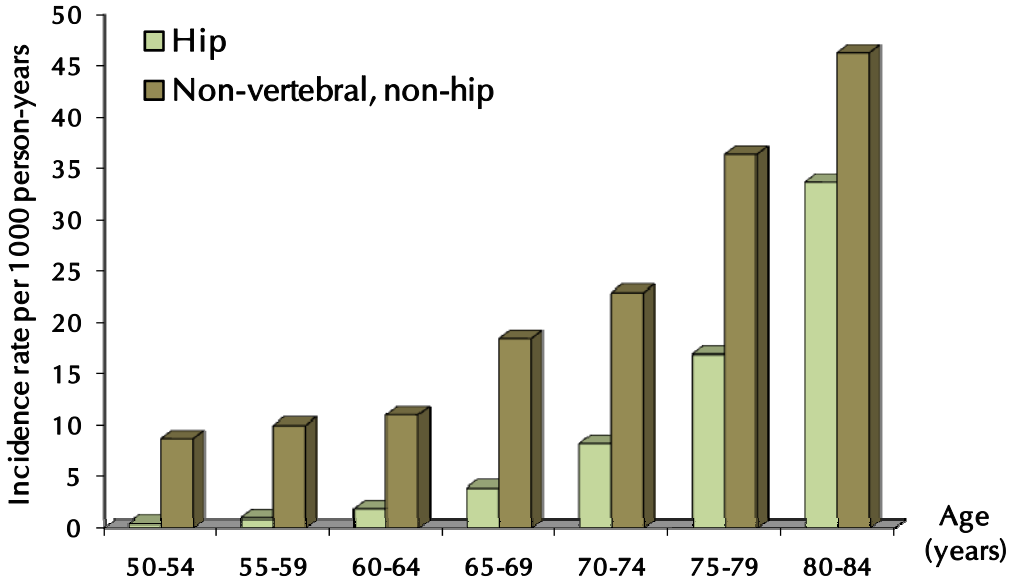

Figure 1.2: Incidence rate of fractures in different sites among post-menopausal women Non-vertebral, non-hip fractures include fractures of the ribs, pelvis, humeral shaft, proximal humerus, clavicle, scapula, sternum, tibia, fibula, distal forearm, and femoral fractures other than hip. Figure is adopted from the Geelong Osteoporosis Study [12].

Hip fractures are associated with a significant increase in mortality, even in the <65 years age group [13, 14]. An estimated 740,000 deaths per year are associated with hip fracture worldwide [15]. Mortality associated with hip fracture increases with age and is higher in men than women. In the UK, the 12-month survival rate after hip fracture for men is 63.3% versus 90.0% expected and for women is 74.9% versus 91.1% expected [4]. In the US, about 8% of men and 3% of women aged over 50 years die while in hospital following their hip fracture [16]. Mortality rates after hip fracture continue to rise over the subsequent months and peak at 1 year, with a rate of 36% for men (higher for the very elderly) and 21% for women [16]. Data from 28.8 million person-years of follow-up from the patient register of Sweden suggested that 17-32% of deaths after hip fracture are directly related to the event, and hip fracture accounted for more than 1.5% of all deaths in the population aged ≥50 years [17]. The Dubbo Epidemiology Study suggested that elevated mortality persists for up to 10 years after hip fracture [18]. Excess mortality after vertebral fracture seems to persist for up to 5 years in both sexes [18, 19], with only 8% of deaths following vertebral fractures directly attributable to osteoporosis. In the UK GPRD study, the observed survival in women 5 years after vertebral fracture was 56.5% versus 69.9% expected [4]. Wrist fractures are not associated with excess mortality (see *Table 1.1*).

Consistent with their effect on mortality, hip fractures contribute most to osteoporosis-associated morbidity. Alongside with acute complications such as pressure sores, bronchopneumonia and urinary tract infections, long-term mobility may be severely impaired. It is estimated that only 50% of hip fracture patients regain their pre-fracture status as judged by the ability to walk and the need for aids at home [20]. In the USA, 25% of formerly independent patients became at least partially dependent following a hip fracture, and 50% of those who were dependent pre-fracture were admitted to residential care [21]. The major clinical consequences of vertebral fracture are back pain, kyphosis, and height loss. This may lead to decreased quality of life and psychological problems

such as depression and social isolation [22]. Although only a minority of vertebral fractures come to clinical attention, symptomatic vertebral fractures account for 52,000 hospital admissions in the USA and about 2,000 in England and Wales each year in patients aged ≥45 years (*Table 1.1*) [23]. Wrist fractures do not seem to be associated with increased long-term morbidity [4].

Table 1.1: Impact of osteoporosis-related fractures in the UK

Impact	Hip	Spine	Wrist
Lifetime risk			
Women	14	28	13
Men	3	6	2
Patients per year	70,000	120,000	50,000
Hospitalisation (%)	100	2-10	5
Relative survival	0.83	0.82	1.00

Costs for all sites combined are estimated at approximately £1.7 billion. Table is reproduced from Reference [23].

Bone fractures are responsible for substantial costs related to hospitalisations, surgery, outpatient care, long-term care and premature death [24]. Fragility fractures account for 0.83% of the burden of non-communicable disease worldwide and 1.75% in Europe [2]. In the year 2000, the projected annual cost of osteoporotic fractures in the European Union was estimated at €32 billion [25], which was more than the annual cost of type 2 diabetes [26]. The projected direct costs are expected to increase to €76.7 billion in 2050 based on the

expected changes in the demography of Europe [27]. When burden of osteoporosis is compared to other health problems, the importance of the disease becomes more evident (*Figure 1.3*). In Europe, osteoporotic fractures accounted for more disability adjusted life years (DALYs) lost than common cancers, with the exception of lung cancer, and diseases such as hypertension, migraine and asthma [2]. For chronic musculoskeletal disorders, the DALYs lost in Europe due to osteoporosis were less than for osteoarthritis but greater than for rheumatoid arthritis.

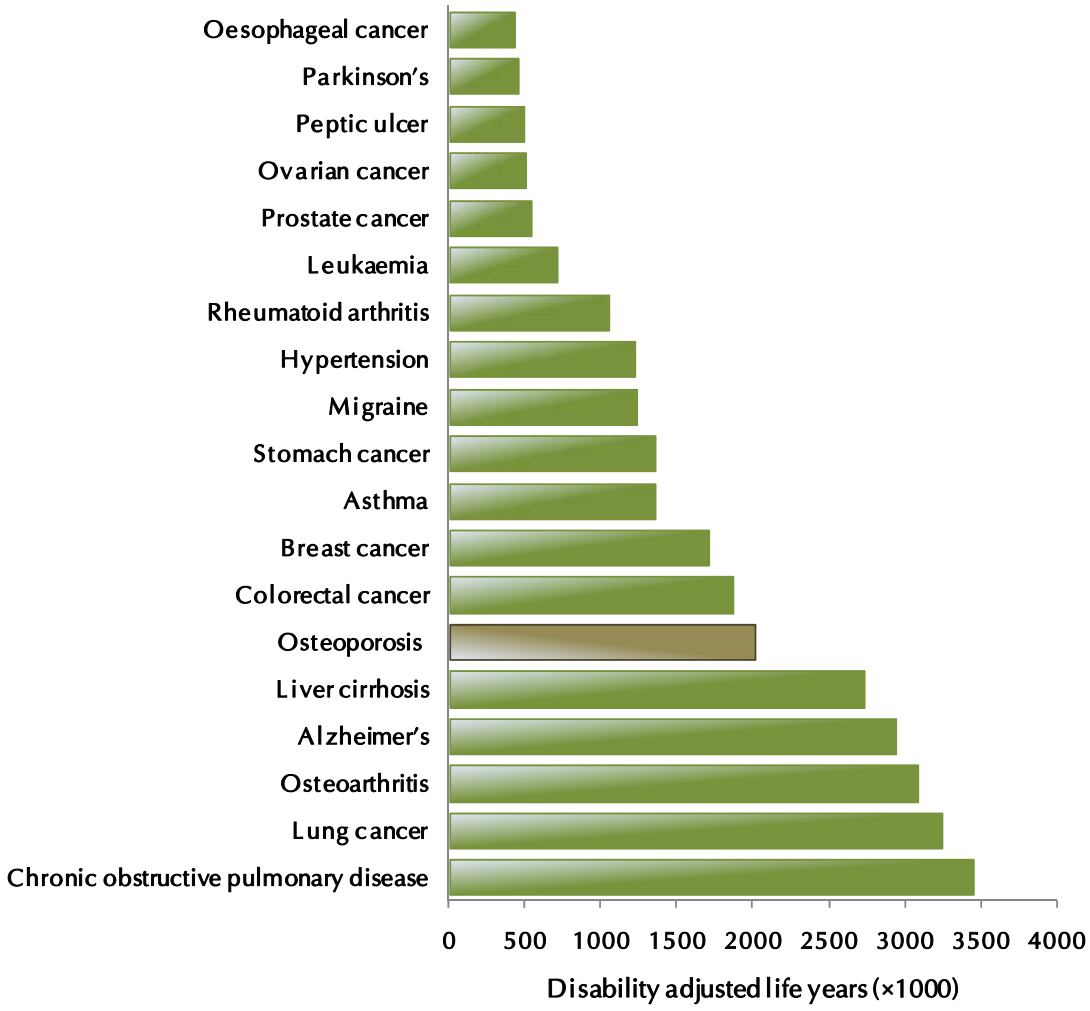

Figure 1.3: The estimated burden of diseases in Europe in 2002

Figure is reproduced from Reference [2].

The prevalence of osteoporosis is continuing to escalate with the increasingly elderly population. The global life expectancy is increasing steadily and the number of elderly individuals is rising in every geographic region. In the United Kingdom, the population aged over 60 is projected to increase by 50% between 2000 and 2030 [28]. By the year 2050, the global population of individuals aged ≥65 years is expected to reach to more than 1.5 billion. Assuming a constant age-specific risk of hip fracture, the projected number of osteoporotic hip fractures worldwide is estimated to increase from 1.66 million in 1990 to 6.26 million in 2050 [29]. Although some recent studies from Switzerland and Finland suggest that the age-adjusted incidence of hip fracture has declined over the last decade [30, 31], studies on the secular changes for hip fracture over the last century in Europe have shown an upward trend in age-adjusted incidence to the present time [23]. It should be noted that the number of elderly individuals is increasing faster in the developing countries of Asia and Latin America. This together with the upward secular trend in age-adjusted hip fracture incidence in these areas is likely to shift the geographical distribution of hip fractures, with only an estimated one-quarter occurring in Europe and North America by 2050 [29]. This trend calls for urgent action regarding the prevention and management of the disease.

Osteoporosis fulfils most of the eight criteria recommended by the World Health Organisation (WHO) for screening diseases [32]. Osteoporosis is a worldwide health problem [15], the natural history of the disease is well understood [33], the disease is detectable pre-clinically [34], effective treatments are available for pre-symptomatic patients [35], several facilities for diagnosis of the disease in inpatient and outpatient clinics are in place [36], and tests for early diagnosis are fairly safe and acceptable to the population [37]. However, considering the expenditure of diagnostic tests and medications for prevention of fractures, screening programmes appear to be cost-effective only in the high risk population [38, 39]. The other unfulfilled criterion is finding a suitable test to detect high risk individuals.

In summary, osteoporosis is a highly prevalent disease and imposes a great burden on the health system of both developed and developing countries. Hip and vertebral fractures are associated with impaired quality of life and a 20% reduction in survival. Future projections are more alarming given the increasing trend of life expectancy throughout the World. Despite the introduction of several new treatments in the past two decades, the disease still affects more than 200 million women throughout the world [40]. Targeting individuals at high risk of fracture using new case-finding strategies is a major clinical and public health challenge.

1.2. Risk factors for osteoporotic fractures

A large number of risk factors for osteoporotic fractures have been identified. The main ones include bone mineral density (BMD), age, sex, and history of fracture. Other risk factors show relatively poor specificity and sensitivity in predicting either bone mineral density or fracture risk [41, 42]. For the purposes of risk assessment, interest lies in those factors that contribute significantly to fracture risk over and above that provided by BMD measurements or age [43]. Here I review the main risk factors for osteoporotic fractures and some of the novel clinical risk factors (CRFs) for fracture and explain the relationships between them.

1.2.1. Bone mineral density

Bone mineral density (BMD) as measured by dual-energy X-ray absorptiometry (DXA) is the main available marker of bone health and is commonly used to diagnose osteoporosis [44]. In 1996, a reference meta-analysis of prospective cohort studies showed that the risk for fracture increases by a factor of 1.5–3.0 for each standard deviation decrease in BMD (*Table 1.2*) [45]. A recent individual-level data meta-analysis on about 40,000 men and women followed for 170,000 person-years confirmed these results [46]. The ability of BMD to predict fracture is comparable to the use of blood pressure to predict stroke, and significantly better than serum cholesterol to predict myocardial infarction [45]. *Table 1.2* indicates that power of BMD for prediction of fractures is improved by site-specific measurements. The highest gradient of risk (relative risk per standard deviation) is found at the hip to predict hip fracture where the gradient of risk is 2.6. Thus, an individual with a T-score of -3 SD at the hip would have a 2.6^3 or greater than 15-fold higher risk than an individual with a T-score of 0 SD. By contrast, the same T-score at the spine would yield much lower risk estimate—approximately 4-fold increase (1.6^3). This emphasises the importance of accuracy or gradient of risk in the categorisation of fracture risk.

Table 1.2: Relative risk of fracture (95% CI) in women for 1 SD decrease in BMD below age-adjusted mean

Site of measurement	Forearm fracture	Hip fracture	Vertebral fracture	All fractures
Distal radius	1.7 (1.4–2.0)	1.8 (1.4–2.2)	1.7 (1.4–2.1)	1.4 (1.3–1.6)
Femoral neck	1.4 (1.4–1.6)	2.6 (2.0–3.5)	1.8 (1.1–2.7)	1.6 (1.4–1.8)
Lumbar spine	1.5 (1.3–1.8)	1.6 (1.2–2.2)	2.3 (1.9–2.8)	1.5 (1.4–1.7)

Table is reproduced from Reference [45].

Despite these performance characteristics, it should be recognised that absorptiometric techniques have high specificity but low sensitivity. Just because BMD is normal, there is no guarantee that a fracture will not occur, but the risk is decreased. Conversely, if BMD is in the osteoporotic range, then fractures are more likely, but not inevitable. *Figure 1.4* shows the data from the National Osteoporosis Risk Assessment (NORA) study on about 200,000 post-menopausal women without known osteoporosis [47]. 7.2% of the study population had osteoporosis (defined as a T-score $\leq$ -2.5). This *Figure* confirms that fracture rates are significantly higher for those with the lowest T-scores. However, the most interesting finding from the study was that, even though the risk of fracture is much higher in individuals with osteoporosis, the greatest absolute number of fractures occurred in individuals with low bone mass (T-scores between -1 and -2.5) since they are roughly five times more than individuals with osteoporosis [47]. At the age of 50 years, the proportion of women with osteoporosis who will fracture their hip, spine or forearm or proximal humerus in the next 10 years (i.e. positive predictive value) is approximately 45% [48]. The detection rate for these fractures (sensitivity) is, however, low and 96% of such fractures would occur in women without osteoporosis [48, 49]. The low sensitivity is one of the reasons why widespread population based screening is not widely recommended in women at the time of the menopause [5].

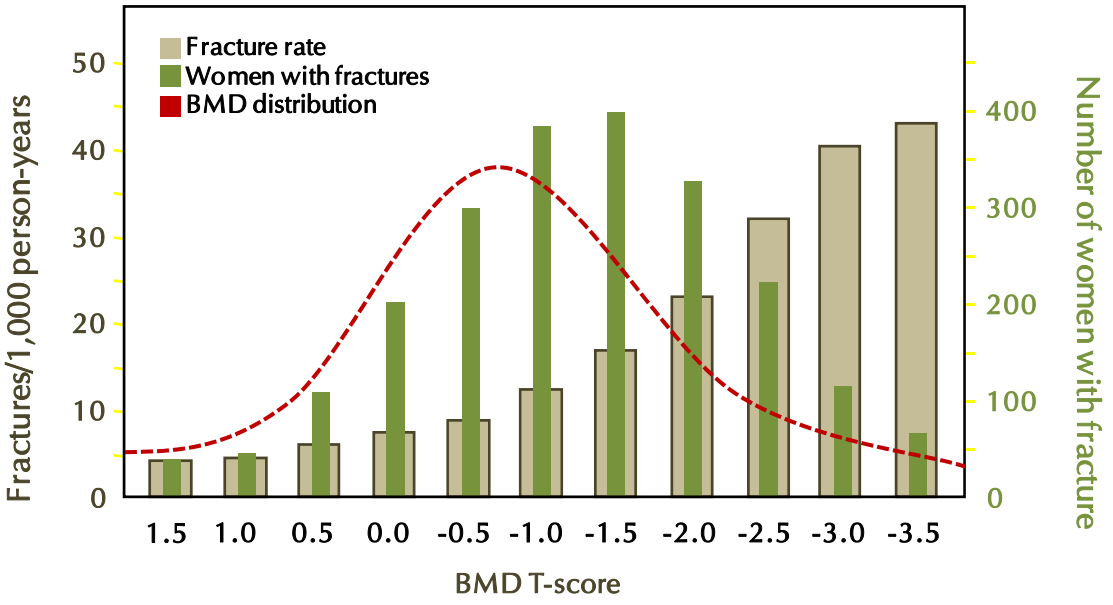

Figure 1.4: Osteoporotic fracture rates, population BMD distribution and number of fractures in post-menopausal women
Data is from the National Osteoporosis Risk Assessment (NORA) study. Figure is reproduced from Reference [50].

1.2.2. Age and sex

Osteoporosis is more common among women and incidence of osteoporotic fractures increases with age. This is a highly consistent feature across all of the studies and brings that all incidence rates should be reported in relation to age and separately for men and women. Moreover, age and sex are independent of BMD and interact with it for fracture risk prediction. For any BMD, fracture risk is much higher in the elderly than in the young [51]. The same T-score with the same technique at any one site has a different significance at different ages. This is because age contributes to risk independently of BMD. The impact of age on hip fracture probability is shown in *Figure 1.5*. In addition, the performance

characteristics of BMD vary with age. For example, at the age of 50 years, hip fracture risk increased 3.7-fold per standard deviation decrease in femoral neck BMD whereas at the age of 80 years the gradient of risk is 2.3 [46]. Thus, the consideration of age and BMD together increases the range of risk that can be identified.

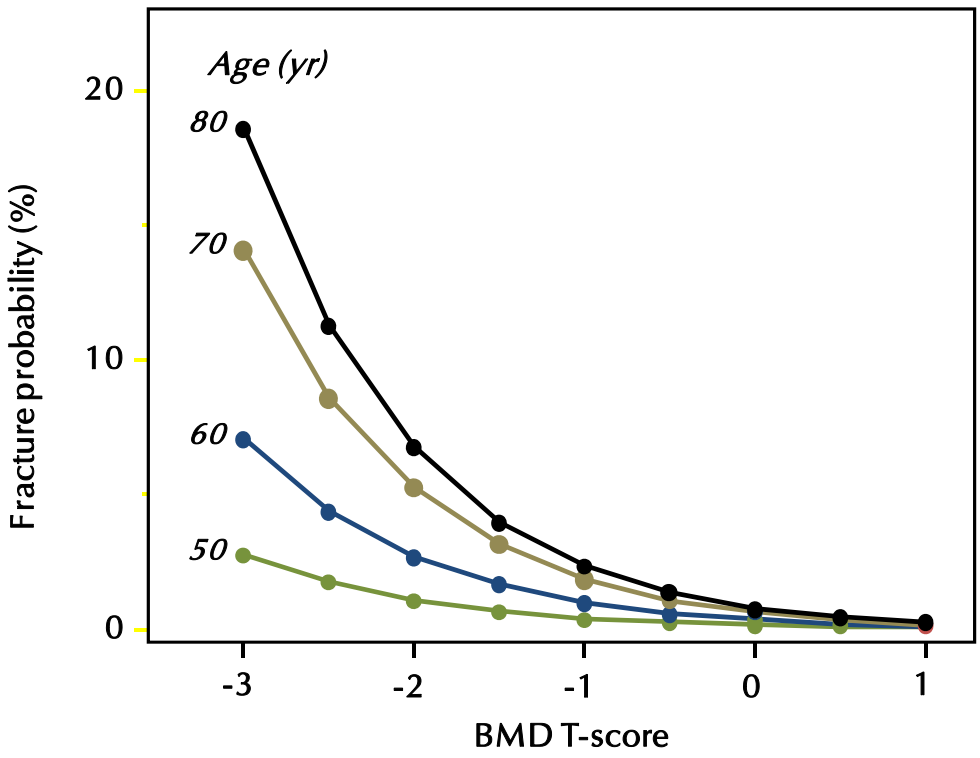

Figure 1.5: The relationship between femoral neck BMD and hip fracture probability in women from Sweden according to age
Figure is reproduced from Reference [51].

Other clinical risk factors may have interaction (effect modification) with age and sex or may vary in importance according to age. For example, risk factors for falling such as visual impairment, reduced mobility and treatment with sedatives, are more strongly predictive of fracture in the elderly than in younger individuals [52].

1.2.3. Previous fractures

A personal history of fragility fracture is a well established and important risk factor for further fractures [53, 54]. The risk for an osteoporotic fracture is approximately doubled in the presence of a prior fracture [55]. The risk is more marked for vertebral fractures where the presence of a prevalent vertebral deformity leads to a 7- to 10-fold increase in the risk of subsequent vertebral deformities [56]. In the case of hip fracture, there is an obvious interaction (effect modification) between age and history of fracture. The predictive value of a prior fracture is most marked at younger ages and attenuates with age (*Figure 1.6*) [53]. The risks are in part independent of BMD. Distal forearm fractures are also shown to be associated with 1.4-fold increase in the risk of subsequent hip fracture in women and a 2.7-fold increase in men [57].

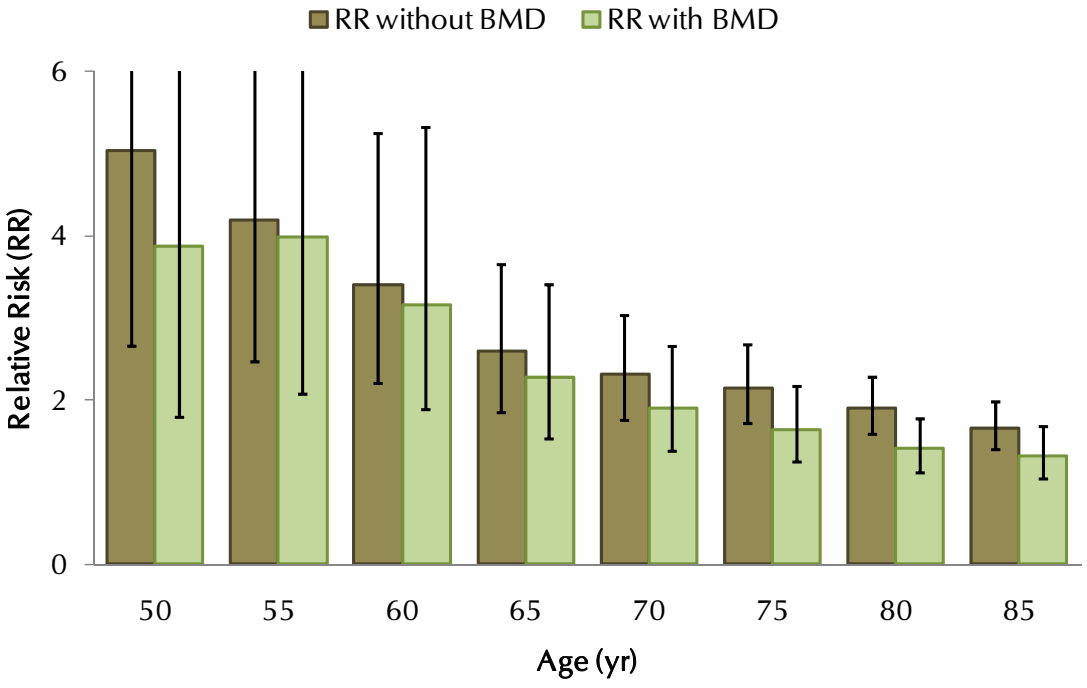

Figure 1.6: Relative risk for hip fracture comparing individuals with and without a prior fracture by age, with and without adjustment for BMD
Figure is reproduced from Reference [53].

Other characteristics of previous fractures may have additional value for risk predictions. Data from the European Prospective Osteoporosis Study (EPOS) demonstrated that prevalent vertebral deformity is a strong predictor of incident hip fracture (with a rate ratio of 2.8-4.5), and the risk of hip fracture increases with the number of previous vertebral deformities [58]. The number and morphometry of baseline vertebral deformities also predict the occurrence of incident vertebral fracture [59]. A recent study showed that the relative risk of subsequent fracture declines with time from the initial fracture [60]. The incidence of new vertebral fracture within one year of an incident vertebral fracture is 19.2% [61]. Finally, data from the Dubbo Osteoporosis Epidemiology Study (DOES) suggested that re-fracture rates in men and women were similar over a 10-year period [62].

1.2.4. Other bone characteristics

Although bone mass is an important determinant of the risk of fracture, other abnormalities occur in the skeleton that contribute to fragility. The term "bone quality" points out to a constellation of properties of bone such as bone turnover, microarchitecture, mineralisation, microdamage, and bone matrix composition. These factors contribute to bone strength independently of bone mineral density [5]. Currently, studies on various aspects of bone quality comprise a large segment of the field of bone research [63]. These include but not limited to: studies on the role of collagen and minerals in composition of bones [64], bone morphology and microcracks [65], biomechanical analysis of shape and geometry of the bones [66], cellular mechanisms for modelling and remodelling of bone [67], role of cellular mechanosensors and osteocytes' communicating networks [68], trabecular thinning and loss of connectivity [69], and cortical thinning and porosity [70]. Unfortunately, assessment of bone quality is hampered by the inaccessibility of bone for investigation and there is no single

measure to cover all aspects of bone quality. This limits the use of these bone characteristics for fracture risk assessment [71]. New imaging techniques for quantitative assessment of macrostructural characteristics (such as bone geometry) and microstructural features (such as relative trabecular volume, trabecular spacing, and connectivity) have been developed recently [72]. These modalities may increase our power for fracture risk prediction but need further studies [73]. Biochemical markers of bone turnover are also suggested to be associated with prospective risk of osteoporotic fractures in women and these associations are independent of BMD and previous history of fracture in several studies [74].

There is a growing interest in the use of quantitative ultrasound (QUS) measurements for the non-invasive assessment of osteoporotic fracture risk in the management of osteoporosis. The attractiveness of QUS lies in the fact that indirect and in vitro experience has suggested that ultrasound may give information not only about BMD but also about architecture and elasticity [75, 76]. QUS is inexpensive, transportable, ionizing radiation free, and proven to predict hip fractures and all osteoporotic fractures in elderly women as accurately as dual-energy X-ray absorptiometry (DXA) [77, 78]. QUS measures have been considered throughout this thesis and I have compared their performance with that of DXA for prediction of fractures (please see Chapter 11).

1.2.5. Other clinical risk factors

Many independent risk factors for osteoporotic fracture have been identified. These include but not limited to: family history of hip fracture, low body weight, cigarette smoking, excessive alcohol consumption, corticosteroids therapy, low dietary calcium intake, vitamin D deficiency, rheumatoid arthritis, premature menopause, primary or secondary amenorrhoea, primary and secondary

hypogonadism in men, Asian or Caucasian race, poor visual acuity, neuromuscular disorders, and prolonged immobilisation [43]. Some of these risk factors are related to non-skeletal factors such as the liability to fall or higher force of impact during a fall. Not all of these risk factors have been verified in different cohorts as showing risk independent of bone mineral density [79]. Moreover, several endocrine or metabolic diseases (e.g., hypogonadism, hyperthyroidism, and primary hyperparathyroidism), nutritional conditions, medications, disorders of collagen metabolism, and other conditions may induce bone loss for patients [80]. These are classified as “secondary osteoporosis” and their management and risk assessment needs consideration of the causal disorder [80].

1.3. Risk assessment methods

The assessment of bone mineral density (BMD) is the main aspect of bone health that can be readily measured in clinical practice and it forms the cornerstone for the general management of osteoporosis. In 1994, the World Health Organisation (WHO) published diagnostic criteria for osteoporosis in postmenopausal women, intended primarily for descriptive epidemiology [44, 81]. Osteoporosis was described as a value for BMD at the femoral neck of 2.5 SD or more below the young female adult mean (T-score $\leq$ -2.5). Severe osteoporosis (established osteoporosis) was described as a T-score of $\leq$ -2.5 for femoral neck BMD in the presence of one or more fragility fractures. The recommended reference range was the Third National Health and Nutrition Examination Survey (NHANES III) reference database for femoral neck measurements in White women aged 20–29 years [82]. The criteria have recently been updated [83]. These diagnostic criteria have been widely accepted and are commonly used to provide intervention thresholds, treatment and inclusion criteria for drug trials, and a basis for health technology assessments.

Although BMD measurements have high specificity for assessment of bone health and fracture risk, they have poor sensitivity and this limits their application in clinical practice. As shown in *Figure 1.4*, most of the fractures in women occur in population with BMD values not in the range of osteoporosis (T-score $\leq$ -2.5). Therefore, clinicians aiming to start preventive treatments for their patients need to consider other risk factors in order to target those who would benefit most from these treatments. Several scientific societies affiliated to the field of bone health (mostly European and North American) have tried to make recommendations for treatment initiation. Most of these recommendations are based on a combination of central DXA measurements and established risk factors of osteoporosis. Some of these recommendations are summarised in *Table 1.3*.

Table 1.3: Current recommendations for specific anti-fracture therapy initiation from different scientific organisations

	Postmenopausal women	Men >60 yrs	Comments
NOF 2003 (USA) [84] & ACOG 2003 (USA) [85]	Prior vertebral (VF) or hip fracture (HF) T-score <-2.0 with no risk factors T-score <-1.5 with ≥1 risk factors		Major clinical risk factors: low trauma peripheral fracture Fragility fracture in a first degree relative weight < 127 lbs current smoking corticosteroids > 3 months
AACE 2006 (USA) [86]	low-trauma fractures T-scores ≤ −2.5 with no risk factors T-score <-1.5 with ≥1 risk factors Women in whom non pharmacologic preventive measures are ineffective (bone loss continues or low trauma fractures occur)		
SIGN 2003 (UK) [87]	≥2 VF T-score <-2.5 ± FF	T-score <-2.5 ± FF	
NAMS 2006 (USA) [88]	Low trauma VF T-score ≤-2.5 T-score ≤-2 with a risk factor		
DVO 2006 (Germany) [89]	VF & T-score <-2.0 10YR for VF+HF > 30% & T-score <-2.0 50-60: T-score -4.0 60-65: T-score -3.5 65-70: T-score -3.0 70-75: T-score -2.5 >75: T-score -2.0	VF & T-score <-2.0 10YR for VF+HF > 30% & T-score <-2.0 60-70: T-score -4.0 70-75: T-score -3.5 75-80: T-score -3.0 80-85: T-score -2.5 >85: T-score -2.0	If clinical risk factor: +1 T-score HF in a parent low trauma peripheral fracture current smoking Multiple falls, immobility
AFSSAPS 2006 (France) [90]	T-score ≤-2.5 & FF T-score <-1.0 & VF or HF T-score <-1.0 & other FF & CRFs T-score ≤-2.5 & 60+ years (T-score <-1.0 & major CRFs)		Clinical risk factors: corticosteroids family hip fracture low BMI current smoking increased risk of falls
OP Ca 2006 (Canada) [91]	50: LR >-2.3 MR: -2.3/-3.9 HR: <-3.9 55: LR >-1.9 MR: -1.9/-3.4 HR: <-3.4 60: LR >-1.4 MR: -1.4/-3.0 HR: <-3.0 65: LR >-1.0 MR: -1.0/-2.6 HR: <-2.6 70: LR >-0.8 MR: -0.8/-2.2 HR: <-2.2 75: LR >-0.7 MR: -0.7/-2.1 HR: <-2.1 80: LR >-0.6 MR: -0.6/-2.0 HR: <-2.0 85: LR >-0.7 MR: -0.7/-2.2 HR: <-2.2		If clinical risk factor: +1 category FF after 40 years Corticosteroids

Abbreviations: PM: postmenopausal; VF: vertebral fracture; HF: hip fracture; FF: fragility fracture; CRFs: clinical risk factors; 10YR: 10 year risk; LR (<10%): low 10YR (hip, spine, forearm, proximal humerus); MR (10-20%): moderate 10YR; HR (>20%): high 10YR

Table 1.3 shows that different societies have emphasised on different sets of clinical risk factors (CRFs). Moreover, they have not included many of other established risk factors as consideration to the interplay between all of these factors is impractical in the clinical setting. The aim of these recommendations is to provide clinicians with simple and accurate (as much as possible) criteria for treatment initiation. Integration of BMD and CRFs is critical for improvement of these clinical criteria.

In general, clinical risk factors for osteoporosis show relatively poor specificity and sensitivity in predicting either bone mineral density or fracture risk [41, 42, 79, 92, 93]. Over the past few years, a series of meta-analyses has been undertaken to identify clinical risk factors that could be used in case finding strategies with or without the use of BMD [55]. These meta-analyses have shown remarkable international consistency for low body mass index [94], a prior history of fracture [53], a family history of hip fracture [95], use of systemic corticosteroids [96], current smoking [97], high intake of alcohol [98], and rheumatoid arthritis [96]. The results of these meta-analyses are summarised in *Table 1.4*.

Table 1.4: Risk ratios for hip fracture associated with risk factors adjusted for age, with and without adjustment for BMD

Risk indicator		Without BMD		With BMD	
		RR	95% CI	RR	95% CI
Body mass index	(20 vs. 25 kg/m2)	1.95	1.71–2.22	1.42	1.23–1.65
	(30 vs. 25 kg/m2)	0.83	0.69–0.99	1.00	0.82–1.21
Prior fracture after 50 years		1.85	1.58–2.17	1.62	1.30–2.01
Parental history of hip fracture		2.27	1.47–3.49	2.28	1.48–3.51
Current smoking		1.84	1.52–2.22	1.60	1.27–2.02
Ever use of systemic corticosteroids		2.31	1.67–3.20	2.25	1.60–3.15
Alcohol intake >2 units daily		1.68	1.19–2.36	1.70	1.20–2.42
Rheumatoid arthritis		1.95	1.11–3.42	1.73	0.94–3.20

Table is reproduced from Reference [55].

Simplicity and applicability of the risk factor assessment in the clinical settings is another important issue. Many studies indicate, for example, that low intake of calcium is a risk factor for hip fracture [99]; however, the quantification of calcium intake is not readily available in general practice. Part of the aims of this thesis was to find clinically applicable and easy-to-use measures for fracture risk assessment. I have studied the role of measured height loss and respiratory function as potential risk identifiers for osteoporotic fractures (Please see Chapter 3 and 4). Moreover, the relationships between osteoporotic fracture risk and some of the important clinical characteristics of patients (namely, physical activity level and obesity) have not been studied well. Physical activity is known to be protective against osteoporotic fractures (reviewed in Chapter 5), but few is known about the detailed associations between physical activity in different domains of life (i.e., at home, at work, for transportation, and at leisure time) and prospective risk of fractures (please see Chapter 6). Also, the shape of association between body mass index and fracture risk is not following a linear trend (as seen in *Table 1.4*) [94] and the specific role of different components of obesity (fat mass and lean mass) in relation to fracture risk is not known. Chapter 7 deals with this problem.

Concerning the integration of risk factors, the multiplicity of clinical risk factors and the interactions between them and BMD poses problems in the units of risk to be used. The T-score becomes of little value in that different T-score thresholds for treatment would be required for each combination of risk factors. Although the use of relative risks is feasible, the metric of risk best suited for clinicians is the absolute risk (or probability) of fracture [100].

The absolute risk of fracture depends upon age and life expectancy as well as the current relative risks (for BMD values and different CRFs). In general, remaining lifetime risk of fracture decreases with age especially after the age of 70 years since the risk of death with age exceeds the increasing incidence of fracture with age. Estimates of lifetime risk are of value in considering the burden of osteoporosis in the community and the effects of intervention strategies [101].

However, for several reasons they are less relevant for assessing risk of individuals in whom treatment might be considered [51]. Hence, the International Osteoporosis Foundation and the World Health Organization recommend that risk of fracture should be expressed as a short-term absolute risk, i.e. probability over a 10-year interval [100]. The period of 10 years covers the likely duration of treatment and the benefits that may continue once treatment is stopped.

The major advantage of using absolute fracture probability is that it standardises the output from a variety of techniques and sites used for BMD assessment. Moreover, it also permits the presence or absence of clinical risk factors other than BMD to be incorporated as a single metric. This is important because there are many risk factors that give information over and above that provided by BMD and age (*Table 1.4*). Models for calculation of 10-year probabilities of fracture can also consider the interactions (effect modifications) between different CRFs and BMD. Estimation of absolute fracture risks has several other applications in research and clinical settings that I have discussed in Chapter 8.

Recently, algorithms that integrate the weight of clinical risk factors for fracture risk, with or without information on BMD, have been developed by the WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield, UK [24]. The FRAX® tool (www.shef.ac.uk/FRAX) computes the 10-year probability of hip fracture or a major osteoporotic fracture (*Figure 1.7*). A major osteoporotic fracture is a clinical spine, hip, forearm and humerus fracture. There is a marked variation in fracture probability in different regions of the world, particularly well documented for hip fracture [102]. There are also differences in mortality. This means that probability models need to be calibrated to the epidemiology of fracture and death of any particular region. FRAX® algorithms are now available for several countries (currently 30 countries in 5 continents), and several more are being developed. Where a country is not represented (because of the lack of epidemiological data) a surrogate may be chosen.

Figure 1.7: The online tool (FRAX®) for calculation of 10-year absolute risk of fracture
The tool estimates risk for patients from different countries based on different clinical risk factors with or without femoral neck BMD. The risk is estimated for hip and major osteoporotic fractures. The website is designed by the WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield, UK and accessed in December 2010.

Figure 1.8 summarises the approach recommended by the WHO for assessment of fracture risk in clinical settings [24, 100]. Measurement of BMD is indicated in individuals who have a high fracture probability (as estimated, for instance, by FRAX®), provided that it will influence the management decision. In some instances, treatment will be justified without measurement of BMD, for example in patients with fragility fractures and other strong risk factors. In other instances, the low cost and absence of side effects justify the use of some agents without BMD measurements in specific populations (e.g. calcium and vitamin D in the institutionalised elderly). Conversely in some patients, the fracture probability may be so low that a management decision will not be changed by information on BMD. An example is a woman at the time of natural menopause without

symptoms and with none of the clinical risk factors [24]. The size of the 'intermediate' group in *Figure 1.8*, in whom a BMD test would be recommended, will vary by region and country. In countries with very limited or no access to assessment with BMD, the size of this segment will be very small. In those countries where screening is recommended (e.g. in women at the age of 65 years or older) this segment will include the majority of women. The measurement of BMD provides the opportunity to reassess fracture probability in the light of the test result and the clinical risk factors (*Figure 1.8*).

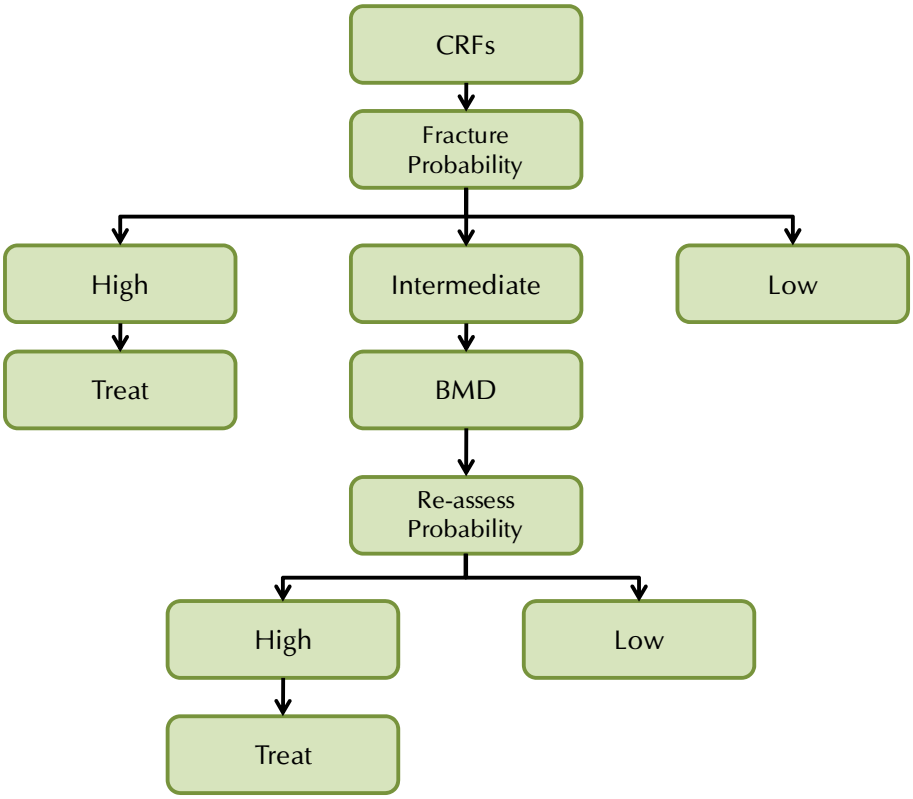

Figure 1.8: Algorithm for the assessment of fracture probability recommended by the WHO Figure is reproduced from Reference [24].

Choice of thresholds for high- and low-risk probabilities is an important issue and these values should ideally come from country-specific health economics studies. A recent study has used FRAX® as a case-finding strategy for men and women in the UK and estimated fracture probabilities at which BMD testing or intervention should be recommended [103]. The results suggested that treatment with generic alendronate therapy (assuming a conservative cost of £95 per year of treatment) was cost-effective at the age of 50 years when the 10-year risk of a major fragility fracture was higher than 7.5%. This rose progressively with age to 30% at the age of 80 years. The thresholds chosen are clearly influenced by a variety of health-economic assumptions, not least the costs of medication and fracture care, as well as the amount society is willing to pay for a given benefit [103]. Further work to validate the FRAX® algorithm as a case-selection tool in the UK is underway. The SCOOP study (Screening of Older Women for Prevention of Fracture) is a seven year trial which is being coordinated by the University of East Anglia and seeks to recruit 12,000 women between the age of 70 and 85 from areas across the UK (http://www.scoopstudy.ac.uk). Recent data from Australia have suggested that FRAX® is able to discriminate between female patients with fragility fracture and controls, although the results for men were less robust [104].

Part of my PhD thesis aimed at development of a model for estimation of absolute fracture risk using available clinical data from a population-based study. The detailed methods are described in Chapter 9. The current recommendations for diagnosis of osteoporosis and assessment of fracture risk centre on the measurement of bone mineral density at the femoral neck using DXA. However, other sites and validated techniques (such as heel QUS) may also be used for fracture prediction. QUS in particular is much more affordable in the clinical settings given its cost and compliance. I further utilised the estimates of fracture probabilities to compare hip DXA and heel QUS (Chapter 10). Finally, the performance of QUS as an independent 'risk factor' for fractures was evaluated using the fracture probabilities (Chapter 11).

1.4. Aims and objectives

The aims of this thesis were based on filling the knowledge gaps on novel risk factors of osteoporotic fractures and developing an all-inclusive model for estimation of absolute risk of fracture among the elderly. EPIC-Norfolk study is a large population-based prospective cohort study with long follow-up that provides an excellent opportunity for unbiased evaluation of clinical risk factors for different outcomes including fractures. The specific objectives for the first part of this thesis were:

- To evaluate measured height loss and respiratory function as potential risk indicators for fractures;
- To assess the association between different aspects of physical activity and prospective risk of fractures among the elderly;
- To evaluate the non-linear association between body fat mass and risk of fracture considering the effects of weight or body mass index.

The specific objectives for the second part of this thesis were:

- To integrate available established risk factors of fracture and develop a statistical model for estimation of 10-year absolute risk of fracture in EPIC-Norfolk population;
- To compare performance of two radiological bone assessment methods for prediction of prospective risk of fracture;
- To assess the additive value of bone ultrasound measurement for improvement of fracture risk prediction models.

Chapter 2: Methods

2.1. Settings and population

The European Prospective Investigation into Cancer and Nutrition (EPIC) project was started in 1989-1990 [105, 106]. It was designed to investigate the relationship between nutrition and cancer, with the potential for studying other major diseases as well. The EPIC is an ongoing multi-centre prospective cohort study with 23 collaborating centres in 10 European countries (France, Germany, Greece, Italy, The Netherlands, Spain, United Kingdom, Sweden, Denmark and Norway). The study has recruited 519,978 participants (366,521 women and 153,457 men), mostly aged 35-70 years. Populations in the study are characterised by large variations in dietary habits and cancer risk. Information on health, diet and other lifestyle variables were obtained from participants at enrolment, which took place between 1992 and 2000 in different collaborating centres. During clinical examination, anthropometric measurements were performed and blood samples taken [106]. In the United Kingdom, the two centres are based in Norfolk and Oxford.

The work in this thesis is based in the EPIC-Norfolk cohort of approximately 25,000 men and women aged 45-74 years from the general population. The recruitment target number of 25,000 represents a balance between the need for large numbers to generate sufficient end points, and the need to include better defined and more discriminating instruments for assessing exposure, including biological assays [107]. The Norfolk region study area includes the city of Norwich and the surrounding small towns and rural areas. This area has little outward migration in this age group and is mainly served by one District General Hospital i.e. Norfolk and Norwich University Hospital. Recruitment began in March 1993 and was completed at the end of 1997. From the outset, the study aims were expanded to include end points other than cancer, including the main causes of disability and death in middle and late life, and exposures other than diet, such as physical activity and psychosocial variables. Ethical permission for

the EPIC-Norfolk study was obtained from the Norwich District Health Authority ethics committee [107].

2.1.1. Baseline health examination

There are 35 local General Practices in the Norfolk County. All eligible individuals on the age-sex registers of these practices were invited to participate in the study. As virtually 100% of people in the UK are registered with their General Practitioners through the National Health Service (NHS), these provide the equivalent of a population-based age-sex register. All individuals who wished to participate completed and signed a consent form. They also completed a detailed health and lifestyle questionnaire and a dietary questionnaire. These participants were then sent an appointment for a health examination at a designated clinic. During the health check, trained nurses performed the health examinations according to standard protocols. During this visit, a non-fasting blood sample was drawn by venipuncture. Participants could choose to complete only selected stages of the study.

A total of 77,630 invitations were sent out and 30,447 consents (39.2%) were obtained. Of those who consented, 25,639 (84%) attended a health examination. There were 1,018 participants outside the target age range of 45 to 74 years due to variation in the coding of birthdates between general practices and in the timing of health check visits. Thus the participants in this study fell into the age range of 40 to 79 years. Health examinations started in 1993 and continued up to early 1997.

2.1.2. Second Health Examination

Between 1998 and 2000, all people who had sent their consent to participate in the study, who may or may not have attended the first health check, were invited for a second health examination. In total, 15,786 individuals attended this visit, of whom 15,028 had attended the first health check. This translated to a response

rate of 58% of those mailed, after excluding those who had moved from the area or died. All participants in this phase completed a detailed health and lifestyle questionnaire, which was similar to the questionnaire filled at baseline visit with some additional items. Besides all the health examinations done in the baseline visit, quantitative ultrasound measurements of the heel and bioelectrical impedance tests were obtained and the DNA bank of EPIC-Norfolk was established. Trained nurses performed the health examinations according to standard protocols. Participants in this health examination aged 42 to 82 years.

2.1.3. Other health questionnaires/examinations

Between 1998 and 2000, EPIC Physical Activity Questionnaire ver.2 (EPAQ2) was posted to all people who consented to participate in the study. The questionnaires were posted accompanying invitation letters for the second health examination. About 15,500 participants returned the questionnaires, most of whom attended the second health examination. Therefore, data related to this questionnaire is analysed with second health check data (see Chapter 6). The questionnaire has been sent again to the participants in 2007-2008 (not used in this thesis).

EPIC-Norfolk study collaborated in the European Prospective Osteoporosis Study (EPOS) between 1993 and 2000 [108]. This was a large multi-centre prospective study on the determinants of vertebral and other osteoporotic fractures conducted in 28 centres across Europe. About 2,000 EPIC-Norfolk men and women aged ≥65 years and without clinical diagnosis of osteoporosis were randomly selected to be invited to participate in this study about 18 months after the baseline visit. About 75% of the invited participants consented and attended the clinic and underwent measurements of hip dual-energy X-ray absorptiometry (DXA) and heel quantitative ultrasound (QUS). More details can be found in Chapter 9.

There are other postal questionnaires sent to EPIC-Norfolk participants (including a 7-day food diary sent in 1993-1998, health questionnaire sent in 1997-2000, follow-up questionnaire sent in 2002-2003, and health questionnaire sent in 2007-2008) that has not been used in this thesis. The third health examination of EPIC-Norfolk was started in 2006 and about 7,500 participants have attended the clinic visit so far. This extends previous health examinations with more detailed assessments in 42 domains of life among the elderly. Data from this health check are not used in this thesis. The flow chart of EPIC-Norfolk study related to this thesis is shown in *Figure 2.1*.

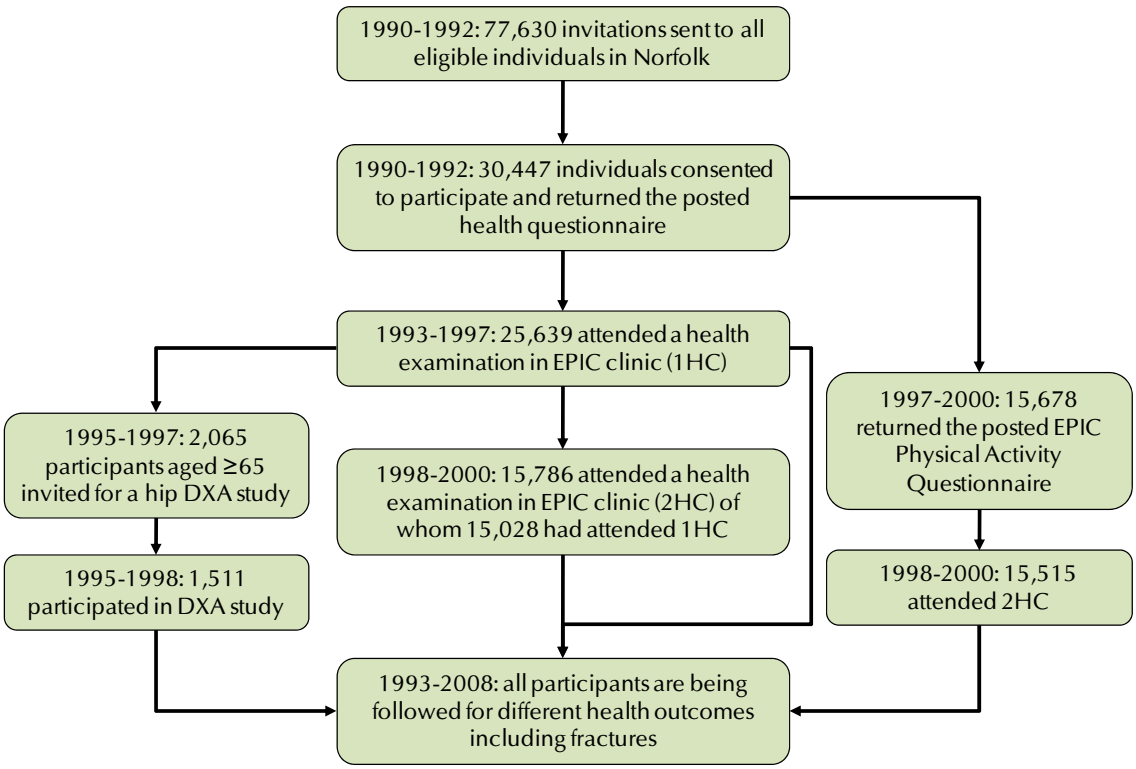

Figure 2.1: Timeline and number of participants in different stages of EPIC-Norfolk study

2.2. Measurements

2.2.1. Health and lifestyle questionnaire

The health and lifestyle questionnaires were posted to the participants for self-completion and they either returned it by post or took that with themselves to the clinic visit (please see Appendix 1). The health and lifestyle questionnaire has a common format across the EPIC cohorts. Demographic data and information on health and lifestyle of participants were collected from the questionnaire. Questions included smoking, alcohol consumption, socio-economic status, social class, occupational history, past history of diseases, short family history of main disease endpoints and a short section on exercise. For women, questions included reproductive history such as menstrual history and use of hormone replacement therapy. Details of medication being taken were also indicated on the questionnaire.

2.2.1.1. History of fracture

Personal medical history was derived from the question: `Has the doctor ever told you that you have any of the following?' A checklist of conditions was provided with a box to tick `yes' and to indicate `age first diagnosed'. The conditions included osteoporosis, fracture of the hip, fracture of the wrist after age 20, and fracture of vertebrae. Information on drugs or medicines taken was also obtained from the questionnaire. These medications were later coded and checked against the British National Formulary. Participants were considered to have had a history of fracture if they answered `yes' to any of the three questions about fractures.

2.2.1.2. Cigarette smoking status

Participants' smoking history was derived from responses to questions on past and present smoking habits. For this study, cigarette smoking status was classified into three categories: never, former and current smoker status. The main questions on cigarette smoking habits in the questionnaire included: `Have you ever smoked as much as one cigarette a day for as long as a year?' and `Do you smoke cigarettes now?' A `no' response to both of the above questions would classify the participants as `never' smokers. An affirmative response to the first question but not to the second question classified the participants as `former' smokers. Participants were defined as `current' smokers if an `affirmative' response was given to the second question.

2.2.1.3. Alcohol intake

Participants were asked the question "Are you a non-drinker/teetotaller now?" Those who answered "yes" were coded as 0 units of alcohol. No distinction was made between former drinkers and never drinkers of alcohol. Those who answered "no" were asked further questions to quantify the amount of alcoholic drinks consumed each week. One unit of alcohol consumption was defined as follows for four types of alcoholic drink: half pint of beer, lager or cider; a glass of wine; a glass of spirits (whisky, gin, brandy, vodka, etc.); and a glass of sherry, port, vermouth or liqueurs. Participants were asked to tick each category based on their average alcohol consumption in the previous year. Average alcohol consumption in units/week was calculated and used for analysis.

2.2.1.4. Menopausal and Menstrual history

For women, additional information such as age at menarche, menopausal status, use of hormone replacement therapy and use of contraceptives were obtained. For this thesis, the use of hormone replacement therapy was categorised into three groups: never, former and current. This was based on the responses to questions: `Have you ever received any hormone replacement therapy?' and `Are you currently taking this treatment?'.

2.2.2. Physical activity questionnaire

Physical activity was assessed using the self-completed EPAQ2 questionnaire that collects data on past year's physical activity behaviours in a disaggregated way. The information obtained by this questionnaire can be re-aggregated according to the dimension of physical activity of interest [109]. The questionnaire consists of four sections: activity in and around the home, during work, transportation to work, and recreational physical activity (please see Appendix 2). With work here we meant being in paid employment or doing regular, organised voluntary work. All transportation and some domestic questions were designed specifically for this study, whereas the questions on occupational activity were derived from the Modified Tecumseh Occupational Activity Questionnaire that has been validated elsewhere [110]. The recreational section of the EPAQ2 was derived from the Minnesota Leisure Time Activity Questionnaire [111], with 30 predetermined sports selected according to their frequency and duration in a UK population (The Sports Council and The Health Education Authority, 1992) and six non-sportive activities, such as mowing the lawn, watering the lawn, digging, weeding, DIY (Do It Yourself; e.g. carpentry, home or car maintenance), and playing music, which are considered as activities undertaken in or around the home. Time spent

participating in recreational activities was derived from responses to frequency and usual time per episode separately for each activity. The questionnaire can be accessed online (http://www.srl.cam.ac.uk/epic/questionnaires/epaq2/epaq2.pdf). The questionnaire was validated against an objective measure of energy expenditure (4-day heart-rate monitoring with individual calibration on four separate occasions over 1 year), and the repeatability of the questionnaire has also been demonstrated [109]. Intensity of physical activity in different domains was calculated by summing energy expenditure derived from applying published metabolic equivalent (MET) values to usual time spent in all activities and is expressed as MET-hours per week (MET.h/wk) [112].

2.2.3. Clinical measurements

Participants in both first and second health examinations were assessed by trained nurses and according to published protocols. All examinations from the first health check were repeated with the same devices and protocols in the second health check. Participants could choose to complete only selected examinations and there might be some errors in the performance and recording of the test results. Thus, the number of participants with complete data for different examinations might be different from the attended participants in the health check. *Table 2.1*: Number of participants with available data in two health examinations of EPIC-Norfolk study shows the number of participants with available data for analysis on different questionnaires and clinical tests in first and second health examinations.

Table 2.1: Number of participants with available data in two health examinations of EPIC-Norfolk study

	First Health Check (1HC)	Second Health Check	
		Attended 1HC	Total
Health & lifestyle questionnaire	25,639	15,028	15,786
EPAQ2 questionnaire	-	14,785	15,515
Anthropometry measures	25,043	15,000	15,758
Spirometry	25,043	14,800	15,542
Bioelectrical impedance	-	14,800	15,548
Quantitative ultrasound	-	14,912	15,668

2.2.3.1. Anthropometry

Height and weight were measured in light clothing without shoes. Height was measured to the nearest millimetre using a stadiometer (CMS Weighing Equipment Ltd., London, UK). Weight was measured to the nearest 100 grams using calibrated digital scales (Salter Industrial Measurement Ltd., West Bromwich, UK). The same devices and protocols were used in both first and second health examinations. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters.

2.2.3.2. Spirometry

Respiratory function was assessed by forced expiratory volume in 1 second, FEV_1, using an electronic turbine spirometer (Micro Medical, Ltd., Rochester, UK). After a practice blow, two measurements were made with the subjects standing and looking forwards. The nurses made a subjective judgement of the participants' spirometry technique. The higher of the two values for FEV_1 were used for analysis. Forced vital capacity (FVC) and peak expiratory flow (PEF) were also recorded for all participants but only FEV_1 is reported in this thesis as the other measures did not add information beyond FEV_1. The machine was chosen for portability and simplicity in operation. The reproducibility was about 2.2% for FEV_1 and the device is assessed as having a comparable accuracy to the Vitalaograph spirometer [113]. Calibration was performed regularly in a weekly basis to ensure the accuracy and precision of both equipment and personnel.

2.2.3.3. Bioelectrical impedance analysis

In the second health examinations, body fat mass was estimated using a standard bio-impedance technique (Bodystat, Isle of Man, UK). This test measures the Resistance (Ω) to the flow of an externally applied electric current through the tissues. This method has previously been shown to be valid [114] and reliable [115]. Total body water and fat-free mass were calculated using the impedance index (height^2/resistance), body weight and resistance according to published equations (see Table 5 of Ref [116]). Fat mass was calculated as body weight minus fat-free mass. Percentage body fat (%BF) used in this thesis was fat mass expressed as percentage of total weight.

2.2.3.4. Quantitative ultrasound of the calcaneus

Quantitative ultrasound (QUS) provides information about the structure, elasticity, and strength of the bones [117, 118]. QUS devices measure broadband ultrasound attenuation (BUA; expressed in dB/MHz) and speed of sound (SOS; expressed in m/s). BUA is the rate of attenuation in the acoustic energy across a broad range of frequency and this attenuation is due to absorption and scattering of ultrasound in the bone and soft tissue. BUA is influenced by both density and structural parameters [119]. SOS is the ratio of propagation distance to the pulse transit time and is affected by bone density and elasticity. Most devices measure the calcaneus because of its accessibility. This is a trabecular skeletal site which has a generally higher metabolic turnover rate than cortical bone [120].

In the second health examination of EPIC-Norfolk, CUBA sonometers (McCue Ultrasonics, Winchester, UK) were used for all participants at least twice on each foot [77, 121]. The CUBA sonometer is a gel-coupled device. The mean of the measures (left and right foot) was used for analysis. Five machines were used, and each was calibrated daily with its physical phantom and monthly with a roving phantom and on one operator's calcaneus. Room temperatures were measured and recorded daily. There was no evidence for the effect of ambient temperature, machine, or machine drift on BUA measures [121]. The short-term coefficient of variation (CV) was 3.5%. Both BUA and SOS in EPIC-Norfolk have been reported to be strong predictors of hip and total fracture risk in men and women independently of known covariates [77].

2.3. Follow-up methods

The EPIC-Norfolk cohort is followed up by an established continuing system for ascertaining health endpoints. The entire cohort has been flagged with the NHS Central Register for death and admission to hospitals. Individuals were flagged for death certification at the UK Office of National Statistics (ONS), with vital status ascertained for the whole cohort. All deaths were also coded for cause of death by trained nosologists using the International Classification of Disease (ICD) revisions 9 and 10. Participants who were admitted to hospital were identified using their unique NHS number by data linkage with ENCORE (East Norfolk health authority database), which identifies all hospital contacts throughout England and Wales for Norfolk residents. Hospital admissions are coded for different diagnoses using the ICD revisions 9 and 10. These diagnostic codes were used to ascertain fractures by site occurring (ICD codes – 9^{th}: 805-829 excluding 815, 816, 825, and 826; ICD codes – 10^{th}: S12, S22, S32, S42, S52, S62, S72, S82, S92 excluding S62.2-S62.8 and S92.3-S92.9). Fractures of skull, face, metacarpals, metatarsals, and phalanges were excluded from the analyses. Records are updated annually via data linkage. In this thesis, available updated records are between March 2006 and March 2008 depending on the time of analysis for each Chapter.

2.4. Statistical methods

Detailed analysis plans for each study are described in the Methods sections of each Chapter. In general, I have used survival analysis using Cox proportional-hazards regression models to look at the association between different risk factors and prospective risk of fractures. Categorising different exposures based on quartiles or sensible clinical cut-offs has been used to improve the power for finding risk trends across the range of values. Given the potentially different nature of risk associations for osteoporotic fractures between men and women, and the power of our studies to detect such differences, I have used sex-specific analyses unless otherwise stated. All multivariable models are adjusted for established risk factors of osteoporosis available in our study, including age, previous history of fracture, body mass index, smoking status, and alcohol intake. Other risk factors have been tested and, if significantly contributed to the models, reported for different studies. Apart from the height loss study (Chapter 3), all the analyses were performed using Stata software, version 10.0. A value of $P<0.05$ was used for statistical significance throughout the thesis.

Multivariable fractional polynomial modelling has been used in Chapters 6 and 7 to search for non-linear associations between risk factors and fracture outcomes. Fractional polynomial (FP) modelling is based on simple power transformations of covariates when non-linearity is suspected. Royston and Altman [122] formalised the simple power models and called them fractional polynomials of degree 1 (FP1), and extended them to FPs of higher degree. An FP1 transformation of a covariate (x) in the regression model with power p is defined as x^p, where p belongs to the set of powers $S = [-2, -1, -0.5, 0, 0.5, 1, 2, \text{and } 3]$. x^0 (i.e. with power $p = 0$) equals the natural log of x rather than 1. An FP1 function or model is defined as:

$$\varphi_1 (x, p) = \beta_0 + \beta_1 x^p$$

For instance, for $p = -2$ the model is $\beta_0 + \beta_1 / x^2$. A second-degree fractional polynomial (FP2) transformation of x with powers $\mathbf{p} = (p_1, p_2)$, or for $p_1 = p_2$ (called 'repeated powers') (p_1, p_1), is the vector $x^{\mathbf{p}}$ with:

$$x^{\mathbf{p}} = x^{(p1,p2)} = \begin{cases} (x^{p1}, x^{p2}), & p_1 \neq p_2 \\ (x^{p1}, x^{p1} \log x), & p_1 = p_2 \end{cases}$$

An FP2 function or model with parameter vector $\beta = (\beta_1, \beta_2)$ and powers $\mathbf{p}$ is:

$$\varphi_2(x, \mathbf{p}) = \beta_0 + \beta x^{\mathbf{p}} = \beta_0 + \beta_1 x^{p1} + \beta_2 x^{p2}$$

For instance, for $p_1 = 2$ and $p_2 = -1$ the model is $\beta_0 + \beta_1 x^2 + \beta_2 / x$. Likewise, for $p_1 = p_2 = 2$ the model is $\beta_0 + \beta_1 x^2 + \beta_2 x^2 \log x$. The set S includes the straight line (i.e. no transformation, p = 1), and the reciprocal, logarithmic, square root, and square transformations. Even though the set is small, the powers offer a considerable flexibility. In practice, the families of eight FP1 and 36 FP2 functions provide a good fit to many biomedical datasets, and higher-order functions are rarely needed [123].

Typically, FP models are fitted by maximum likelihood. Since an FP model is linear in transformed x for any power(s) $\mathbf{p}$, maximum likelihood estimation amounts to finding the β which maximizes the likelihood of models with linear predictors $\beta_0 + x^{\mathbf{p}} \beta$. For a given class (FP1 or FP2), this is done for each possible $\mathbf{p}$ with powers in S. The best fitting model is the one whose $\mathbf{p}$ gives the highest likelihood. For the FP1 class, eight models must be fit, whereas 36 models are examined for FP2.

For hypothesis testing, all tests are based on χ^2 statistics from deviance differences. Deviance, also known as the entropy of a model, is defined as minus twice the maximised log likelihood (–2 × log likelihood). The best FP1 model for x is that with the smallest deviance among the eight models with one power term.

Similarly, the best FP2 model is that with the lowest deviance among all 36 possible pairs of powers from *S*. As all FP1 models are nested within a second-degree one, the deviance of the latter is guaranteed to be smaller. The deviance difference between best-fitting FP2 model and best-fitting FP1 model as well as the deviance difference between best-fitting FP1 model and linear model is calculated and compared with the 95th percentile of χ^2 distribution with relevant degrees of freedom. Ignoring the 1 degree of freedom (d.f.) for the intercept β_0, an FP model of degree m is considered to have $2m$ d.f.: 1 d.f. for each β and 1 d.f. for each power. Hence, for comparison of FP2 and FP1 best-fitting models the χ^2 distribution with 2 d.f. will be considered and for comparison of best-fitting FP1 and linear model 1 d.f. will be considered. Using this algorithm, if FP2 model is not significantly more predictive than FP1 model, the FP1 model will be preferred and compared to linear model. If the deviance difference between FP1 best-fitting model and linear model is also not significant, the linear model will be chosen as the best fitting model.

This method has been extended to multivariable modelling and has been implemented in several statistical packages, including Stata version 9 and later. In Chapters 6 and 7, I have used this method using the 'mfp' command in Stata to look for the non-linear associations between physical activity as well as body fat mass and risk of fractures.

Chapter 3: Measured Height Loss

The work presented in this Chapter has been published in:

Moayyeri A, Luben RN, Bingham S, Welch A, Wareham NJ, Khaw KT. Measured height loss predicts fractures in middle aged and older men and women: the EPIC-Norfolk prospective population study. Journal of Bone and Mineral Research 2008 Mar;23(3):425-32

Please see Appendix 3.

3.1. Abstract

Height change can be easily measured and may contribute to fracture risk prediction. We assessed measured height loss and fracture incidence in the Norfolk cohort of the European Prospective Investigation into Cancer (EPIC-Norfolk). In this prospective population study, height was measured in first health check (1993-1997) and repeated (1998-2000) with the same device and protocols. Incident fractures up to 2006 were ascertained by hospital record linkage. In 14,921 men and women aged 42-82 years, during a mean follow-up period of 7.1 years, there were 390 fractures, including 122 hip fractures. Prior annual height loss in those who had an incident fracture (1.8 ± 0.3 mm) was significantly greater than other participants (0.9 ± 0.2 mm; $p<0.001$). Participants with annual height loss >0.5 cm had an age and sex adjusted hazard ratio of any fracture of 1.76 (95%CI 1.16-2.67) and of hip fracture of 2.08 (95%CI 1.07-4.05) compared to those with no height loss. Each centimetre per year height loss was associated with a hazard ratio of 1.86 (95%CI 1.28-2.72) for all fractures and 2.24 (95%CI 1.23-4.09) for hip fracture after adjustment for age, sex, past history of fracture, smoking, body mass index, alcohol intake, and heel ultrasound measures. Annual height loss of 1 cm was comparable to having a past history of fracture and equivalent to being about 14 years older in chronological age in terms of the magnitude of relationship with fracture risk. In conclusion, middle-aged and older men and women with annual height loss >0.5 cm are at increased risk of hip and any fracture. Serial height measurements can contribute to fracture risk prediction.

3.2. Introduction

Height loss is a frequent manifestation among the elderly and is simple to evaluate in the clinical settings. Several non-pathological mechanisms have been proposed for height loss associated with age such as changes in the vertebral body shape and height, loss of inter-vertebral disc height, and postural changes [124]. Previous studies have shown that, when compared to the recalled height at the third decade of life, historical height loss is a risk factor for osteoporotic fractures in the elderly [125-133]. Most of these studies showed the association between height loss and vertebral fractures [127, 129, 132, 133]. However, whether serial measurements of height in the shorter term can improve fracture risk prediction in middle-aged and older people has not been established prospectively. The relationship between height loss and fractures other than vertebral is also uncertain [125, 126, 128, 130]. In this study, we aimed to examine the association between recent height loss, as measured in two visits of EPIC-Norfolk study, and incident fractures.

3.3. Methods

The detailed design and operation of the EPIC-Norfolk study have been described in Chapter 2. In this study, participants who attended both first and second health examinations were considered. In first and second visits, height was measured to the nearest 0.1 cm using the same stadiometer (CMS Weighing Equipment Ltd., London, UK). Weight was measured using Salter digital scales and body mass index (BMI) was calculated as weight (in kilograms) divided by height squared (in meters). Smoking status, weekly alcohol intake, and use of hormone replacement therapy (HRT) in women were derived from the health and lifestyle questionnaires in the second health check. Quantitative ultrasound of the calcaneus was measured in the second health examination.

To assess the prospective impact of height loss on fractures, participants who had developed a fracture between two visits were excluded from the analysis. We used diagnostic codes to ascertain fractures by site occurring in the cohort up to the end of July 2006 for present analyses, a mean follow-up time from the second visit of 7.1 years (SD 0.7; range 5.8–8.5 years).

Characteristics of those who had developed fracture after second visit were compared with other participants using student t-tests for continuous variables and chi-square test for categorical variables. Alcohol intake was not normally distributed and was compared between two groups using Mann-Whitney U test. We also compared the characteristics of the subset of individuals who had a hip fracture with other participants. Height loss and known risk factors of fracture were entered into a Cox proportional-hazards model to determine their independent contribution to the risk of fracture. Clinically applicable cut-offs were used to categorise patients based on their annual height loss and hazard ratios for these categories were calculated in comparison to the group with no height change. A value of $P<0.05$ was used for statistical significance. Values are expressed as mean ± SD unless otherwise stated. Sex-specific analyses were performed using SPSS for Windows Version 14 (SPSS Inc., Chicago, Illinois).

3.4. Results

3.4.1. Characteristics of the study participants

After exclusion of fracture sufferers between two visits, 14,921 participants were entered into the analysis. *Table 3.1* summarises the characteristics of this population. There were significant differences between men and women for the descriptive variables and sex-specific analyses were used throughout this Chapter. The interval between two visits was 3.7 ± 0.7 years on average and participants were followed for 103,136 person-years after the second visit. 390 fractures of any type (122 hip fractures, 69 vertebral fractures, 99 wrist fractures, and 100 other types including ribs, sternum, clavicle/scapula, humerus, pelvis, shaft/distal femur, patella, tibia/fibula, and ankle fractures) occurred in the study period. In women, the incidence of hip fracture and any fracture were 145.2 and 467.3 per 100,000 person-years, respectively. The corresponding numbers for men were 77.7 and 251.6 per 100,000 person-years, respectively. On average, fractures occurred 4.0 years (SD 2.1) after the second visit.

Table 3.1: Characteristics of 14,921 men and women aged 40-79 years at baseline and follow up visit and fracture rates 1998-2006

	Women n=8,381	Men n=6,540
First visit 1993-1997		
Age (years)	57.9 (8.9)	59.3 (8.9)
Height (cm)	161.3 (6.1)	174.2 (6.5)
Weight (kg)	67.4 (11.3)	80.1 (10.9)
Body Mass Index (kg/m2)	25.9 (4.1)	26.4 (3.1)
Past history of any fracture	620 (7.4%)	373 (5.7%)
Smoking (Current)	758 (9.0%)	608 (9.3%)
(Former)	2612 (31.2%)	3544 (54.2%)
(Never)	4939 (58.9%)	2340 (35.8%)
Alcohol intake (units/week)	4.6 (5.6)	10.2 (11.6)
Second visit 1998-2000		
Age (years)	61.6 (9.0)	62.9 (9.0)
Height (cm)	160.9 (6.2)	173.9 (6.6)
Weight (kg)	68.7 (11.8)	81.4 (11.5)
Body Mass Index (kg/m2)	26.5 (4.4)	26.9 (3.3)
Smoking (Current)	672 (8.0%)	515 (7.9%)
(Former)	2725 (32.6%)	3651 (56.1%)
(Never)	4955 (59.3%)	2345 (36.0%)
Alcohol intake (units/week)	4.5 (5.7)	9.8 (11.4)
Height change (mm)	5.2 (6.6)	4.6 (6.0)
Height change per year (mm)	1.0 (2.4)	0.8 (2.3)
BUA (dB/MHz)	72.2 (16.5)	90.1 (17.5)
SOS (m/sec)	1624.8 (40.2)	1645.3 (39.9)
Fracture (any type)	274 (3.3%)	116 (1.8%)
Fracture (hip)	86 (1.0%)	36 (0.6%)

Continuous variables are reported as mean (standard deviation in parenthesis)
BUA: broadband ultrasound attenuation; SOS: speed of sound

3.4.2. Height loss and fractures

When characteristics of participants with and without fracture were compared (*Table 3.2*), height loss was significantly higher in the group of fracture sufferers. Annual height loss was almost double in men and women with any fracture compared to those without fracture and differences were even greater for the subgroup of patients with hip fracture. Patients with fractures were significantly older and a higher proportion reported a past history of fracture. Hormone replacement therapy (both current and former) was associated with lower fracture risk in women. Ultrasound measures were significantly lower in men and women with any or hip fracture in comparison to other participants. While women with hip or any type of fracture had significantly lower consumption of alcohol, this pattern was not observed for men. Other variables (height, weight, BMI, and smoking) were not different between two groups (*Table 3.2*).

Participants were categorised according to their annual height loss into three groups (no change, 0.1-0.5 cm annual height loss, and >0.5 cm annual height loss). Patients with higher height measurement in the second visit (2565 cases) were included in the no change group. Fracture incidence was higher in the group with >0.5 cm height loss per year with an age and sex adjusted hazard ratio of any fracture of 1.76 (95%CI 1.16-2.67) and of hip fracture of 2.08 (95%CI 1.07-4.05) compared to those with no height loss. These differences were apparent in subgroups stratified by sex and age groups <60, 60-69, and ≥70 years (*Figure 3.1*). In women, the fracture incidence in those with no height loss compared to those with annual height loss of >0.5 cm were 222 and 499 per 100,000 person-years, respectively, in those aged <60 years and 997 to 1291 per 100,000 person-years, respectively, in those aged >70 years. A similar pattern was apparent in men with fracture incidence of 160 and 309 per 100,000 person-years, respectively, in those <60 years and 260 and 737 per 100,000 person-years, respectively, in those >70 years. While in *Figure 3.1* there is a suggestion that the association between height loss and fractures may be modified by age group and sex, none of age-sex interactions were statistically significant.

Table 3.2: Comparison of baseline characteristics of those who subsequently had any incident or only hip fracture

		No Fracture	Any Fracture	P value	Hip Fracture	P value
Women						
N		8,107	274		86	
Age (years)		57.7 (8.9)	63.9 (8.2)	<0.001	67.0 (7.2)	<0.001
Height (cm)		161.3 (6.1)	160.5 (5.9)	0.05	160.6 (5.9)	0.27
Weight (kg)		67.4 (11.3)	66.5 (10.6)	0.18	65.2 (10.2)	0.07
Body Mass Index (kg/m^2)		25.9 (4.1)	25.8 (3.9)	0.63	25.2 (3.6)	0.14
Past history of any fracture		567 (7.0%)	53 (19.3%)	<0.001	19 (22.1%)	<0.001
Smoking	(Never)	4769 (59.3%)	170 (62.5%)	0.57	56 (65.1%)	0.53
	(Current)	736 (9.2%)	22 (8.1%)		6 (7.0%)	
	(Former)	2532 (31.5%)	80 (29.4%)		24 (27.9%)	
Alcohol intake (units/week)		2.5	1.5	0.003	1.3	0.008
HRT	(Never)	5390 (66.5%)	206 (75.5%)	0.007	73 (84.9%)	0.001
	(Current)	1742 (21.5%)	40 (14.7%)		6 (7.0%)	
	(Former)	968 (11.9%)	27 (9.9%)		7 (8.1%)	
Height change (mm)		3.6 (8.3)	6.8 (9.5)	<0.001	9.3 (10.4)	<0.001
Height change per year (mm)		1.0 (2.4)	1.9 (2.7)	<0.001	2.5 (2.9)	<0.001
BUA (dB/MHz)		72.5 (16.4)	62.7 (16.1)	<0.001	56.4 (16.1)	<0.001
SOS (m/sec)		1625.6 (40.0)	1601.4 (39.2)	<0.001	1589.3 (37.8)	<0.001
Men						
N		6,424	116		36	
Age (years)		59.3 (8.9)	61.8 (9.1)	0.003	67.3 (6.9)	<0.001
Height (cm)		174.2 (6.5)	175.0 (6.7)	0.17	174.2 (6.5)	0.54
Weight (kg)		80.1 (10.9)	82.3 (10.9)	0.03	81.6 (12.2)	0.41
Body Mass Index (kg/m^2)		26.4 (3.1)	26.9 (3.2)	0.09	27.1 (3.9)	0.16
Past history of any fracture		361 (5.6%)	12 (10.3%)	0.03	6 (16.7%)	0.004
Smoking	(Never)	2301 (36.1%)	39 (33.9%)	0.39	14 (38.9%)	0.84
	(Current)	593 (9.3%)	15 (13.0%)		4 (11.1%)	
	(Former)	3483 (54.6%)	61 (53.0%)		18 (50.0%)	
Alcohol intake (units/week)		6.5	7.7	0.58	5.7	0.69
Height change (mm)		3.0 (8.1)	5.5 (9.1)	0.001	7.5 (1.1)	0.001
Height change per year (mm)		0.8 (2.3)	1.5 (2.6)	0.001	2.0 (2.8)	0.003
BUA (dB/MHz)		90.2 (17.5)	83.1 (17.2)	<0.001	80.0 (18.3)	0.001
SOS (m/sec)		1645.7 (39.7)	1622.7 (40.9)	<0.001	1610.4 (46.6)	<0.001

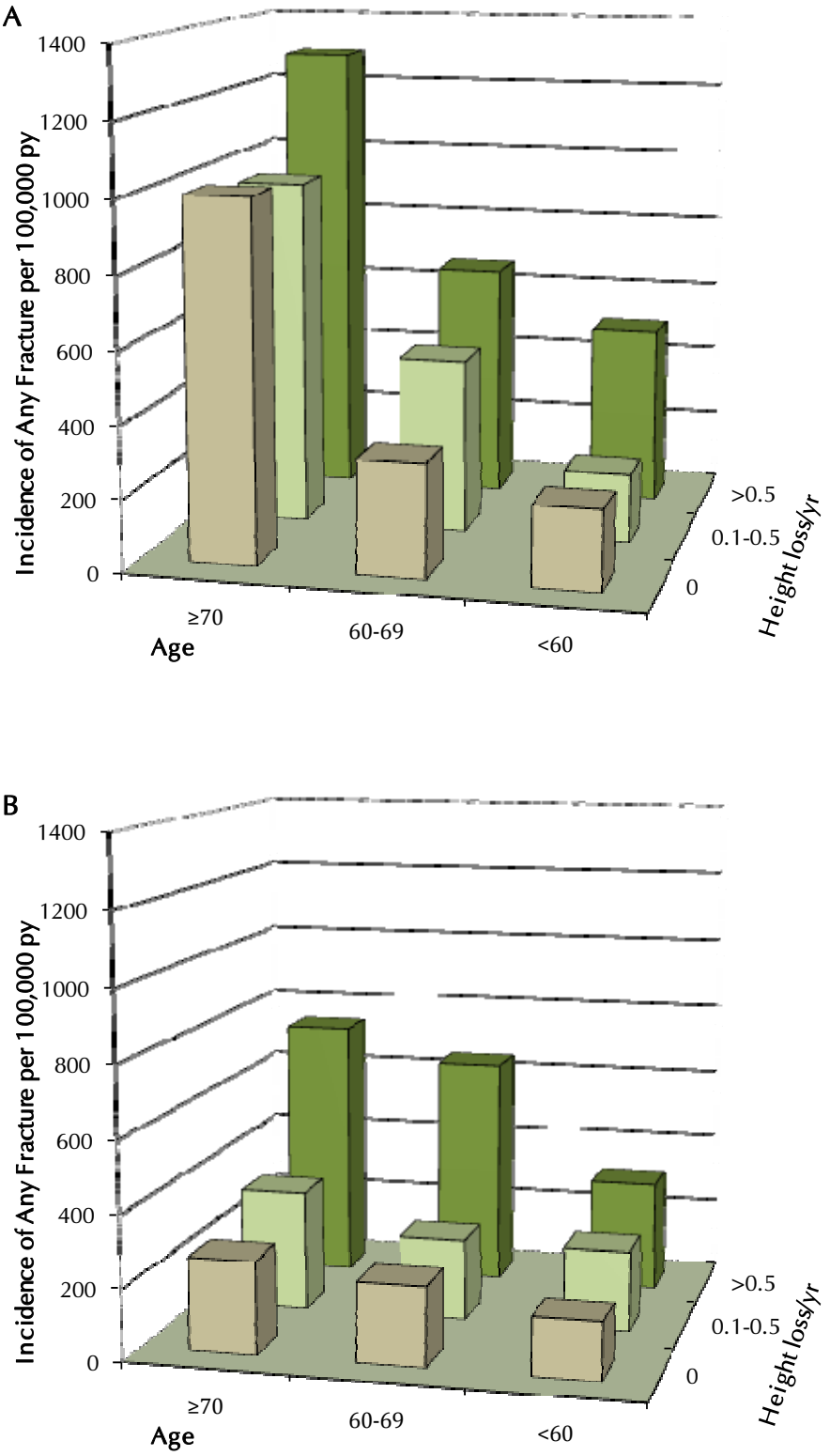

Figure 3.1: Incidence rate of any fracture among 8,381 women (A) and 6,540 men (B) according to the categories of age (years) and annual height loss (cm)

3.4.3. Height loss as a predictor of fractures

For Cox proportional-hazards models, we further categorised participants with >1 cm annual height loss to create four categories for height loss. Results of the analyses are summarised in *Table 3.3*. Compared to those who had not lost height, participants with height loss of >1 cm had a significantly higher risk of developing fractures and this risk remained significant after adjustment for other variables including age, sex, past history of fracture, smoking, BMI, alcohol intake, and heel ultrasound measures. Sex-specific analysis showed a similar pattern of risk in men and women. Models for hip fracture showed higher hazard ratios but with larger confidence intervals given the lower number of events (*Table 3.3*).

When height loss was entered to the model as a continuous variable (*Table 3.3*, right column), it remained a significant risk factor of both any fracture and hip fracture in the multivariate model. The hazard ratios of annual height loss for vertebral (1.48; 95 CI 0.57-3.86) and wrist fractures (1.57; 95 CI 0.73-3.38) were in a similar direction but not statistically significant. *Table 3.4* shows the Cox proportional-hazards model for any type of fracture in all male and female participants. Annual height loss (as a continuous variable), age, past history of fracture, and BUA were the significant predictors of any fracture in this model. The hazard ratio for any fracture was 1.86 (95% CI 1.27-2.71) for every 1 cm height loss per year. Table 4 shows that 1 cm height loss per year is comparable to past history of fracture and equivalent to being about 14 years older in chronological age in terms of magnitude of relationship with future fracture risk. The effect of 1 cm annual height loss on fracture risk was also equivalent to about 30 dB/MHz decrease in BUA, which is nearly two times the standard deviation of BUA among our participants. The sex differential in future fracture risk was not apparent after inclusion of BUA into the model. Further analyses excluding the 993 men and women who had a past history of fracture gave consistent results with a hazard ratio of 1.81 (95% CI 1.17-2.79) for any fracture per 1 cm annual height loss.

Table 3.3: Hazard ratios (95% CI in parentheses) of annual height loss for incident fractures in EPIC-Norfolk study, 1998-2006

		Annual height loss (centimeters)				
		Categorical				Continuous
		0	0.1-0.5	0.6-1.0	>1.0	Per 1 cm
All		**N=5,313**	**n=8,991**	**n=557**	**n=60**	**n=14,921**
Any Fracture	N (%)	104 (2.0%)	252 (2.8%)	27 (4.8%)	7 (11.7%)	
	Age & sex-adjusted HR	1	1.10 (0.87-1.39)	1.56 (1.01-2.40)	3.20 (1.48-6.95)	2.09 (1.44-3.02)
	Multivariable-adjusted HR*	1	1.06 (0.84-1.34)	1.37 (0.89-2.12)	2.93 (1.34-6.39)	1.86 (1.28-2.72)
Hip Fracture	N (%)	26 (0.5%)	80 (0.9%)	13 (2.3%)	3 (5%)	
	Age & sex-adjusted HR	1	1.13 (0.72-1.77)	2.05 (1.04-4.05)	3.38 (1.01-11.3)	2.64 (1.48-4.71)
	Multivariable-adjusted HR*	1	1.05 (0.67-1.65)	1.66 (0.83-3.30)	2.95 (0.87-9.99)	2.24 (1.23-4.09)
Women		**N=2,895**	**n=5,101**	**n=345**	**n=40**	**n=8,381**
Any Fracture	N (%)	70 (2.4%)	180 (3.5%)	19 (5.5%)	5 (12.5%)	
	Age-adjusted HR	1	1.05 (0.79-1.39)	1.25 (0.75-2.10)	2.29 (0.91-5.72)	1.86 (1.20-2.87)
	Multivariable-adjusted HR*	1	0.99 (0.75-1.32)	1.08 (0.64-1.83)	2.15 (0.85-5.41)	1.64 (1.05-2.56)
Hip Fracture	N (%)	17 (0.6%)	57 (1.1%)	10 (2.9%)	2 (5%)	
	Age-adjusted HR	1	1.15 (0.67-2.00)	2.00 (0.90-4.45)	2.55 (0.58-11.2)	2.52 (1.30-4.90)
	Multivariable-adjusted HR*	1	1.02 (0.58-1.78)	1.52 (0.68-3.43)	2.11 (0.47-9.44)	2.03 (1.01-4.05)
Men		**N=2,418**	**n=3,890**	**n=212**	**n=20**	**N=6,540**
Any Fracture	N (%)	34 (1.4%)	72 (1.9%)	8 (3.8%)	2 (10%)	
	Age-adjusted HR	1	1.20 (0.79-1.82)	2.26 (1.03-4.95)	6.25 (1.49-26.2)	2.69 (1.31-5.52)
	Multivariable-adjusted HR*	1	1.16 (0.76-1.76)	2.05 (0.93-4.51)	4.59 (1.07-19.7)	2.16 (1.05-4.43)
Hip Fracture	N (%)	9 (0.4%)	23 (0.6%)	3 (1.4%)	1 (5%)	
	Age-adjusted HR	1	1.09 (0.50-2.37)	1.96 (0.52-7.35)	6.63 (0.83-53.1)	2.66 (0.79-8.90)
	Multivariable-adjusted HR*	1	1.05 (0.48-2.31)	1.59 (0.42-6.04)	5.67 (0.67-47.7)	2.24 (0.65-7.66)

*Variables in the equation: age, body mass index, smoking habit, alcohol intake, past history of any fracture, broadband ultrasound attenuation (and history of hormone replacement therapy for women)

Table 3.4: Cox proportional-hazards model to predict any type of fracture among 14,921 EPIC-Norfolk participants

	Cox β coefficient	Hazard Ratio	95% Confidence Interval
Height change (cm/year)	0.623*	1.86	1.27-2.71
Age (years)	0.045*	1.05	1.03-1.06
Sex (male)	-0.250	0.78	0.60-1.02
Past history of any fracture (yes)	0.662*	1.94	1.47-2.55
Body Mass Index (kg/m^2)	0.008	1.01	0.98-1.03
Smoking (current)	-0.199	0.82	0.57-1.18
Alcohol intake (units/week)	0.002	1.00	0.99-1.02
BUA (per 15 dB/MHz)	-0.309*	0.73	0.66-0.81

* Statistically significant at level of $p<0.05$

3.5. Discussion

Height change is an easily measured variable that can help identify those at increased risk of future fractures. Those with height loss greater than 1 cm/year compared to those with no height loss were at nearly three-fold increased risk of future fracture, after adjustment for age, sex, past history of fracture, body mass index, smoking, alcohol intake, and hormone replacement therapy use (in women). Intriguingly the relationship was also independent of bone characteristics as assessed by heel ultrasound and suggests that some mechanisms other than simply lower bone density may play a role here. This study indicates that middle aged and older men and women with a height loss of more than 2 cm in a 4 year period (i.e. 0.5 cm annual height loss) are at increased risk of fractures.

Generally, stature decreases with age through several non-pathological mechanisms such as changes in vertebral body shape and height, loss of inter-vertebral disc height, and postural changes [124]. The magnitude of this height loss is variable and unpredictable. All types of vertebral deformity (crush, wedge and biconcave deformities) are associated with height loss with crush deformity being the most hazardous one [134]. The pathophysiology of these deformities and their relation to osteoporosis are still uncertain. A potential explanation for the contribution of these deformities to the increased risk of non-spine fractures might be their relationship to the risk of falls among older people. Falling is the strongest known risk factor of non-spine fractures [135, 136] and its attributable risk for fracture is considered to be even more than established osteoporosis [137]. Kyphosis, inter-vertebral disc degeneration and other postural changes can be considered as general indicators of frailty among the elderly. Poor muscle strength, poor movement, and poor balance in frail individuals may lead to increased risk of falling and fractures. We could not, however, evaluate this hypothesis in our study as we have not measured the incidence of injurious or total falls in our population.

Height loss may also result from vertebral fractures that are highly related to osteoporosis [127, 129, 132, 133]. As trabecular bone in the spine becomes more porous, vertebral fractures occur and cause the vertebrae to collapse or curve forward resulting in a loss of height [134, 138]. However, only a small proportion of these fractures come to medical attention [139]. A weakness of the present study is that we had only access to clinically apparent vertebral fractures, which are likely to be a small fraction of the actual vertebral fractures in our population (considering the low number of these fractures comparing to hip fractures). As no spinal X-rays were performed at baseline or follow-up visits, we cannot be sure of how far non-clinically apparent vertebral fractures could account for the association between height loss and other clinical fractures. Nevertheless, people in the general population are not routinely screened by X-rays for vertebral fractures. Whatever the mechanism for the relationship, this study suggests that measured height loss may be a clinically useful early indicator of future clinically evident vertebral and non-vertebral fractures.

Osteoporosis is defined as a systemic disease with two main characteristics: low bone density and low bone quality [1]. Currently there is no simple way to assess and quantify bone quality and our knowledge about osteoporosis comes mainly from bone density. Dual-energy X-ray absorptiometry (DXA) is the standard method of measurement of bone mineral density (BMD) and current diagnostic criteria for osteoporosis are mainly based on this measure. However, QUS is an emerging alternative method due to its affordability and comparable predictive power. The diagnostic sensitivity of ultrasound measurement of the calcaneus in the prediction of hip fracture has been shown to be similar to hip BMD measured with DXA and superior to spine BMD [140]. QUS provides comparable diagnostic sensitivity to spine BMD in vertebral fractures and there is a general consensus that both bone quality and bone density have effects on QUS measures [140]. People with lower BMD as assessed by DXA lose height substantially faster than those with higher BMD [141-143]. The current study, however, did not show such an association between height loss and BUA measures. The correlation coefficient was 0.11 among our participants. Since the hazard ratio of

annual height loss for any fracture remained significant after inclusion of BUA into models, our study suggests that height loss may provide some additional information predicting fracture risk that may improve predictive models for fracture risk assessment.

Previous studies evaluating the role of height loss on fractures were mostly restricted to postmenopausal women [126, 129, 131-133, 144-147]. Although osteoporosis is more common in women, men are, with a time lag, also affected and morbidity and mortality after osteoporotic fractures appears to be more serious in men than in women [148]. However, there is a general paucity of prospective data on fracture risk in men. Moreover, retrospective assessment of height loss using self-reported maximum lifetime height, which is used in most of these studies [126, 129, 131-133, 146, 147, 149], is prone to recall bias. Relying on an older person's memory to remember an exact number after more than 30 years may not be practical and the choice of cut-off for clinical application based on these figures is highly inconsistent [144, 149].

Few prospective studies have evaluated the role of measured exact height loss in the elderly on incident vertebral fractures [144, 145, 150]. Some retrospective studies have found a significant relationship between stature loss and hip fracture and other fragility fractures [125, 128, 130]. The current study confirms the role of height loss as an independent risk factor for osteoporotic fractures. The pattern of this relationship seems to be very similar between men and women. Height loss is probably an indicator of vertebral bone loss and might therefore be expected to be most strongly predictive for future vertebral fractures. However, height loss was in fact predictive of fractures at all sites, and in particular hip fractures, representing that it is a good indicator of bone health in general.

It might be argued that measurement of height loss in clinical settings is not an easy and straightforward task. Accurate and precise stadiometers might not be available in some clinics and clinicians need to consider other factors like general health status of the patients or the time of measurement of height (given the diurnal variations of height) [151]. However, availability and feasibility of height

measurement in the clinical setting is an unquestionable advantage over other modalities for assessment of bone health and clinicians can benefit considerably from useful information derived from simple height measurement for making more knowledgeable decisions for their patients. Moreover, when viewed in the context of family practice, detection of 2 cm height loss over a period of 4 years (rapid height losers with >0.5 cm per year) is quite achievable for all practices and even with less precise stadiometers. Therefore, height registration by the units of millimetres can be recommended for general practices.

Possible limitations of this study include incomplete ascertainment of fractures as not all fractures are admitted to hospital. The distribution of fractures among our population seems to be skewed toward hip fracture in comparison to wrist and vertebral fractures. Nevertheless, hospital admissions are likely to reflect fractures which have the most clinical impact [2]. There are also likely to be some potential errors in height measurement including assessment in different times of the day by different measurers. However, these random errors are more likely to attenuate any associations between exposure and outcomes. We were able to measure height change in about 15,000 participants who attended the second visit out of about 25,000 baseline participants. Although these participants at the second visit are likely to be healthier than non-respondents, bias in selection of healthier population is unlikely to explain our results as the relationship between height loss and fractures is unlikely to be in the opposite direction among non-respondents. Again, selection bias is more likely to attenuate findings in our study.

Identifying individuals at increased risk of fracture for targeted interventions has moved from simple threshold definitions of osteoporosis based on bone density measures to attempts to quantify absolute fracture risk. There is a general trend towards appreciation of clinical risk factors as important contributors to the fracture risk instead of bone density measures [152, 153]. However, there is still a paucity of population-based data as to which clinical risk factors may contribute most to absolute fracture risk charts. In this general population of middle-aged

and older men and women, the magnitude of increased fracture risk associated with height loss of 1 cm per year was comparable to having a past history of fracture and equivalent to being 14 years older in chronological age after adjustment for other known risk factors. This study suggests that height change may be an important and easily-measurable factor to help identify those at increased risk of fracture for preventive interventions and should be considered in fracture risk assessment tools for middle-aged and older people.

Chapter 4: Respiratory Function

The work presented in this Chapter has been published in:

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Please see Appendix 4.

4.1. Abstract

Identification of those at high risk of osteoporosis and fractures using clinically available tests beyond bone density measures is a major clinical challenge. We examined forced expiratory volume in 1 second (FEV_1), an easily obtainable measure of respiratory function, as a clinical measure for fracture prediction. In this EPIC-Norfolk study analysis, 8,304 women and 6,496 men aged 42-81 years underwent a health check including spirometry and heel quantitative ultrasonography between 1998 and 2000 and were followed up for incident hip fractures until 2007. The Main Outcome Measures were broadband ultrasound attenuation (BUA) of the heel (cross-sectional analysis) and hip fracture risk (prospective analysis). In multivariate regression models, 1 litre increase in FEV_1 was associated with a statistically significant 2.2 dB/MHz increase in BUA independent of age, smoking, height, body mass index, history of fracture and use of corticosteroids. Mean FEV_1 was significantly lower among 84 women and 36 men with hip fracture compared to other participants. In multivariate proportional-hazards regression models, the hazard ratio (HR) of hip fracture associated with 1 litre increase in FEV_1 was 0.5 (95% confidence interval, 0.3–0.9, $P<0.001$) for both men and women. HR of hip fracture for 1 SD increase in FEV_1 was approximately equivalent to 0.5 SD increase in BUA among women (1 SD among men) and about 5 years decrease in age among both men and women. In conclusion, middle-aged and older people with low respiratory function are at increased risk of osteoporosis and hip fracture. FEV_1, an easy, low cost and feasible clinical measure, may help improve the identification of high-risk groups.

4.2. Introduction

Projections suggest that, in the next few decades, numbers of fractures worldwide are likely to increase substantially [29]. Therefore, early identification of groups at high risk of fracture who may benefit most from preventive interventions is a major challenge [154]. Though low bone mineral density (BMD) is an established predictor of increased fracture risk, the majority of fractures occur in patients with BMD above the thresholds commonly used to diagnosis osteoporosis. Identification of other factors that independently predict fracture risk may not only help improve identification of high-risk groups, but also help understanding of the pathophysiology of the disease. A number of previous studies have suggested a link between respiratory function and BMD [155-157]. Some pathophysiologic mechanisms also plausibly support an association between pulmonary function and bone health. Apart from demographic and anthropometric factors like age, sex, and height, this association can be mediated via modifiable behavioural risk factors, namely physical activity and smoking [97, 158-160]. In this study, we investigated whether pulmonary function testing is associated with bone characteristics (as assessed by quantitative ultrasound measurement) and prospective risk of hip fracture.

4.3. Methods

This study is based on data from participants in the second health examination of EPIC-Norfolk study. Details of the recruitment and assessment procedures are described in Chapter 2. Briefly, in the second health examination in 1998-2000, 15,028 participants returned for a health visit and completed a self-administered health and lifestyle questionnaire. Respiratory function was assessed by forced expiratory volume in 1 second, FEV_1, using an electronic turbine spirometer (Micro Medical, Ltd., Rochester, UK). The higher of the two values for FEV_1 measurements were used for analysis. Forced vital capacity (FVC) and peak expiratory flow (PEF) were also recorded for all participants but only FEV_1 is reported here as the other measures did not add information beyond FEV_1. The reproducibility of the test was about 2.2% for FEV_1 and calibration was performed regularly in a weekly basis to ensure the accuracy and precision of both equipment and personnel [107].

Height and weight were measured during the health examination and body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Smoking status, weekly alcohol intake, current or ever use of corticosteroid drugs, bronchodilators, and hormone replacement therapy (HRT) as well as history of respiratory diseases were derived from the questionnaires. Quantitative ultrasound scanning was used to measure broadband ultrasound attenuation (BUA; db/MHz) and speed of sound (SOS; m/s) of the calcaneus with the use of the CUBA sonometer (McCue Ultrasonics, Winchester, UK). International Classification of Diseases (ICD) 9 and 10 diagnostic codes were used to ascertain fractures by site occurring in the cohort up to the end of March 2007 for present analyses, a mean follow-up time of 7.7 years (SD=0.8).

As bone characteristics differ considerably between men and women, sex-specific analyses were used throughout this Chapter. For assessment of the association between FEV_1 and QUS measures, characteristics of participants in four sex-specific quartiles of FEV_1 were compared using one-way ANOVA for continuous

variables and chi-square test for categorical variables. Assumption of normality was checked beforehand for all continuous variables. Pearson's correlation coefficients were estimated for the correlations between FEV_1 and ultrasound characteristics of the participants. Univariate general linear models were used to assess the linear trend of crude and adjusted BUA in different quartiles of FEV_1. To predict the sex-specific difference in BUA, multivariate linear regression models were run with FEV_1 with different levels of adjustment. The Wald test was used to test the significance of β coefficients. Pre-specified interactions between FEV_1 and other factors were checked. Regression models were rerun for different subgroups of participants.

To assess the predictive power of FEV_1 for incident osteoporotic fractures, characteristics of those who had developed hip fracture during the follow-up were compared with other participants. FEV_1 and known fracture risk factors were entered into a Cox proportional-hazards model to determine their independent contribution to the risk of fracture. Hazard ratios of hip fracture for sex-specific quartiles of FEV_1 were calculated in comparison to the lowest quartiles for men and women. FEV_1 was also entered into models as a continuous variable. To enable comparisons between FEV_1 and other continuous variables for prediction of fractures, we used intervals of approximately one standard deviation (0.5 litres). Goodness-of-fit for different models were verified graphically by comparison of Kaplan-Meier curves for observed and predicted values. A set of pre-specified interactions between FEV_1 and other factors was also checked, but not included in the final models due to non-significance. Values for continuous variables are expressed as mean ± SD throughout the Chapter unless otherwise stated. All the analyses were performed using Stata software, version 10.0 (StataCorp LP., College Station, TX, USA).

4.4. Results

4.4.1. Characteristics of the study participants

After exclusion of 228 participants with unsatisfactory spirometry (due to mechanical problems, poor cooperation, coughing, or recent abdominal or chest surgery), 8,304 women and 6,496 men aged 42-81 years comprised the study population. Characteristics of the study population are summarised in Table 1. Mean (SD) of FEV1 was 2.1 (0.5) litre among women and 2.6 (0.7) litre among men. Men had significantly higher bone measures (both BUA and SOS) and experienced a lower number of hip fractures during the follow-up. *Table 4.1* shows the significant differences between women and men regarding key variables, supporting the need for sex-specific analyses.

Table 4.1: Baseline characteristics of participants

		Women	Men	*P* value
		n=8,304	n=6,496	
Age (years)		61.6 (9.0)	62.9 (9.0)	<0.001
Height (cm)		160.9 (6.2)	173.9 (6.6)	<0.001
Weight (kg)		68.7 (11.8)	81.4 (11.5)	<0.001
Body Mass Index (kg/m^2)		26.5 (4.4)	26.9 (3.3)	<0.001
Smoking	(Current)	664 (8.0%)	515 (7.9%)	<0.001
	(Former)	2,697 (32.5%)	3,609 (55.6%)	
	(Never)	4,876 (58.7%)	2,326 (35.8%)	
Alcohol intake (units/week)*		2 (6)	6 (12)	<0.001
History of fracture		620 (7.5%)	375 (5.8%)	<0.001
History of corticosteroid use		263 (3.2%)	162 (2.5%)	0.015
FEV_1 (litre)		2.1 (0.5)	2.6 (0.7)	<0.001
BUA (dB/MHz)		72.2 (16.5)	90.1 (17.6)	<0.001
SOS (m/sec)		1,624.7 (40.2)	1,645.2 (40.0)	<0.001
Hip fracture†		84 (1.0%)	36 (0.6%)	0.002

Data are mean (standard deviation) or number of participants (percentage)
* Values are medians (inter-quartile range)
† Number of incident hip fractures up to March 2007

4.4.2. Respiratory function and quantitative ultrasound

Significant and positive correlations were observed between FEV_1 and BUA among both women (Pearson correlation coefficient r=0.32; P<0.001) and men (r=0.11; P<0.01). The corresponding coefficients for FEV_1 and SOS were 0.26 for women and 0.08 for men (P<0.01 for both). Age, height, and weight also significantly correlated with both FEV_1 and ultrasound measures. Given the high correlation of BUA and SOS in both women (r=0.72) and men (r=0.69), only BUA was used as the measure of bone health for further analyses.

Figure 4.1 shows the crude and adjusted means of BUA using generalised linear modelling approach among different quartiles of FEV_1 in both sexes. Multivariate-adjusted mean BUA was higher by 3.7 dB/MHz among women and 2.9 dB/MHz among men from first to fourth quartile of FEV_1. Although the magnitude of the difference was reduced after adjustment, there was still a significant linear trend for increment of BUA across quartiles of FEV_1. The trend of increasing BUA with increasing FEV_1 quartiles was more noticeable among women.

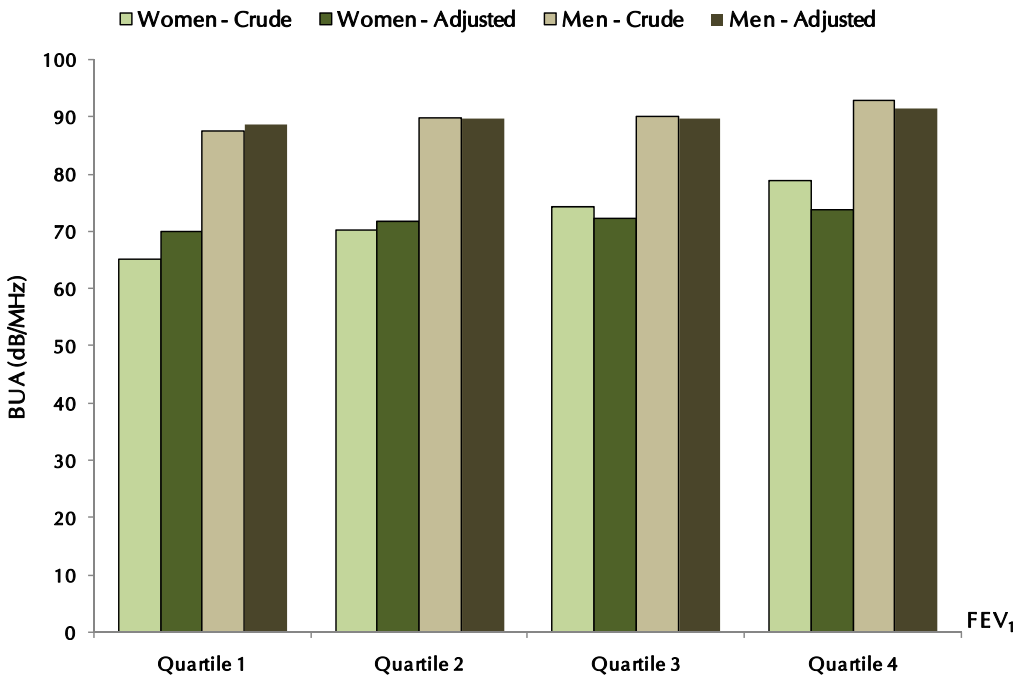

Figure 4.1: Crude and adjusted mean of BUA in quartiles of FEV_1 in EPIC-Norfolk
BUA measures are adjusted for age, smoking status, height, body mass index, past history of fracture, and use of corticosteroid using generalised linear models.

Results of the multivariate linear regression models to predict heel BUA are summarised in *Table 4.2*. A significant and positive relationship between FEV_1 and BUA, independent of age, smoking, height, BMI, history of fracture, and use of corticosteroids was observed among both men and women. In the multivariate models, a unit change in FEV_1 (1 litre) was associated with a statistically significant 2.21 dB/MHz difference in BUA among women and 1.47 dB/MHz difference in BUA among men. Excluding participants with self-reported respiratory disease or use of corticosteroids or bronchodilators did not materially alter the regression slopes (*Table 4.2*).

Table 4.2: Crude and adjusted regression coefficients (standard errors) of FEV_1 for prediction of calcaneal BUA

	Women			Men		
	N	β (s.e.)	*P value*	N	β (s.e.)	*P value*
Crude	8,304	10.08 (0.33)	<0.001	6,496	2.69 (0.11)	<0.001
Adjusted for age	8,304	3.12 (0.39)	<0.001	6,496	2.52 (0.36)	<0.001
Adjusted for age & smoking	8,183	3.13 (0.40)	<0.001	6,402	2.18 (0.36)	<0.001
Multivariate adjusted*	8,175	2.21 (0.41)	<0.001	6,391	1.47 (0.39)	<0.001
Multivariate adjusted*†	6,683	2.37 (0.47)	<0.001	5,396	1.31 (0.45)	0.003

* Adjusted for age, smoking status, height, body mass index, past history of fracture, and use of corticosteroids

† Excluding participants with known respiratory diseases, bronchodilator users, and corticosteroid users

4.4.3. Respiratory function and hip fractures

120 participants (84 women) developed a hip fracture during 114,346 person-years of follow-up (64,049 person-years in women). Characteristics of participants who did or did not develop a hip fracture in the study period are summarised in *Table 4.3*. Women with subsequent fractures were significantly older, shorter, and lighter and had significantly lower ultrasound measures and FEV_1 (1.7 litres in average comparing to 2.1 litres for others). Women with hip fracture were less likely to have used hormone replacement therapy, more likely to have a history of fracture in earlier life, and had lower intake of alcoholic drinks. Smoking was not different among these groups in women. Age, past history of fracture, FEV1, and ultrasound measures were significantly different between men with and without subsequent hip fracture (*Table 4.3*). Mean age of men with hip fracture was about 8 years higher than other participants and they had lower FEV_1 of about 0.7 litres on average compared to others.

Table 4.3: Comparison of characteristics of participants with and without subsequent hip fracture in EPIC-Norfolk study

		Women			Men		
		No Fracture	Hip Fracture	*P value*	No Fracture	Hip Fracture	*P value*
N		8,220	84		6,460	36	
Age (years)		61.4 (8.9)	70.7 (7.4)	*<0.001*	62.9 (9.0)	71.0 (7.3)	*0.004*
Height (cm)		161.0 (6.2)	159.6 (6.0)	*0.047*	173.9 (6.6)	172.8 (6.1)	*0.292*
Weight (kg)		68.7 (11.8)	65.0 (11.4)	*0.004*	81.4 (11.5)	81.0 (13.3)	*0.116*
BMI (kg/m^2)		26.5 (4.4)	25.5 (4.1)	*0.027*	26.9 (3.3)	27.1 (4.1)	*0.274*
Past history of any fracture		594 (7.3%)	19 (22.6%)	*<0.001*	368 (5.7%)	6 (16.7%)	*0.005*
Smoking	(Never)	4800 (59.1%)	54 (64.3%)	*0.587*	2305 (36.0%)	14 (38.9%)	*0.926*
	(Current)	655 (8.1%)	5 (6.0%)		511 (8.0%)	3 (8.3%)	
	(Former)	2660 (32.8%)	25 (29.8%)		3583 (56.0%)	19 (52.8%)	
Alcohol intake (u/wk)*		2 (6)	1.5 (4)	*0.003*	6 (12)	6.5 (10.5)	*0.587*
Corticosteroid use		258 (3.2%)	5 (6.0%)	*0.143*	160 (2.5%)	2 (5.6%)	*0.242*
HRT	(Never)	5447 (66.6%)	71 (84.5%)	*0.002*	-	-	-
	(Current)	1749 (21.4%)	6 (7.1%)		-	-	
	(Former)	978 (12.0%)	7 (8.3%)		-	-	
FEV_1 (litre)		2.1 (0.5)	1.7 (0.5)	*<0.001*	2.9 (0.7)	2.2 (0.8)	*0.004*
BUA (dB/MHz)		72.4 (16.4)	55.9 (14.7)	*<0.001*	90.2 (17.5)	80.0 (18.3)	*<0.001*
SOS (m/sec)		1625.1 (40.0)	1589.6 (35.1)	*<0.001*	1645.4 (39.8)	1610.4 (46.6)	*<0.001*

** Values are medians (interquartile range).*

Table 4.4 shows the results of Cox regression models to predict hip fracture among participants. There was a trend of decreasing risk of hip fracture in subjects with higher FEV_1. Multivariate models showed a significant reduction of about 47% in hip fracture risk per 1 litre increase in FEV_1 in both sexes (*Table 4.4*, right column).

Table 4.4: Cox regression models by FEV_1 for hip fractures in the EPIC-Norfolk study

		FEV_1 (litre)				
		FEV_1 Quartiles				Continuous
		1st	2nd	3rd	4th	Per 1 litre
Women		**n=2,072**	**n=2,093**	**n=2,062**	**n=2,077**	**n=8,304**
Hip Fracture	N (%)	49 (2.4%)	22 (1.1%)	9 (0.4%)	4 (0.2%)	84 (1.0%)
Crude HR		1	0.44 (0.27-0.73)	0.18 (0.09-0.38)	0.08 (0.03-0.23)	0.21 (0.14-0.31)
Age-adjusted HR		1	0.71 (0.42-1.19)	0.50 (0.23-1.07)	0.37 (0.12-1.14)	0.51 (0.30-0.87)
Multivariable-adjusted HR*		1	0.66 (0.39-1.12)	0.46 (0.21-1.01)	0.32 (0.10-1.00)	0.53 (0.31-0.90)
Men		**n=1,636**	**n=1,611**	**n=1,638**	**n=1,611**	**N=6,496**
Hip Fracture	N (%)	19 (1.2%)	9 (0.6%)	6 (0.4%)	2 (0.1%)	36 (0.6%)
Crude HR		1	0.49 (0.22-1.08)	0.32 (0.13-0.81)	0.11 (0.03-0.49)	0.35 (0.23-0.53)
Age-adjusted HR		1	0.67 (0.30-1.50)	0.69 (0.26-1.84)	0.43 (0.09-2.12)	0.53 (0.32-0.91)
Multivariable-adjusted HR*		1	0.72 (0.31-1.64)	0.69 (0.25-1.94)	0.42 (0.08-2.22)	0.52 (0.30-0.90)

*Variables in the equation: FEV_1 (forced expiratory volume in 1 second) age, body mass index, smoking habit, alcohol intake, past history of any fracture, broadband ultrasound attenuation, corticosteroid use (and history of hormone therapy for women)

Table 4.5 shows the results of sex-specific multivariate Cox regression analyses to predict hip fracture. FEV_1 was a significant predictor of hip fractures among both men and women with a hazard ratio of about 0.6 per 1 SD (0.5 litres). Age, height, alcohol intake and BUA were the other significant predictors of hip fractures among women. The other significant predictors were age and BUA among men. Past history of fracture was associated with a marginally significant 70% increased risk of hip fracture among women and a non-significant 130% increased risk among men (*Table 4.5*).

Table 4.5: Cox proportional-hazard models to predict hip fracture among 8,304 women and 6,496 men in the EPIC-Norfolk study

	Women		Men	
	β coefficient	Hazard Ratio (95% CI)	β coefficient	Hazard Ratio (95% CI)
FEV_1 (per 0.5 litre)	-0.42*	0.66 (0.45-0.95)	-0.44*	0.64 (0.43-0.96)
Age (per 5 years)	0.41*	1.51 (1.25-1.81)	0.46*	1.58 (1.20-2.10)
Height (per 5 cm)	0.26*	1.29 (1.07-1.57)	0.21	1.23 (0.94-1.63)
Body Mass Index (per 4 kg/m^2)	-0.13	0.88 (0.69-1.11)	0.13	1.14 (0.77-1.70)
Past history of any fracture (yes)	0.50	1.65 (0.99-2.81)	0.85	2.33 (0.89-6.08)
Smoking (current)	0.12	1.14 (0.45-2.86)	0.34	1.41 (0.33-6.25)
Alcohol intake (per unit/week)	-0.06*	0.94 (0.89-0.99)	0.00	1.00 (0.97-1.03)
BUA (per 20 dB/MHz)	-0.88*	0.41 (0.29-0.59)	-0.50*	0.60 (0.40-0.91)
Corticosteroid use(yes)	0.13	1.14 (0.45-2.87)	0.24	1.27 (0.29-5.61)

* Statistically significant at level of $p<0.05$

4.5. Discussion

To our knowledge, this is the first population-based study evaluating the association between respiratory function and bone health as assessed by quantitative ultrasound measurement and fracture incidence over time. In our study, there was a significant positive and continuous relationship between FEV_1 and BUA of the heel in middle-aged and older women and men. The magnitude of this relationship, however, was not large after adjustment for covariates; the mean BUA measures of women and men in the highest FEV_1 quartile were only 5% and 3%, respectively, higher than the mean BUA of women and men in the lowest quartile (*Figure 4.1*). Furthermore, in multiple regression analysis, a 1 litre increase in FEV_1 was accompanied by approximately 2.2 dB/MHz increase in BUA for women and 1.5 dB/MHz increase in BUA for men (*Table 4.2*), in comparison with a standard deviation of BUA around 17 dB/MHz.

However, there was a significant and strong association between FEV_1 and incidence of hip fracture, greater than might be predicted from the association with BUA. Indeed, this association remained significant even after adjustment for BUA and other known risk factors including age and past history of fracture (*Table 4.4* and *Table 4.5*). The hazard ratio for 1 SD (0.5 litres) increase in FEV_1 was about 0.6 (95% confidence interval, 0.4–0.9) for both men and women. β coefficients provided in *Table 4.5* can be used to compare the relative effect of different variables for prediction of hip fractures [161]. This shows that 1 SD increase in FEV_1 was equivalent approximately to 0.5 SD increase in BUA among women (1 SD among men) and about 5 years decrease in age among both men and women (*Table 4.5*). This suggests that the relationship between respiratory function and bone health is independent of bone properties measured by quantitative ultrasound and FEV_1 may be a useful marker of fracture risk independent of bone characteristics in older men and women. Evaluation of the mechanisms by which FEV_1 can affect the bone health is beyond the scope of this study, but we can suggest that inclusion of this measure (FEV_1) in fracture

prediction charts, especially for hip fracture, might be helpful and needs further consideration.

Currently we are facing a universal shift towards use of long-term fracture risk estimation in the field of osteoporosis research and clinical practice guidelines. The FRAX® tool, a newly-launched online program for estimation of 10-year absolute risk of fracture for individuals, is likely to be a source for future routine clinical practice in this field [24, 162]. This tool currently considers several clinical risk factors and BMD measurements in the femoral neck. The results of this tool can be replicated for different populations using prospective studies with long follow-ups. Moreover, other potential risk factors (including clinical, radiological and biochemical factors) can be added to or replaced with the current set of risk factors. While use of subjective measures like history of smoking or physical activity might be prone to several biases, more objective measures such as spirometry results may increase the accuracy of our risk estimates. Future studies need to consider this point and use it to improve the predictive power of forthcoming risk assessment tools.

The first studies examining the association between respiratory function and bone health were in patients with pulmonary diseases. Some clinical studies in patients with cystic fibrosis and bronchial asthma found significant associations between measures of respiratory function and BMD [163-165]. It should be noted, however, that patients with these conditions are exposed to a variety of other factors that might impair their bone health (for instance, cystic fibrosis is associated with pancreatic malabsorption and bronchial asthma is often treated with long-term corticosteroids). Cross-sectional studies among community-dwelling adults have shown a correlation between respiratory function and BMD measured with DXA [155-157]. Two cross-sectional studies from Cambridge, UK, found a positive and continuous relationship between FEV_1 and BMD at the hip across the whole normal range of respiratory function in women and men [156, 157]. This association was evident in young, middle, and older age groups almost to the same extent. After adjusting for potential confounding factors, mean hip

BMD of women in the highest FEV_1 quartile was approximately 3-5% higher than the mean BMD in women in the lowest quartile [156]. This difference was slightly lower, but still significant, for men (2-3.5%) [157]. This magnitude is comparable to that observed for BUA in the current study. As far as we know, no prospective study, however, has investigated the predictive power of pulmonary function testing for osteoporotic fractures, or assessed the association of respiratory function and QUS measures among healthy members of the community.

Impaired respiratory function is associated with morbidity [166] and mortality [166, 167]. Poor respiratory function predicts overall mortality, as well as death due to cancer [168], pulmonary disease [169], cardiovascular disease [166, 168], and stroke [166]. This relation could simply reflect the effect of cigarette smoking, respiratory illness, or other pre-existing diseases [170, 171]. Researchers have advised that the use of FEV_1 as part of any health assessment of middle aged patients should be considered [168]. The current study shows that FEV_1 can be used as a marker of bone characteristics as assessed by QUS. Moreover, even after adjustment for BUA in multivariate Cox regression analysis, FEV_1 was a significant predictor of hip fracture. This suggests a potential association between respiratory function and some unmeasured bone characteristics or other fracture risk factors such as tendency to falls. One plausible explanation is that respiratory function and bone health both reflect common but as yet unknown determinants [156].

This study has some limitations. Respiratory function was evaluated using the better of two blow manoeuvres in this study. This may induce some imprecision in the estimated respiratory function as most of the recent guidelines recommend use of at least 3 blow attempts for determination of FEV_1 [172, 173]. This is mainly due to the fact that the original design and start of the EPIC-Norfolk study goes back to 1992 before development of these guidelines and the investigators chose to continue with a consistent procedure of spirometry throughout the study follow-up [107]. Moreover, random measurement error in FEV_1 values is more

likely to underestimate the magnitude of the relationship between FEV_1 and BUA [174]. Other measures of respiratory function like FVC, PEF, and FEV_1/FVC ratio did not add additional information to our results and we chose to only report FEV_1 as the most widely used and straightforward measure.

Participants in the baseline visit for this study (which was the second health check in EPIC-Norfolk) are likely to be healthier than general population. About 60% of participants in the original cohort returned for this health check and this may induce a healthy selection bias. We have previously compared characteristics of those who attended the second health examination with those who did not, and as expected, non-attendees were older [107]. However, selection of participants in the first instance and the method of follow-up were not related to or influenced by the exposure level in this study. Moreover, it is unlikely that the association observed in this study between respiratory function and bone health would be different or in the opposite direction in non-attending population. In fact, pathophysiology would suggest that the link between respiratory function and bone health would be stronger in people with poorer health status due to common risk factors like smoking and physical activity levels [97, 158-160]. This, though, needs evaluation in further studies. Dual-energy x-ray absorptiometry (DXA), as the current gold standard for bone density measurement, was also not used in this study. Although the method used for ascertainment of fractures (data linkage of all participants with National Health Service hospital records and death certification) has the advantage of ascertainment of all hospitalised fractures and does not rely on follow-up self reports which can be incomplete, there would be a potential for under-ascertainment of non-hospitalised fractures. Nevertheless, this method identifies the fractures with the most clinical impact. In particular, almost all of hip fractures are hospitalised in the UK.

There is a well-established epidemiological relationship between smoking and respiratory function [160, 175] and several studies have suggested a significant association between smoking and fracture risk [97, 176]. In our study, the association between respiratory function and fracture risk appeared independent

of cigarette smoking habit. Though the association between respiratory function and fracture risk is independent of major known determinants like age, smoking, and bone ultrasound measures, we cannot exclude residual confounding from these or other unknown factors. However, the magnitude of the association indicates that residual or unknown confounding factors would have to be substantial to account for this association between respiratory function and fracture risk.

This is the first population-based prospective study examining the association between respiratory function and bone health using both bone measurements (QUS method) and fracture endpoints. There is particularly a paucity of data on fracture risk determinants among men [177]. This study shows that the pattern of association between respiratory function and bone health is similar among men and women. These findings need replication in future prospective studies in different settings and different populations before being generalised and used in fracture risk prediction tools. If the association between FEV_1 and hip fracture risk is confirmed, spirometry is a simple, feasible and low cost measurement that could be used in general practice to help in fracture risk prediction in older men and women.

Chapter 5: Physical Activity Review

The work presented in this Chapter has been published in:

Moayyeri A. The association between physical activity and osteoporotic fractures: A review of the evidence and implications for future research. Annals of Epidemiology 2008 Nov;18(11):827-35

Please see Appendix 5.

5.1. Abstract

Physical activity helps maintain mobility, physical functioning, bone mineral density (BMD), muscle strength, balance and, therefore, may help prevent falls and fractures among the elderly. Meanwhile, it is theoretically possible that physical activity increases risk of fractures as it may increase risk of falls and has only a modest effect on BMD. This review aims to assess the potential causal association between physical activity and osteoporotic fractures from an epidemiological viewpoint. As the medical literature lacks direct evidence from randomised controlled trials (RCTs) with fracture endpoints, a meta-analysis of 13 prospective cohort studies with hip fracture endpoint is presented. The current evidence base regarding the link between exercise and fracture risk determinants (namely, falls, BMD, and bone quality) are also summarised. Moderate to vigorous physical activity is associated with a hip fracture risk reduction of 45% (95% CI 31-56%) and 38% (95% CI 31-44%), respectively, among men and women. Risk of falling is suggested to be generally reduced among physically active people with a potential increased risk in the most active and inactive people. Positive effects of physical activity on BMD and bone quality are of a questionable magnitude for reduction of fracture risk. The complexity of relationship between physical activity and osteoporotic fractures points out to the need for RCTs to be conducted with fractures as the primary endpoint.

5.2. Introduction

Risk for osteoporotic fracture is mainly determined by three factors: the risk of falling, bone strength, and force of impact in the event of a fall. Established risk factors for falls include older age, impaired balance and orthostatic hypotension, decreased reaction time, impaired vision and cognition, lower-extremity muscle weakness, decreased lean body mass, and overall impaired mobility [178-181]. Medications, particularly sedative and psychotropic drugs, alcohol intake, inappropriate footwear, and physical factors in the environment such as stairs, lighting, and streets have also been cited as important factors [178, 180]. Acute situational factors, including the force of movement, body position, location of impact, and protective responses during a fall also influence whether an injury will occur. Aside from the risk of falling, primary risk factors for osteoporotic fractures include low BMD, architectural deterioration of bone, older age, female gender, white race and lower body weight [41].

Physical activity has been identified as a lifestyle factor that may influence the risk of falls and fractures among older adults. Physical activity is likely to influence the risk for fractures mainly through the musculoskeletal and neuromuscular systems and by direct influence on three main risk determinants of fracture (falls, bone density, and bone quality) [182, 183]. It is also important to consider that physical activity could increase risk for injurious falls because physical activities involve skeletal muscle movement that displaces the body's centre of gravity and balance. Not surprisingly, walking and going up and down stairs are the most common circumstances of non-syncopal falls, accounting for 39% and 20% of events, respectively, among older adults [180]. However, as is the case with risk for sudden cardiac death, physical activity could have multiple long-term protective effects while simultaneously increasing acute risk for an event. It should be noted that hip and wrist fractures risk is thought to be influenced by both the tendency to fall and bone strength, while vertebral fractures have not been causally related to falls and may be more solely related to bone and muscle strength [184].

Figure 5.1 shows a theoretical model of how physical activity may influence the risk for falls and fractures.

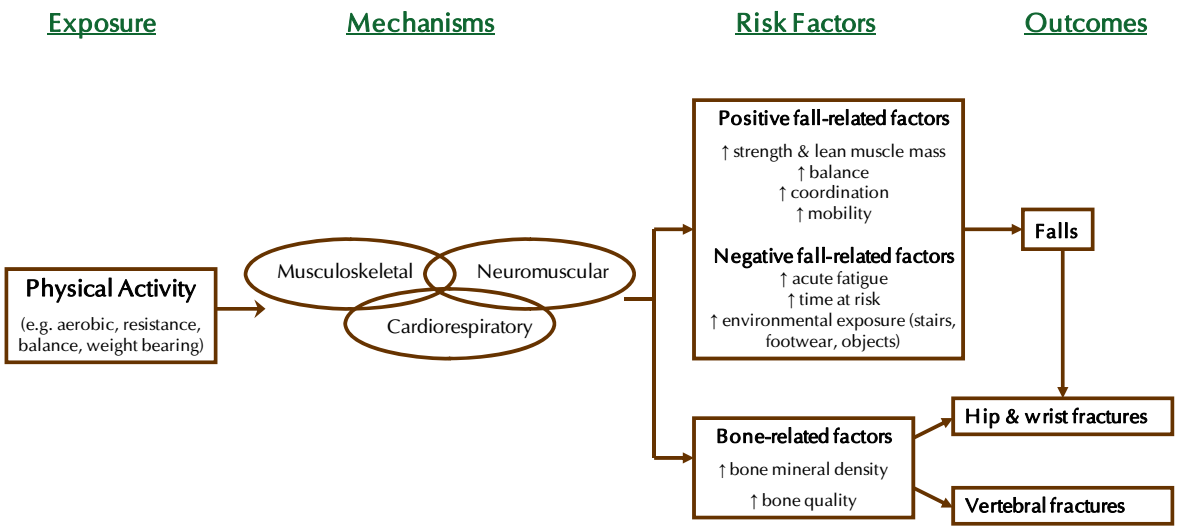

Figure 5.1: Potential mechanisms for associations between physical activity and risk of falls and fractures

In this Chapter, I aim to review the epidemiological evidence related to the association between physical activity and the risk of osteoporotic fractures among older adults. The association between physical activity and intermediate outcomes (namely, falls, BMD and bone quality) is summarised from review papers and the implications for future research are discussed from an epidemiological perspective.

5.3. Methods

Given the enormous number of studies evaluating the effects of physical activity on bones, the literature search was restricted to find randomised controlled trials (RCTs), prospective studies and review articles on the topic. Peer-reviewed articles were identified in the PubMed Central using MeSH (Medical Subject Headings) terms "Motor Activity" and "Exercise" for the exposure and MeSH terms "Fractures, Bone", "Osteoporosis", "Bone Density", "Densitometry, X-Ray", "Accidental Falls", and "Calcaneus ultrasonography" for primary and secondary endpoints. Various combinations of the search terms and a variety of limitations were employed to make specific searches for randomised controlled trials, prospective cohort studies (including nested case-control studies), and reviews. Searches were repeated without use of MeSH terms to find newly cited potential references. Reference sections of retrieved papers were also searched for citations.

Studies were required to operationally define physical activity as bodily movement produced by skeletal muscles that results in energy expenditure [185]. Studies were included if they attempted to measure physical activity or exercise performed as part of leisure and occupation, but were excluded if they just evaluated participants' ability or estimated fitness carrying out a particular physical activity. Other exclusion criteria were studies on younger adults (<40 years old) and non-English articles.

A particular attempt was made to find randomised controlled trials evaluating the direct association between physical activity and fractures among middle aged and older adults. These were trials in which physical activity was a primary component of the intervention and was used as a preventive strategy for fractures (not for treatment or rehabilitation). Protocols for the relevant RCTs were also searched in online databases (ClinicalTrials.gov and Cochrane Central Register of Controlled Trials). Despite these attempts, no RCT was found with fracture as the primary endpoint.

Out of 65 observational studies retrieved evaluating the direct association between physical activity and osteoporotic fractures, 21 studies fulfilled the inclusion criteria. A meta-analytic approach was utilised only for pooling the results of prospective studies with hip fracture endpoints given the concern about the validity and comparability of retrospective studies and the small number of studies with other osteoporotic fractures endpoints. Thirteen studies (out of 14 retrieved) were entered into the meta-analysis. The study by Joakimsen et al. was excluded due to dissimilar classification of outcome (weight-bearing and non-weight-bearing fractures instead of specific location of fractures) [186]. A pre-tested data extraction form was used to derive the relative risks (RR) and confidence intervals for hip fracture in different levels of physical activity. When a study reported several RRs, the estimate judged to be the nearest to moderate or vigorous activity was used. Random-effects meta-analysis stratified for sex was performed using the metan procedure in Stata software, version 10 (Stata Inc., College Station, TX, USA) [187]. Weights for the included studies and estimates of heterogeneity were calculated and potential for publication bias was evaluated using funnel plots derived from the Begg-Mazumdar test [188]. Results of studies for intermediate outcomes (falls, BMD, bone quality) are mainly derived from 18 review articles and meta-analysis papers.

5.4. Results

5.4.1. Physical activity and hip fractures

Numerous studies have evaluated the association between physical activity and bone health using different endpoints like fractures, risk of falls, and BMD. Hip fracture, as the most important type of osteoporotic fractures, has attracted considerable attention among researchers. Practically all patients with hip fracture seek clinical attention and this point facilitates use of hip fracture as an endpoint for epidemiological studies [189]. Most of the prospective studies evaluating the association between physical activity and hip fracture risk have found significant risk reductions among either men or women [41, 158, 186, 190-200] . The NHANES I follow-up study found that women reporting moderate to vigorous physical activity had a 47% lower risk of hip fracture than those reporting no physical activity [190]. Nurses' Health Study showed that active women with at least 24 metabolic equivalent (MET)–hours per week of activity had a 55% lower risk of hip fracture compared with sedentary women with less than 3 MET-hr/week [191]. Study of Osteoporotic Fractures found self-reported walking for exercise to be associated with a significant 30% reduction in hip fracture risk after 4.1 years and 40% after 7.6 years of follow-up in postmenopausal white women [41, 158]. Tromso study in Norway found similar protective effects of leisure and work physical activity on weight-bearing fracture sites (hip and ankle) among men but not among women [186].

Meta-analysis of these studies (*Figure 5.2*) shows that moderate to vigorous physical activity is associated with a hip fracture risk reduction of 45% (95% CI 31-56%) and 38% (95% CI 31-44%), respectively, among men and women. Studies for women comprise 79% of weight of the analysis and this is mainly due to underpowered studies among men and their imprecise relative risk estimates (as a result of lower incidence of fracture among men that demands studies with longer follow-ups in larger and older cohorts comparing to studies in women). Despite inconsistent approaches of different studies to measurement of exposure, their results indicate a high level of homogeneity (I^2=7.4% for men and 2.5% for

women). Cochrane Q test for heterogeneity among studies is also non-significant and this confirms a relative consistency of the findings across the studies. The funnel plots, however, suggest a potential for publication bias given the absence of negative studies involving small sample sizes.

While individual studies bear the risk of a type II error (finding no association by chance when there is a true association), this meta-analysis confirms that there is an association between physical activity and hip fracture (*Figure 5.2*). However, despite the relative consistency, magnitude of effect, biological plausibility, and diversity of populations across these prospective studies (some conditions of the Bradford Hill criteria for causation) [201], there is still a great need for randomised controlled trials as the observed association can be merely due to potential confounders. In the absence of RCTs, we have to rely on prospective cohort studies (a step down in the evidence hierarchy), not forgetting that causality cannot be proven in such observational studies.

Health status is the most powerful confounder for the association between physical activity and osteoporotic fractures and it can only be treated appropriately by randomisation. Healthier individuals may choose to be active, while less healthy persons exercise less because of their illness. The causal link may be between the illness and fracture, and the illness and lack of exercise, not the fracture and lack of exercise. Conversely, persons with higher muscular capacity and function usually perform better in sports and are probably more likely to choose a physically active lifestyle. The genetically-inherited larger muscle mass and stronger bones may confer a lower fracture risk, not the higher activity level. Hence, even meta-analyses of these cohort studies cannot exclude the risk of confounding. In other words, the observed association may be a 'real', but confounded, association.

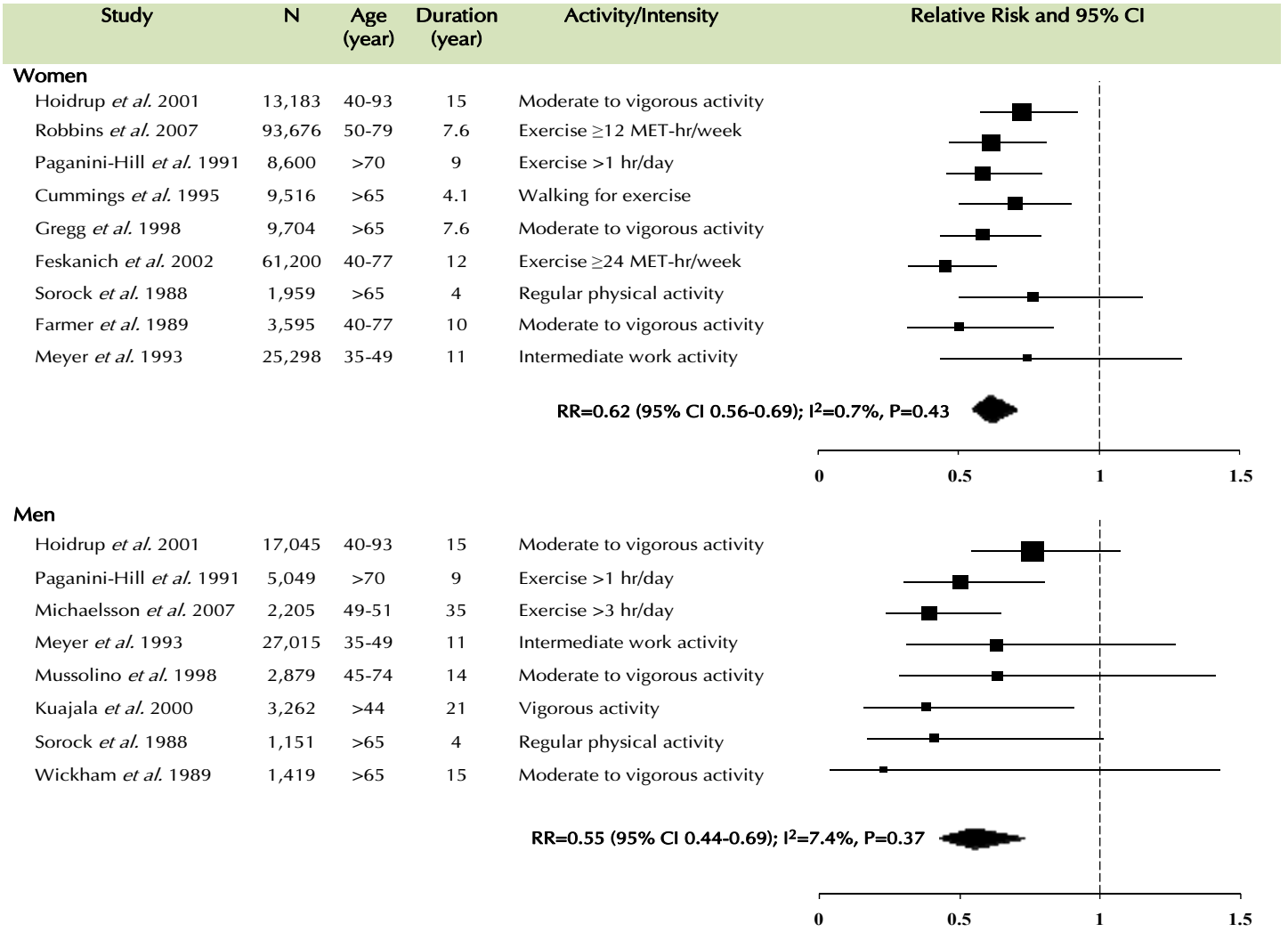

Figure 5.2: Meta-analysis of thirteen prospective studies for the association between physical activity and hip fracture.

Consideration to unusual low weight of study by Meyer et al. may lead to some important implications for future research in this area. This study follows 52313 participants for 11 years [194] but only accounts for about 5% of weights in the meta-analysis (*Figure 5.2*). This is mainly because of two factors. Firstly, participants of this study were younger comparing to other studies (35-49 years) and the rate of fracture among this population has to be lower (as depicted by observation of only 210 fractures in this case) [194]. Lower number of outcome events would inevitably lower the precision of estimates for any relative risk. Secondly, choice of the method for measurement of exposure shows its impact extremely in this case. They have divided physical activity to two main categories of "at work" and "during leisure" and classified each of them to sedentary, moderate, intermediate, and intense physical activity levels. This has also decreased their power in estimation of effects as the already low number of events should be divided between eight categories and one category, for instance, had no participants with fracture [194]. This problem is also evident, with lower impact, on some other studies included in the meta-analysis.

Different reviews [202-209] point out to several case-control studies suggesting that hip fracture sufferers are more likely than controls to report being inactive in the recent past (before fracture) or earlier in their life. Reductions in the odds of fracture among women engaging in physical activity programs versus controls have typically ranged from 20 to 60% [203]. Analyses conducted among men have tended to find similar results but have typically lacked statistical significance due to smaller sample sizes [203, 206]. These findings are encouraging, but case-control studies are inherently vulnerable to recall and detection biases and results can be heavily influenced by the selection of controls. Matching or adjustments have been used for different sets of variables in different studies and diverse definitions are used for the exposure [204]. Additionally, many of these studies depend on historical physical activity questionnaires, which have limited empirical testing of their reliability and validity. Of particular concern is the

measurement error due to recall bias attributed to fracture events. Publication bias related to this type of study should also be considered.

5.4.2. Physical activity and other osteoporotic fracture sites

Few epidemiologic studies have examined the association of physical activity with other fracture sites and the results are mainly non-significant [158, 186, 210-216]. Two case-control studies found positive effects (non-significant) for vertebral fractures attributed to physical activity [210, 211]. The European Vertebral Osteoporosis Study (EVOS), including 6,646 women aged 50–79 years, of whom 884 had a vertebral deformity, showed that current walking or cycling for more than 30 minutes each day resulted in a 20% reduction in the risk of developing a vertebral deformity as compared to inactive women; there were no significant findings among men [216]. The prospective Study of Osteoporotic Fractures did not find total leisure-time physical activity or heavy chores to be related to vertebral fracture risk, but moderate to vigorous activity (> 2 hours/day) reduced the vertebral fracture risk by 33% as compared to no activity [158].

The situation seems to be in the opposite direction, however, for upper limb fractures. Two case-control studies found non-significant increased odds of wrist fracture associated with walking [213, 215]. Data from the Tromso study showed that among women, but not men, high levels of physical activity were related to a significant 50% increased risk of non-weight-bearing fracture sites, including the wrist, proximal humerus, hand, and finger [186]. The Study of Osteoporotic Fractures also found a nearly significant increased risk of wrist fracture associated with moderate to vigorous physical activity [158, 212]. Finally, among men enrolled in the Dubbo Osteoporosis Epidemiology Study in Australia, each standard deviation increase in leisure-time physical activity was associated with a

statistically non-significant 14% decrease in risk of any fragility fracture [214]. This suggests that physical activity has different impacts on different types of fracture and this issue needs more exploration in future studies.

In summary, data from observational studies suggest that physical activity is associated with reduced hip fracture risk. This may be correct, but consistently replicated sampling bias and confounded association may have produced this observation. Evidence regarding vertebral and wrist fractures is even more limited.

5.4.3. Physical activity and risk of falls

Prospective observational studies evaluating the association of usual physical activity with risk of falling suggest a general decrease in risk while the most inactive and the most active persons may be at a higher risk (U-shaped association) [178, 181, 217-219]. Some studies have suggested increased risk of falls associated with certain types of physical activity (such as brisk walking and aerobics) [181, 217, 220]. All of these observations may be highly confounded by baseline mobility impairment of participants. Meanwhile, several randomised controlled trials of exercise programs to reduce falls have been reported [221-234], of which the general results are still inconclusive. A pre-planned meta-analysis of the studies involved in the Frailty and Injuries: Cooperative Studies of Intervention Techniques (FICSIT), a coordinated trial that consisted of eight independent studies [221, 228-230, 233, 234], showed a marginally significant 10% reduction (RR = 0.90, 95% CI = 0.81-0.99) in falls risk associated with general exercise and a 17% reduction (RR = 0.83, 95% CI = 0.70-0.98) associated with balance training but no significant effect of endurance, resistance,

or flexibility training [230]. Many of other RCTs have found no significant differences between exercise interventions and controls, although some of these trials may have lacked statistical power [224-232]. This has resulted in the reviews of evidence concerning the role of physical activity in preventing falls to mainly advise for further research to be conducted in this field [203, 235-237]. The reasons for this inconclusiveness can be the use of different exercise modalities, multidisciplinary interventions in some studies [230, 233], and different definitions of outcome (single [219, 221, 222, 230, 234] versus multiple falls [225-227, 231]).

5.4.4. Physical activity and bone characteristics

Physical activity has direct effects on bone mineral density [238-241]. Randomised controlled trials suggest that exercise in elderly women prevents bone loss and may increase BMD by a few percentage points [207, 238, 242, 243]. Brisk walking [220], stepping block training [244], weight-bearing training [226, 245], resistance training [246], and strength training [183, 247] are all training programs with reported benefits to the BMD of the spine. However, the exercise leads to a BMD benefit of questionable biological significance [41, 248, 249]. For instance, aerobic exercise for 6-24 months, at best, stops bone loss or increases BMD by less than 3%, which can have little effect on the fracture risk [250, 251]. The results for the femoral neck are usually described as even less promising [220, 244]. One meta-analysis involving 230 postmenopausal women from six prospective randomised or non-randomised trials reported that aerobic activity for 8 to 24 months increased BMD in the hip by 2.4% compared to controls [252]. A similar meta-analytic approach for men found similar results

[253]. No randomised prospective study has been done to evaluate the skeletal effects of lifelong exercise. Observational studies suggest an association between lifelong and current exercise level and BMD in the elderly [211, 254]. This observation, however, may reflect either sampling bias or the possible long-term effects of exercise undertaken during growth.

Our current knowledge of bone quality is severely limited and studies aiming to explore this factor are mainly restricted to quantitative ultrasound (QUS) measures. QUS parameters have been correlated with trabecular number and separation, elasticity, and the compressive strength of bone [63]. Few studies have shown a positive effect of leisure-time physical activity and brisk walking on QUS measures [255-258]. The interesting point is that non-weight-bearing exercises (like swimming) may have a similar positive effect on QUS measures as weight-bearing exercises [259, 260]. These data, however, should be interpreted with caution since the actual properties of QUS measures and the degree to which they are truly independent of BMD remains controversial [63].

In summary, no exercise modality has been shown in different RCTs to be consistently effective in reducing risk for falls. Positive effects of physical activity on spine and hip BMD, confirmed via several RCTs and meta-analyses, is still of a questionable magnitude for reduction of fracture risk. Limited evidence supports for a positive role of physical activity on bone quality.

5.5. Discussion

A thorough search of literature on the topic did not reveal any randomised controlled trial specifically designed to evaluate the role of physical activity in reduction of fracture rates. Moreover, no protocol for such an RCT is registered in the U.S. National Library of Medicine registry for clinical trials (ClinicalTrials.gov) and the Cochrane Central Register of Controlled Trials. Obviously, the main factor that has prevented the research community so far from conducting an RCT with fracture endpoints is the enormous sample size needed for such a study. A sensitivity analysis for calculation of sample size indicates that even RCTs on high-risk populations with optimistic estimates of risk reduction need to involve thousands of participants.

Table 5.1 shows the estimated sample sizes needed for various scenarios to conduct a 5-year trial with hip fracture as the primary endpoint. Probabilities of 0.05 and 0.2 are considered for type I and type II errors, respectively [261]. The incidence rates for fractures are approximated by cumulative incidence rates based on estimates from a recent unpublished review. Expected rate ratios (70% as the initial) were optimistically derived from prospective cohort studies as there is no pilot RCTs on hand. This *Table* shows that, given the extreme low rates of hip fracture incidence among populations, anyone who wants to conduct an RCT even among high-risk individuals need to recruit a substantial number of participants (about 7,000 in two groups for high-risk women assuming a rate ratio of 75%). The task is much tougher for other low-risk groups like men. It should be noted that increasing these numbers by at least 20% is highly recommended to account for drop-outs and noncompliance (considering the long period of the study and the challenging intervention among elderly people). However, the benefits of physical activity extend beyond bone health and such a large RCT can be highly informative regarding different health outcomes (e.g., cardiovascular events, diabetes mellitus, hypertension, cognitive impairments, osteoarthritis, etc).

Table 5.1: Sample size estimation for randomised controlled trials of exercise in the prevention of hip fracture

Rate Ratio	Population	Cumulative Incidence Rate		Sample Size per Group
		Control	Intervention	
0.70	European women	0.03	0.021	4812
	Scandinavian women	0.04	0.028	3576
	High-risk women (>65 years)	0.06	0.042	2341
	European men	0.01	0.007	14696
0.75	European women	0.03	0.0225	7129
	Scandinavian women	0.04	0.03	5298
	High-risk women (>65 years)	0.06	0.045	3467
	European men	0.01	0.0075	21781
0.80	European women	0.03	0.024	11452
	Scandinavian women	0.04	0.032	8508
	High-risk women (>65 years)	0.06	0.048	5565
	European men	0.01	0.008	34998

Model assumptions: 5-year trial, type I error: 0.05, type II error: 0.20, two-sided test, no drop-outs and 100% compliance

Table 5.1 also shows that our assumption about rate ratio plays a very important role on determining the sample size needed for conducting such a study as even 5% change in this ratio can have an immense impact on the estimated number of participants. Sample size of 4,812 per group for ideal intervention in European women will more than double to 11,542 per group with change of assumption from rate ratio of 70% to 80%. Clearly, the use of an aggregate endpoint (e.g., any fracture) could increase power by increasing event rates; however, the intervention may be less effective on non-hip fracture outcomes (expected rate ratio would be nearer to 1).

This review of the association between physical activity and risk of osteoporotic fractures suggests that a physically active lifestyle reduces the risk of hip fracture (based on strong evidence from observational studies). Although there is no direct evidence from fracture RCTs, the consistency of cohort studies and the strength of association (relative risk of about 60%) suggest that older adults should be encouraged to maintain a regularly active lifestyle. However, it is unclear whether physical activity is associated with the risk of osteoporotic fractures at sites other than the hip. Few studies have examined this issue and findings have been ambiguous.

There is a big debate on the role of physical activity in prevention of falls. Given the U-shape association and increased risk of fall with certain types of exercise, the most optimistic estimates show a 10% reduction in risk of falls among the elderly. Whether a 10% reduction is considered important from a public health standpoint will depend on the burden of falls and fractures on the population, the financial costs of effective interventions, and whether extra benefits occur from these interventions.

Exercise during adulthood produces small increments in BMD, or may prevent bone loss, but even if reaching a statistical significance, the increments in BMD are questionable in terms of reducing fracture risk in elderly persons. Given our restricted knowledge, comment on the impact of exercise on bone quality is more limited at present. The complexity of relationships between risk factors and fractures confirm the need for randomised trials to be done with fractures as the primary endpoint. Pathophysiologic reasoning may well mislead us in this situation [262]. RCTs would be required to ensure that this association is not confounded by pre-existing health status, but the sample size requirements would make such trials extremely costly and probably impractical.

It should be noted that different types of exercise have different effects on various aspects of bone health. Exercise modalities aiming to improve risk of falls, BMD or bone quality may have opposing effects on the other factors and their overall impact on the risk of fracture may vary as it is a product of all these factors. Most

importantly, the current set of activities advised by practitioners mainly for cardiovascular benefits (e.g., for prevention of progress in hypertension or type II diabetes mellitus) [263, 264] may not be as ideal for the bones. Studies on various types of physical activity interventions could help refine the type and quantity of interventions necessary for optimal effects on fracture risk and to determine which subpopulations (e.g. institution-dwelling or home-dwelling older adults) will have the most to gain from structured exercise programs or leisure physical activities.

Another issue that has not been considered by researchers so far is the cost imposed by physical activity on communities (e.g. training costs for exercise campaigns or the cost of additional nutritional requirements for exercisers). Cost-effectiveness analyses as extensions to forthcoming RCTs are needed to fully evaluate risks and benefits of physical activity in association with osteoporotic fractures.

Based on current available evidence, we cannot be convinced that there is a causal association between physical activity and osteoporotic fractures. The association might be quite similar to that of hormone replacement therapy and cardiovascular mortality (which was a protective factor in cohort studies and shown to be a risk factor in a large RCT) [265]. According to Bradford Hill criteria, potentially powerful confounders should be treated by experimental evidence [201]. The proof for causative association rests on a demonstration of a reduction in fractures by well-designed and well-executed, prospective, probably multi-centre, randomised controlled studies.

Chapter 6: Physical Activity

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Please see Appendix 6.

6.1. Abstract

A large body of epidemiological evidence suggests an inverse relationship between physical activity and risk of fractures. However, it is unclear how this association varies according to the domain of life in which the activity is undertaken. In this analysis of the European Prospective Investigation of Cancer-Norfolk study, we assessed total and domain-specific physical activity using a validated questionnaire (EPAQ2) in 14,903 participants (6,514 men, mean age 62 yr) who also underwent quantitative ultrasound of the heel. After a median follow-up of 8 years, there were 504 fractures of which 164 were hip fractures. In multivariable linear regression analysis, broadband ultrasound attenuation (BUA) was positively associated with total and leisure time activities while showing no association with transportation and work activities. Home activities were associated with a lower BUA among younger participants. In multivariable Cox proportional-hazards models, moderate activities at home and in leisure time were associated with lower hip fracture risk among women (hazard ratios [HR] 0.51 and 0.55, 95%CI 0.29-0.90 and 0.30-0.93, respectively). Among men, leisure time activities were associated with lower risk of hip fracture (HR=0.58; p for trend<0.001) whereas activities at home were associated with higher risk of any fracture (HR=1.25; p for trend=0.008). Walking for leisure or transport was associated with lower risk of fracture in both men and women. Multivariable fractional polynomial modelling showed a U-shaped association between home activities and fracture risk especially among women. This study suggests that different domains of physical activity may relate differently to fracture risk and these relationships may vary by age and sex.

6.2. Introduction

Physical activity has been identified as a lifestyle factor that may influence the risk of falls and fractures among older adults. This appears to be mediated mainly through the musculoskeletal and neuromuscular systems by influencing three main risk determinants of fracture (falls, bone density, and bone quality) [182]. Observational studies strongly suggest that a physically active lifestyle reduces the risk of hip fracture (please see the meta-analysis in Chapter 5). However, it is unclear whether physical activity is associated with the risk of osteoporotic fractures at sites other than the hip [158, 186, 214, 216]. There is a debate on the role of physical activity in prevention of falls given the U-shaped association of physical activity with risk of falls, and increased risk of fall with certain types of exercise [178, 217, 219, 266]. Exercise during adulthood produces small increments in bone mineral density (BMD) [267, 268], or may prevent bone loss in the elderly [238, 252, 253], but any increments in BMD have questionable translation to reducing fracture risk in elderly people. Our current knowledge of the effects of physical activity on other characteristics of bone such as elasticity and micro-architecture (as measured by quantitative ultrasound) is also limited [258, 260].

Physical activity is undertaken in different contexts or domains: at home, during work, for transportation, and during leisure time (for sport or exercise). Due to the heterogeneity in how physical activity is assessed in different studies as well as the nature of the populations studied, with some being restricted to the working participants, our knowledge of the association between domain-specific activities and fractures risk is limited. This information may be important because activities performed in different domains of life are likely to differ between men and women and at different ages, which may affect the physical activity-disease associations. In this chapter, I aim to assess the associations between different domains of physical activity and bone strength (as measured by quantitative ultrasound of the heel) as well as fracture risk.

6.3. Methods

Men and women in this study participated in the second health examination of EPIC-Norfolk. Full details of participant recruitment and study procedures have been described in Chapter 2. Briefly, between January 1998 and October 2000, 15,515 participants completed the EPIC Physical Activity Questionnaire (EPAQ2) and returned for a clinical visit. EPAQ2 is a self-completed questionnaire that collects data on past year's physical activity behaviours in a disaggregated way so that the information may be re-aggregated according to the dimension of physical activity of interest (please see Appendix 2 for a copy of the questionnaire). The questionnaire consists of four sections: activity in and around the home, during work, transportation to work, and recreational physical activity. With work here we meant being in paid employment or doing regular, organised voluntary work. All transportation and some domestic questions were designed specifically for this study, whereas the questions on occupational activity were derived from the Modified Tecumseh Occupational Activity Questionnaire that has been validated elsewhere [110]. The recreational section of the EPAQ2 was derived from the Minnesota Leisure Time Activity Questionnaire [111], with 30 predetermined sports selected according to their frequency and duration in a UK population (The Sports Council and The Health Education Authority, 1992) and six non-sportive activities, such as mowing the lawn, watering the lawn, digging, weeding, DIY (Do It Yourself; e.g. carpentry, home or car maintenance), and playing music, which are considered as activities undertaken in or around the home. Time spent participating in recreational activities was derived from responses to frequency and usual time per episode separately for each activity. The questionnaire was validated against an objective measure of energy expenditure (4-day heart-rate monitoring with individual calibration on four separate occasions over 1 year), and the repeatability of the questionnaire has also been demonstrated [109]. Intensity of physical activity in different domains was calculated by summing energy expenditure derived from applying published metabolic equivalent (MET) values to usual time spent in all activities and is expressed as MET-hours per week (MET.h/wk) [112].

Quantitative ultrasound scanning was used to measure broadband ultrasound attenuation (BUA; db/MHz) and speed of sound (SOS; m/s) of the calcaneus as described in Chapter 2. Anthropometric measures and behavioural variables (smoking and alcohol intake) were derived from second health examination of EPIC-Norfolk. Participants were followed for all health outcomes including fractures up to the end of March 2007 for present analyses. Fractures of skull, face, metacarpals, metatarsals, and phalanges were excluded from the analyses.

Within each domain of physical activity, sex-specific quartiles of physical activity were computed. The associations between quartiles of physical activity in different domains and BUA were analysed using sex-specific linear regression models. Cox proportional-hazards regression was used to assess the associations between different levels of physical activity and prospective risk of fractures. To investigate the potential non-linearity of the association between physical activity and fracture risk, fractional polynomial modelling was used. Fractional polynomial modelling compares models with different combinations of linear and nonlinear transformations of continuous variables and selects the best fitting models. The method proposed by Royston and Sauerbrei [123] is a systematic and validated approach to investigate possible non-linear functional relationships. All regression models were adjusted for baseline values of age, height, body mass index (BMI), smoking status, and alcohol consumption. When examining the domain-specific association of physical activity with fractures, Cox models were additionally adjusted for BUA as well as the other domains of activity. Hip fracture was considered as a separate outcome for survival analysis. Risk modification by sex, age, and history of fracture as well as the interaction between the different domains of physical activity were tested by adding the respective interaction terms to the Cox models, and their significance was tested by the likelihood ratio statistic. All database management and statistical analyses were performed using Stata software, version 10.0 (StataCorp LP., College Station, TX, USA).

6.4. Results

6.4.1. Characteristics of the study population

After exclusion of participants with incomplete data, 14,903 were entered into the analysis. The mean age at baseline was 63 years among 6,514 male and 61.5 years among 8,389 female participants. There were 504 fractures of any type in the study population of which 164 were hip fractures. Time to fracture from baseline assessment was 4.5 ± 2.2 years for all fractures and 4.7 ± 2.2 years for hip fractures. Average follow-up time was 7.5 ± 1.3 years. The mean physical activity at all domains was 114.2 ± 62 MET.h/week among men and 115.6 ± 49 MET.h/week among women. Higher levels of physical activity at/around home was correlated with lower levels of leisure-time activities (Pearson correlation coefficient = -0.12; $p<0.001$), activities at work (coefficient = -0.33; $p<0.001$), and for transportation (coefficient = -0.17; $p<0.001$). There was no significant pair-wise correlation between other domains of physical activity.

The baseline characteristics of the study population stratified by working status are summarised in *Table 6.1*. Participants not in paid employment were 11 years older, and 68% of all fractures (83% of hip fractures) occurred in this group. Both BUA and SOS were significantly higher among working participants and the history of fracture was twice as high in the nonworking women compared to working women. Among the nonworking participants, 29.4% were categorised as being active or moderately active compared with 72.3% in the working group. Differences in total physical activity between the two groups were largely explained by differences in occupational activity because the level of transport-related activity was similar across all groups and the levels of home or leisure-time activities were higher in the nonworking participants (*Table 6.1*).

Table 6.1: Baseline characteristics by working status among 14,903 participants of the EPIC-Norfolk study who completed EPAQ2 questionnaire

	Women		Men	
	Working Participants n=3838	Nonworking Participants n=4551	Working Participants n=3313	Nonworking Participants n=3201
Age (yr)	55.9 (7.0)	66.4 (7.6)	57.3 (7.2)	68.9 (6.5)
Height (cm)	162 (6.1)	160 (6.1)	175.1 (6.4)	172.7 (6.6)
Weight (Kg)	68.6 (11.7)	68.7 (11.9)	82.2 (11.7)	80.5 (11.4)
Body Mass Index (Kg/m^2)	26.1 (4.3)	26.8 (4.4)	26.8 (3.3)	27.0 (3.3)
Current smokers	356 (9.3%)	306 (6.8%)	285 (8.6%)	226 (7.1%)
Alcohol intake (u/wk)*	4.9 (5.9)	4.1 (5.4)	10.5 (11.6)	9.1 (11.2)
Physical activity (MET.h/wk)				
All domains combined	137.6 (47.1)	97.2 (43.1)	146.1 (61.1)	80.9 (43.4)
At home	57.0 (26.9)	64.3 (30.6)	20.0 (15.8)	30.2 (23.8)
At work	46.8 (33.7)	-	82.0 (53.5)	-
For transportation	2.2 (5)	3.0 (6.6)	2.7 (7.0)	1.8 (3.7)
At leisure time	26.9 (24.2)	28.4 (26.6)	35.9 (29.9)	44.2 (34.9)
History of fracture	179 (4.7%)	445 (9.8%)	175 (5.3%)	200 (6.3%)
BUA (dB/MHz)	77.1 (15.6)	67.9 (16)	91.2 (17.2)	88.8 (17.9)
SOS (m/s)	1637.2 (38.5)	1614.1 (38.6)	1648.4 (39.6)	1641.8 (40.1)
Follow-up time (yr)	7.5 (1.1)	7.4 (1.5)	7.5 (1.2)	7.1 (1.8)
Follow-up Person-years	28765	33061	24788	22879
Any type of fracture	97 (2.5%)	263 (5.8%)	63 (1.9%)	81 (2.5%)
Hip fracture	17 (0.4%)	105 (2.3%)	10 (0.3%)	32 (1%)

Values are mean (standard deviation) for continuous variables and frequency (percentage) for categorical variables. BUA = broadband ultrasound attenuation; SOS = speed of sound
* Values are medians (inter-quartile ranges)

6.4.2. Physical activity and heel ultrasound

After adjustment for age, sex, history of fracture, BMI, smoking and alcohol intake, total physical activity energy expenditure was positively associated with BUA (linear regression coefficient 0.48, $p < 0.001$). Among subdomains of physical activity, leisure time and home activities were significantly associated with BUA ($p<0.01$) but in different directions. While higher leisure time activities were associated with higher levels of BUA (coefficient +0.76, $p<0.001$), more physical activity at home was associated with reduced BUA among both men and women (coefficient 0.42, $p=0.006$). These associations were observed in all working and nonworking men and women. Physical activity at work or for transportation was not associated with BUA.

There was a significant interaction (effect modification) between age and physical activity at home for prediction of BUA ($p=0.016$). While higher amounts of physical activity at home were associated with a reduced BUA among younger participants (both men and women <65 years of age; $p<0.001$), there was no such association among older participants ($p=0.2$). *Figure 6.1* shows the interaction between age and physical activity at home. Increased physical activity at home was associated with increased total physical activity in both age groups but it was associated with decrease in BUA only among younger participants. There was no significant interaction between sex, history of fracture, and any subdomain of physical activity.

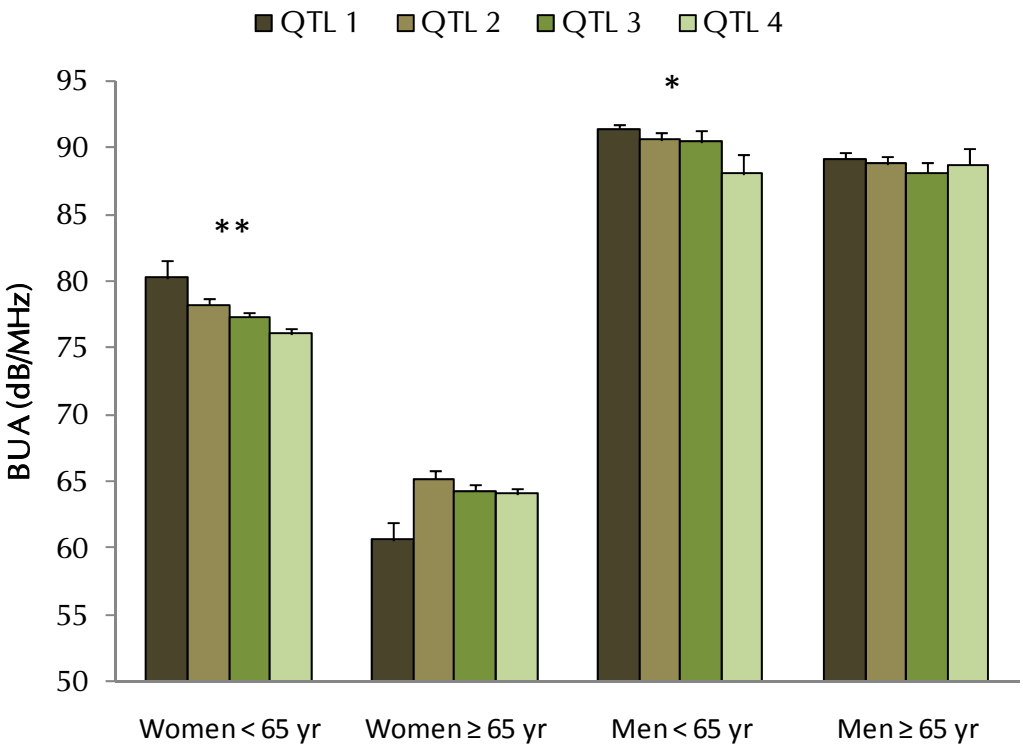

Figure 6.1: Distribution of BUA in 4 quartiles of physical activity at or around home in different age groups of men and women
* denotes significant difference at $p<0.05$ and ** at $p<0.01$.

In multivariable linear regression analysis, there was a significant positive association between stair climbing at home and BUA among both men and women (p<0.001; *Figure 6.2*). Cycling for leisure or transport was associated with a higher BUA only among men (P=0.021). Walking for leisure or transport was associated with increased BUA among both women and men but the association was not linear among men. Men with ≤ 90 minutes of walking per week showed a higher increase in BUA (average increase = 2.2 dB/MHz) compared to those with > 90 min/week (average increase = 1.9 dB/MHz). Swimming was associated with higher levels of BUA among both men (p=0.014) and women (p<0.001). Duration of TV viewing was significantly associated with BUA only among women. Women who reported higher TV watching durations had lower BUA (regression coefficient = -0.08, p<0.001).

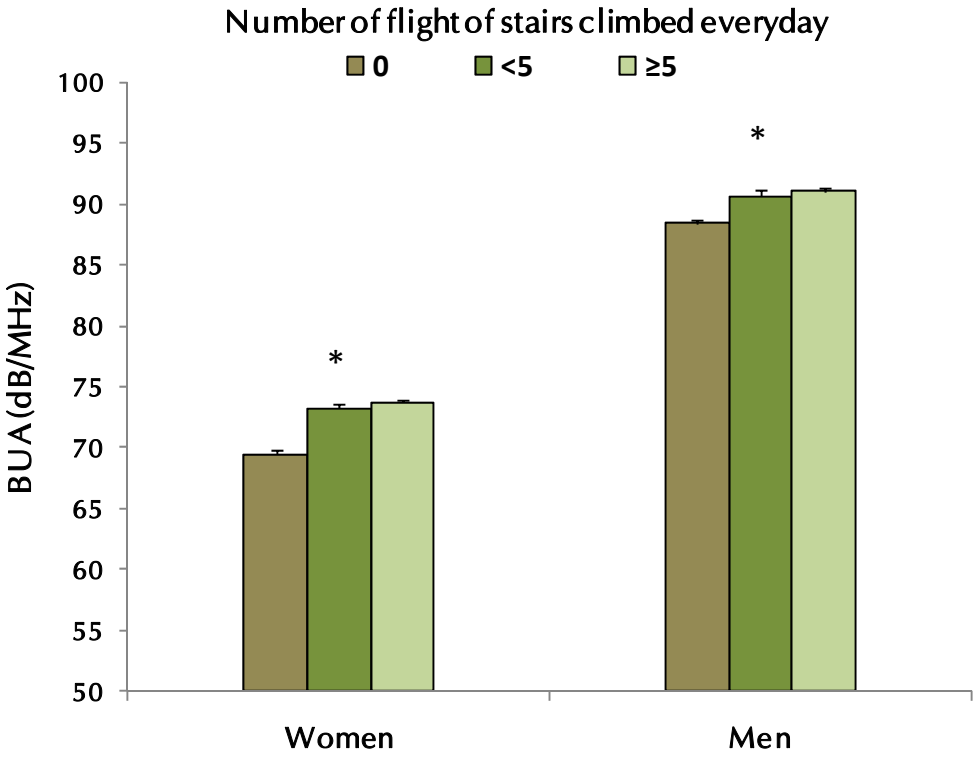

Figure 6.2: Mean of BUA in different groups of men and women based on number of flight of stairs climbed everyday at home or work
* denotes significant difference at p<0.01.

6.4.3. Physical activity and risk of fracture

Table 6.2 summarises the results of multivariable Cox regression analysis for the associations between different domains of physical activity and fractures in men and women. There was a U shaped association between total physical activity and risk of fracture among men. This shape of association was also observed between home and leisure time activities and hip fractures among women but not in men. Physical activity at home increased the risk of any fracture (in particular, clinical vertebral fractures) among men. However, leisure activities were associated with a linear and sizable decrease in hip fracture risk among men. Physical activity for transportation increased the risk of any fracture (in particular, wrist fractures) among men. Among working participants, there was a significant increase in fracture risk among moderately active women (*Table 6.2*).

Table 6.2: Associations between physical activity (PA; total and by domains) and fracture (any type and hip fracture) among 8,389 women and 6,514 men participating in the EPIC-Norfolk study

	Women								Men							
	Any type of fracture (360 events)				Hip fracture (122 events)				Any type of fracture (144 events)				Hip fracture (42 events)			
	n	HR	95% CI	*P* for linear trend	N	HR	95% CI	*P* for linear trend	n	HR	95% CI	*P* for linear trend	n	HR	95% CI	*P* for linear trend
Total PA																
Quartile 1	136	1.00		0.237	60	1.00		0.537	40	1.00		0.062	21	1.00		0.576
Quartile 2	77	0.85	0.63-1.15		25	0.63	0.38-1.05		30	0.73	0.43-1.23		6	0.30	0.11-0.81	
Quartile 3	78	1.07	0.78-1.47		21	0.86	0.50-1.48		32	1.07	0.64-1.79		8	0.66	0.27-1.58	
Quartile 4	69	1.20	0.85-1.68		16	0.85	0.45-1.59		42	1.58	0.94-2.66		7	0.95	0.36-2.54	
PA at/around home																
Quartile 1	100	1.00		0.306	41	1.00		0.237	24	1.00		**0.008**	7	1.00		0.503
Quartile 2	82	0.88	0.64-1.20		19	**0.51**	0.29-0.90		33	1.23	0.68-2.21		12	0.65	0.23-1.89	
Quartile 3	95	0.87	0.64-1.19		33	0.61	0.35-1.04		32	1.70	0.98-2.93		9	1.01	0.40-2.57	
Quartile 4	83	0.84	0.61-1.16		29	0.71	0.43-1.19		55	**1.91**	1.11-3.26		14	1.16	0.48-2.82	
PA at leisure time																
Quartile 1	109	1.00		0.686	45	1.00		0.914	42	1.00		0.346	17	1.00		**0.001**
Quartile 2	81	0.72	0.52-1.01		24	**0.55**	0.30-0.93		34	0.83	0.50-1.36		11	0.74	0.34-1.57	
Quartile 3	80	0.88	0.64-1.22		27	0.89	0.52-1.52		37	0.93	0.57-1.51		9	0.48	0.20-1.13	
Quartile 4	90	1.02	0.75-1.39		26	0.87	0.51-1.50		31	0.74	0.44-1.23		5	**0.12**	0.02-0.52	
PA for transportation																
Quartile 1	326	1.00		0.894	119	1.00		0.097	118	1.00		**0.012**	39	1.00		0.721
Quartile 2	12	0.93	0.52-1.67		2	0.54	0.13-2.22		8	1.53	0.71-3.32		3	2.85	0.86-9.45	
Quartile 3	9	0.83	0.41-1.69		0	-	-		10	1.95	0.97-3.94		0	-	-	
Quartile 4	13	1.08	0.57-2.06		1	0.42	0.06-3.07		8	2.15	0.91-5.06		0	-	-	
PA at work																
Quartile 1	32	1.00		0.310	7	1.00		0.560	15	1.00		0.277	3	1.00		0.123
Quartile 2	23	1.19	0.64-2.21		2	0.58	0.11-3.06		14	1.24	0.51-3.03		1	0.75	0.06-8.84	
Quartile 3	28	1.98	1.07-3.64		5	1.51	0.36-6.37		16	1.36	0.55-3.35		1	1.12	0.09-14.6	
Quartile 4	14	1.14	0.55-2.37		3	1.31	0.27-6.39		18	1.60	0.67-3.80		5	3.87	0.56-26.6	

HR = hazard ratio; CI = confidence interval; significant values at the level of $p<0.05$ are shown in boldface.

As depicted in *Table 6.3*, stair climbing at home was associated with a significant increased risk of hip fracture among men. House work activities (including preparing food, cooking, washing up, cleaning, shopping, caring for pre-school children and babies, and caring for handicapped, elderly or disabled people at home) were associated with lower risk of all fractures among women while accompanied higher risk of fractures of any type among men. Walking for leisure or transport for <90 min/week was associated with reduced risk of fracture (any type and hip fracture) among women. In combined analysis considering both men and women, walking for any duration was associated with reduced risk of fracture (any fracture HR = 0.74, 95%CI 0.58-0.93; hip fracture HR = 0.57; 95%CI 0.37-0.87). There was no significant association between cycling, swimming or TV viewing and fractures among all participants (*Table 6.3*). Similarly, activities around home (including mowing the lawn, watering the lawn, digging, shovelling, weeding or pruning, and DIY) were not associated with fracture risk.

Table 6.3: Associations between different types of physical activity and fracture (any type and hip fracture) among 8,389 women and 6,514 men participating in the EPIC-Norfolk study

	Women								Men							
	Any type of fracture (360 events)				Hip fracture (122 events)				Any type of fracture (144 events)				Hip fracture (42 events)			
	n	HR	95% CI	P for linear trend	n	HR	95% CI	P for linear trend	n	HR	95% CI	P for linear trend	n	HR	95% CI	P for linear trend
Stair climbing at home																
None (n=5,336)	148	1.00		0. 172	43	1.00		0.843	47	1.00		0.131	5	1.00		**0.009**
< 10 stairs/day (n=6,436)	132	0.74	0.57-0.95		48	1.04	0.6-1.6		59	1.02	0.7-1.5		25	**3.65**	1.38-9.64	
≥ 10 stairs/day (n=3,131)	80	0.99	0.7-1.3		31	1.46	0.88-2.4		38	1.45	0.92-2.3		12	**3.90**	1.35-11.2	
Housework activity level*																
Low (n=4,796)	49	1.00		0.077	24	1.00		0.085	71	1.00		**<0.001**	23	1.00		0.608
Moderate (n=5,314)	132	**0.58**	0.40-0.85		36	**0.34**	0.19-0.61		52	**1.76**	1.18-2.60		11	0.85	0.40-1.81	
High (n=4,793)	179	**0.60**	0.42-0.86		62	**0.43**	0.25-0.74		21	**2.63**	1.55-4.45		8	1.51	0.60-3.79	
Cycling for leisure/transport																
None (n=11,646)	320	1.00		0.846	113	1.00		0.704	106	1.00		0.101	40	1.00		0.252
≤ 30 min/week (n=1,720)	19	0.67	0.4-1.12		4	0.62	0.2-1.7		17	1.24	0.7-2.26		2	0.35	0.05-2.6	
> 30 min/week (n=1,537)	21	1.05	0.64-1.7		5	1.15	0.46-2.9		21	1.52	0.9-2.56		0	-	-	
Walking for leisure/transport																
None (n=3,299)	115	1.00		0.115	50	1.00		**0.049**	46	1.00		0.123	16	1.00		0.078
≤ 90 min/week (n=6,064)	125	**0.71**	0.5-0.94		39	**0.56**	0.35-0.9		55	0.82	0.5-1.27		19	1.03	0.5-2.11	
> 90 min/week (n=5,540)	120	0.78	0.6-1.04		33	0.62	0.39-1.01		43	0.70	0.44-1.1		7	0.43	0.17-1.08	
Swimming																
None (n=9,783)	259	1.00		0.269	93	1.00		0.768	104	1.00		0.962	35	1.00		0.408
< once a week (n=2,710)	37	0.89	0.60-1.3		15	0.95	0.47-1.92		23	1.01	0.62-1.6		4	0.60	0.18-1.99	
≥ once a week (n=2,410)	64	1.23	0.9-1.65		14	0.92	0.51-1.67		17	0.98	0.55-1.7		3	0.70	0.21-2.32	
TV viewing																
< 3 hrs/day (n=8,028)	164	1.00		0.776	48	1.00		0.334	77	1.00		0.694	19	1.00		0.584
≥ 3 hrs/day (n=6,875)	196	0.97	0.77-1.2		74	1.22	0.82-1.82		67	1.08	0.75-1.5		23	1.20	0.62-2.31	

HR = hazard ratio; CI = confidence interval; significant values at the level of $p<0.05$ are shown in boldface.

* Low: <25 MET.h/week; Moderate: ≥ 25 & <55 MET.h/week; High: ≥ 55 MET.h/week (see text for description of housework activities)

Figure 6.3 depicts the associations between total and domain-specific physical activity and risk of hip fracture based on second-degree fractional polynomial modelling. Graphs show the hazard ratios (in logarithmic scale) and 95% confidence intervals for each level of physical activity (in units of MET.h/wk) compared to the mean level of physical activity in that population. Graphs for total physical activity show a significant risk of hip fracture among sedentary men and women with a sharp decrease in risk with moderate levels of physical activity and no further change with higher levels of activity. Home activities especially for women show a U-shaped association with the lowest risk among participants in the middle of the distribution and increased risk for participants with low and high levels of home activities. High levels of leisure time activities among men were associated with reduced risk of hip fracture (*Figure 6.3*). This Figure also shows that the absolute levels and range of physical activity in various domains are very different in men and women (horizontal axes). Therefore, while we can examine the relationship across the usual sex-specific quartiles, direct comparison between men and women are limited due to the different ranges of activity levels in different domains.

In total, 2,623 of our participants reported practicing a high-impact exercise (including mountain climbing, aerobics, competitive running, tennis or badminton, squash, table tennis, football, rugby, hockey, cricket, rowing, basketball, volleyball, horse-riding, boxing, and wrestling) for at least once a month. None of 42 hip fractures in men and only 6 out of 122 hip fractures in women occurred in this population. Floor exercises (including stretching, bending, keeping fit, yoga, and dancing) were not associated with risk of fracture in our population.

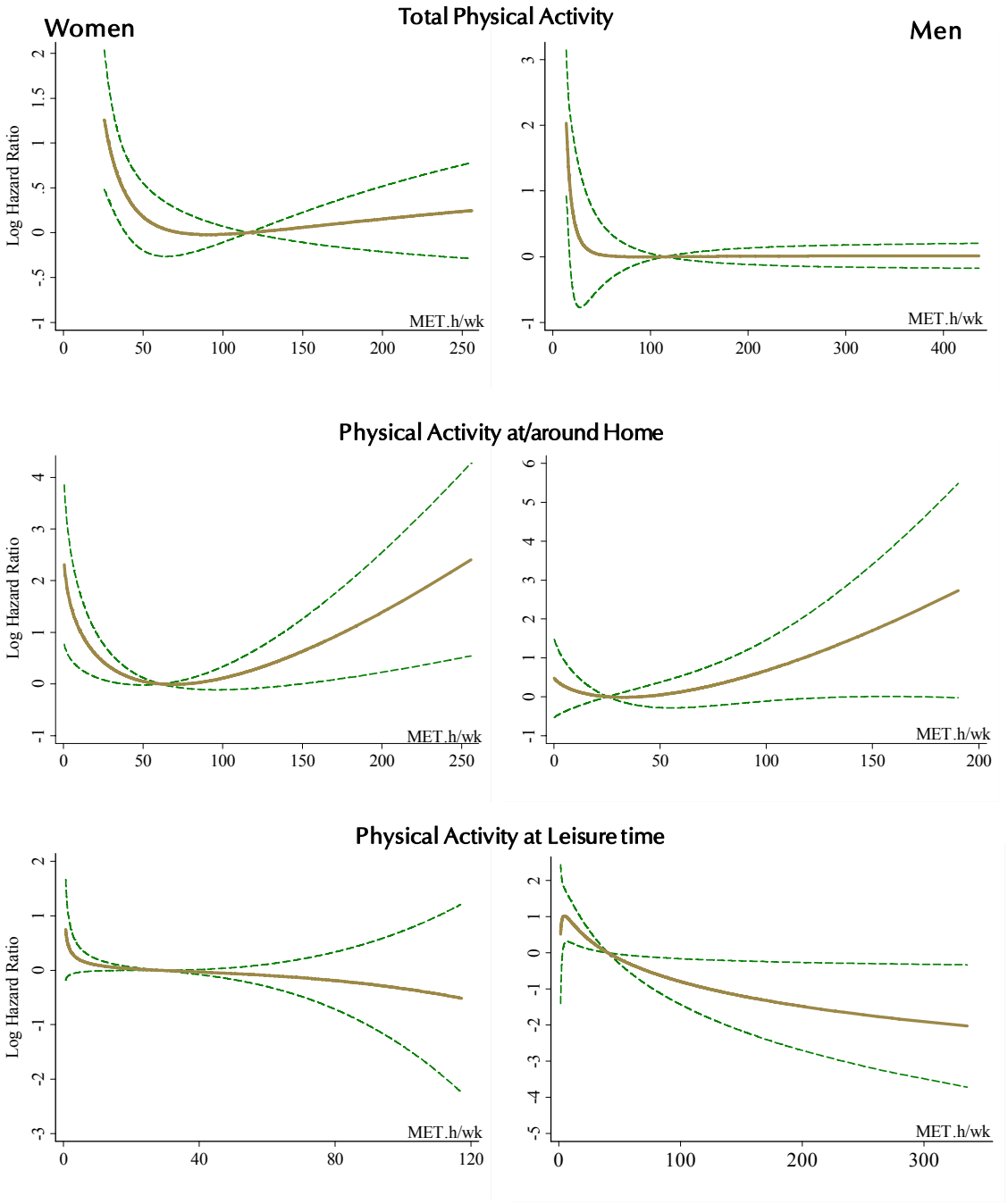

Figure 6.3: Non-linear associations observed between physical activity and risk of hip fracture in EPIC-Norfolk study
Fitted lines (solid) and 95% confidence intervals (dashed) are derived from Cox proportional-hazards regression analysis using fractional polynomial modelling.

6.5. Discussion

This study shows that different domains of physical activity may relate differently to fracture risk and these relationships may vary by age and sex. Two main domains of physical activity associated with risk of fracture were home and leisure time activities. The associations observed between physical activity and bone ultrasound measures did not translate to fracture risk estimates as, for instance, physical activity at home was associated with lower heel BUA and lower risk of fracture among women. Multivariable fractional polynomial models showed a non-linear association between physical activity (especially at home domain) and fracture risk. There were noticeable differences in effects of physical activity on fracture risk between men and women.

Total physical activity among our participants was not associated with prospective risk of all fractures. However, moderate physical activity was associated with a reduced risk of hip fracture (not significant for women but significant among men). Previous studies have also shown an association between physical activity and hip fracture but not with all fractures. Meta-analysis of 13 prospective cohort studies (Chapter 5) confirms that moderate-to-vigorous physical activity is associated with a hip fracture risk reduction of 45% (95% CI 31-56%) and 38% (95% CI 31-44%), respectively, among men and women. It should be noted that most of these observational studies [190-193, 195, 197-199] have only considered leisure-time or recreational activities (which we have considered as a specific subdomain of physical activity in this study). Our results suggest that reduced risk of hip fracture among men is mainly mediated via leisure activities while this risk is reduced among women with moderate home and leisure time activities.

More attention to physical activity at or around home as a risk factor for fracture is needed. This risk factor appears to relate differently to fracture risk among men and women. While moderate home activities in women are associated with a lower risk of hip fracture, increasing levels of home activities were linearly

associated with increased risk of any fracture among men. Particularly men who were very active at home had almost 2 times fracture risk compared to inactive men at home. Fractional polynomial modelling showed a U-shaped association with hip fracture only among women. More detailed examination of the nature of this relationship indicated that a major part of it is related to housework activities (*Table 6.3*). Similarly, stair climbing at home was associated with fractures differently in men and women. This finding needs verification in specifically designed studies, but there are a number of potential hypotheses for this observation. A possibility is that men who remain in the house are more likely to be frail and more fracture prone. Also, those who are less engaged in work or recreational activity might tend to over-report their housework activities, which leads to spurious observations. Other potential hypotheses include increased risk of falls in closed areas for men or unfamiliar environments.

Among different types of physical activity, walking for leisure or transport showed a consistent association with fracture risk in our study. Previous studies have also confirmed the relationship between walking and BMD [248] and fracture risk [41, 191]. In the Nurses' Health Study among 61200 postmenopausal women followed for 12 years, moderate levels of walking were associated with substantially lower risk of hip fracture [191]. Study of Osteoporotic Fractures found self-reported walking for exercise to be associated with a significant 30% reduction in hip fracture risk after 4.1 years and 40% after 7.6 years of follow-up [41, 158]. European Vertebral Osteoporosis Study (EVOS) showed a 20% reduction in the risk of developing a vertebral deformity in women who walk for more than 30 minutes per day as compared to inactive women [216]. Clinical practice guidelines have recommended brisk walking and other weight-bearing exercises for prevention of fractures and treatment of osteoporosis [248, 269].

Stair climbing has been shown to be associated with increased BMD among postmenopausal women [270]. We also found a positive association between stair climbing and ultrasound attenuation. However, this effect did not translate to reduced risk of fracture. This can be related to the increased risk of injurious falls

with stair-climbing at home [180]. TV viewing is shown to be related to less bone accrual in young children [271] and, in a previous analysis of the EPIC-Norfolk study, a significant negative association was observed in women between time spent watching television and heel BUA (which is confirmed in this analysis too) [272]. This association is not extended to the fracture risk in our population. Moreover, participation in high-impact exercise activities accompanied a significant reduction of hip fracture risk.

Few studies have previously shown a positive effect of leisure-time physical activity and brisk walking on QUS measures [256, 257]. These associations are confirmed in this study. However, physical activity at or around home showed a significant association in the reverse direction which warrants consideration in future studies. Swimming was also associated with increased BUA as shown in previous studies [260] but this did not lead to lower fracture risk among swimmers. It should be noted that heel QUS cannot be considered a perfect surrogate for site-specific dual-energy X-ray absorptiometry (DXA) scans in prediction of osteoporotic fractures.

Grouping of the physical activity subdomains and different activities in our study suggests for non-linear association of several aspects of physical activity and fracture risk. In particular physical activity at home and in leisure time as well as walking induced a decrease in fracture risk only among participants with moderate activity (no association with higher activity and even increased fracture risk with high activity at home among men). This is in concordance with previous studies evaluating the effects of physical activity on risk of falls among the elderly populations [178, 181, 217]. Attention to this point is necessary for evaluating the effects of different interventions and developing new strategies for prevention of falls and fractures [237].

Our study has several methodological strengths, including its prospective design and the high proportion of individuals followed up. In addition, the population-based sample of our study makes the results more generalisable compared with studies that have focused on defined groups. Limitations of this study are

common to most of the studies in the field. Although we have extensively validated EPAQ2 questionnaire in a large sample with sensible clinical measures [109], capability of a questionnaire to accurately estimate a multi-dimensional exposure like physical activity can always be questioned. EPAQ2 has not been specifically designed for evaluation of activities related to osteoporosis and fracture risk assessment. Hence, we could not evaluate the effects of weight-bearing exercises or specific types of activities on our outcomes. The questionnaire has been filled once at the start of the study and the pattern and level of physical activity might have changed in some participants during 7.5 years of follow-up. Physical activity at young ages may have long-lasting effects on bones and asking elderly participants about their activity levels in the past year might not be a good representation of the lifelong exposure. Another limitation of this study is lack of data on incident falls as a major determinant of risk of fractures. Other prospective studies with available data on incident falls may elucidate more details about the association between physical activity and fractures. Moreover, some of the trends of association between subdomains of physical activity and fracture risk have not reached to the significance level (especially for the hip fracture outcome) and this can be related to the limited power of this study to detect them. Further prospective studies or meta-analyses will be helpful to uncover such associations.

In conclusion, engaging in moderate levels of home and leisure time activities are independently associated with reduced risk of hip fracture compared with being physically inactive. In contrast, physical activity at work and for transportation did not confer a fracture risk reduction. Walking is the activity most consistently associated with fracture risk reduction in both men and women. These findings may contribute to the recommendations about the kinds of physical activities which can help reduce fracture risk in older people.

Chapter 7: Percentage Body Fat

7.1. Abstract

Obesity has generally been associated with higher bone density and lower fracture risk. However, weight-related indices of obesity (such as body mass index) may relate differently to health endpoints from fat-related indices (such as body fat distribution and fat mass), as they may capture different dimensions of obesity and associated biological effects. We examined the association between percentage body fat (%BF) and prospective risk of fracture in the European Prospective Investigation into Cancer (EPIC)-Norfolk study. From 14,789 participants (6,470 men) aged 42-82 years at baseline, 556 suffered a fracture (184 hip fractures) during 8.7 ± 0.8 years of follow-up. Risk of hip fracture decreased linearly with increasing %BF values among women but not among men. After adjustment for age, body mass index (BMI), smoking, history of fracture, alcohol intake and heel broadband ultrasound attenuation (BUA), the hazard ratio (95% CI) for a 10% higher %BF on risk of hip fracture was 0.56 (0.39-0.79) among women and 0.92 (0.39-2.21) in men. The effect size in women was approximately equivalent to 5 years difference in age or 1 standard deviation (17 dB/MHz) higher BUA. A non-linear negative association was also observed between %BF and risk of 'any type of fracture' among women but not men. Percentage body fat appears to predict hip fracture risk in women independently of BMI and with an effect size comparable to bone heel ultrasound. This effect was not observed in men. Understanding differences in relationships between different indices of obesity (such as %BF and BMI) as well as sex differences may help elucidate the metabolic and other underlying mechanisms involved in bone health and fracture risk.

7.2. Introduction

Obesity and osteoporosis are two major epidemics of the modern world. It is estimated that globally there are more than 1 billion overweight adults of whom at least 400 million are obese with the definition of body mass index (BMI) over 30 kg/m^2 [273]. National surveys have shown that, for instance, more than 22% of the population of UK and 30% of US citizens are obese [274, 275]. Osteoporosis is another major public health problem, characterized by excessive skeletal fragility and susceptibility to low-trauma fracture among the elderly. Globally between 30% and 50% of women and 13% and 30% of men will suffer from a fracture related to osteoporosis in their lifetime [276]. Recent studies suggest that there might be some relationships between obesity and osteoporosis at molecular and clinical levels [277].

Fat mass is a component of total body weight and one of the indices of obesity. Body fat mass and bone mineral density (BMD) are known to be under strong genetic regulation and the association between fat mass and fracture susceptibility may be plausible from a genetic point of view [278]. Several lines of clinical evidence support a beneficial effect of fat mass on increasing BMD, hence reducing the risk of osteoporosis [279-283]. In contrast, several other groups have suggested that excessive fat mass may not protect against osteoporosis [284-287]. Both groups have compelling evidence from in vitro and in vivo studies and several potential biological mechanisms have been proposed for either direction [288, 289]. These inconsistent findings reflect the inherently complicated nature of this relationship and call for new approaches and strategies to explore the potential effects of fat mass on bone [289].

Epidemiological studies have reported a non-linear relationship between BMI (a combined measure of weight and height) and risk of osteoporotic fractures [94]. Meta-analysis of 12 prospective studies on about 60,000 men and women suggested that most of the effect of BMI on non-hip fractures is probably mediated by the effects of weight on BMD (as adjustment for BMD removed most of the

observed association), but at the hip there is a component which is BMD-independent [94]. However, it is not clear what proportion of the BMI association may be related to the fat component of body weight. Importantly, there is only a limited number of prospective studies with fracture outcomes and direct assessment of body fat [285, 290, 291]. Most of the previous clinical studies have used dual-energy X-ray absorptiometry (DXA) for assessment of both fat mass and bone mass. Bioelectrical impedance analysis (BIA) is another known valid method for evaluation of body fat in obese persons [292]. Moreover, while DXA only measures the density of the bone, other techniques such as bone ultrasound are known to reflect elasticity and micro-architecture of the bone and to predict fractures as effectively as DXA [77, 78]. There are limited evidence from studies using these bone measurements [293, 294]. In this Chapter, we assess the association between fat mass (as measured by BIA) and quantitative ultrasound of the heel and prospective risk of fracture in EPIC-Norfolk population.

7.3. Methods

This study uses data from the second health examination of EPIC-Norfolk study and prospective follow-up from this date. Full details of participant recruitment and study procedures have been described in Chapter 2. Briefly, 15,786 of EPIC-Norfolk participants returned for a second health examination and were assessed by several health measurements including quantitative ultrasound (QUS) of the heel and bioelectrical impedance analysis. Electrical resistance (Ω) was assessed using a standard bio-impedance technique (Bodystat, Isle of Man, UK). This method has previously been shown to be valid [114] and reliable [115]. Total body water and fat-free mass were calculated using the impedance index (height^2/resistance), body weight and resistance according to published equations [116]. Fat mass was calculated as body weight minus fat-free mass. Percentage body fat (%BF) was fat mass expressed as percentage of total weight.

Height and weight were measured in light clothing without shoes. Height was measured to the nearest millimetre using a free-standing stadiometer (CMS Weighing Equipment Ltd., London, UK). Weight was measured to the nearest 100 grams using calibrated digital scales (Salter Industrial Measurement Ltd., West Bromwich, UK). Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Quantitative ultrasound scanning was used to measure broadband ultrasound attenuation (BUA; db/MHz) and speed of sound (SOS; m/s) of the calcaneus as described in Chapter 2. Due to high correlation between BUA and SOS (pairwise correlation coefficient = 0.73), only BUA was considered as the outcome for this analysis. Smoking status and alcohol consumption were derived from the questionnaires. Participants were followed for different health outcomes including fractures up to the end of March 2008 for present analyses. Fractures of skull, face, metacarpals, metatarsal, and phalanges were excluded from the analyses.

The associations between fat and bone measures as well as fracture risk are suggested not to follow a linear trend. Moreover, methods like categorisation of

patients according to arbitrary cutpoints or percentiles have less statistical power to detect associations. We conducted regression analysis using fractional polynomial modelling to explore the association between %BF and BUA with and without adjustment for BMI. Fractional polynomial modelling proposed by Royston and Sauerbrei [123] is a systematic approach to investigate possible non-linear functional relationships of continuous variables. This method compares models with different combinations of linear and nonlinear transformations of continuous variables (first- and second-degree transformations) and selects the best fitting model with backward elimination. In case of no significant difference between models, the model with lower degrees of freedom (linear rather than first- and second-degree models) will be selected as the best fitting model. Cox proportional-hazards regression analysis with fractional polynomial modelling was used to assess the associations between %BF and prospective risk of fractures. All regression models were adjusted for age, history of fracture, smoking status, and alcohol consumption. Cox models were additionally adjusted for BUA. Effects of %BF on BUA and fracture risks are specifically illustrated in models with and without adjustment for BMI. Hip fracture was considered as a separate outcome for survival analysis. All database management and statistical analyses were performed using Stata software, version 10.0 (StataCorp LP., College Station, TX, USA).

7.4. Results

7.4.1. Characteristics of the study population

After exclusion of participants with incomplete data, 14,789 participants were entered into the analysis. The mean age at baseline was 63 years among men and 61.8 years among women. Percentage body fat (%BF) was significantly higher among women as compared to men (39.7 9.1% vs. 23.5 6.1%; $p < 0.001$). Comparison of baseline characteristics of participants according to quartiles of %BF (*Table 7.1*) shows that, apart from history of fracture (and age for men), other known risk factors of fracture were significantly different among participants with different levels of fat mass. As expected, there was a strong linear association between BMI and %BF in both men and women. Crude mean BUA generally increased with higher levels of fat mass among men and women (*Table 7.1*).

Table 7.1: Characteristic of EPIC-Norfolk participants according to percentage body fat quartiles

	Percentage body fat				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P value*
Women	*(<34%)*	*(34-39%)*	*(39.5-45%)*	*(>45%)*	
	n=2,198	*n= 2,116*	*n=1,964*	*n=2,041*	
Age (years)	60.6 (9.7)	61.3 (9.1)	62.1 (8.7)	62.1 (8.3)	<0.001
Height (cm)	161.9 (6)	161.3 (6)	160.5 (6)	159.9 (6)	<0.001
Weight (kg)	58.6 (6.6)	65.4 (7.0)	70.9 (8.1)	80.7 (11.4)	<0.001
BMI (kg/m^2)	22.3 (2.0)	25.1 (2.0)	27.5 (2.4)	31.5 (3.9)	<0.001
Current smoking	222 (10.2%)	173 (8.2%)	128 (6.6%)	139 (6.9%)	0.001
Alcohol intake (units/wk)*	2.5 (6)	2.5 (6)	2 (5.5)	2 (4.5)	0.004
Past history of fracture	171 (7.8%)	152 (7.2%)	133 (6.8%)	156 (7.7%)	0.6
BUA (dB/MHz)	68.6 (17.1)	71.5 (16.3)	72.9 (15.3)	76.0 (16.1)	<0.001
SOS (m/sec)	1621.2 (43)	1624.2 (40)	1625.1 (39)	1629.2 (37)	<0.001
Incident hip fracture	53 (2.4%)	37 (1.7%)	24 (1.2%)	20 (1.0%)	<0.001
Any incident fracture	122 (5.5%)	96 (4.5%)	83 (4.2%)	92 (4.5%)	0.2
Men	*(<20%)*	*(20-23%)*	*(23.5-27%)*	*(>27%)*	
	n=1,724	*n= 1,572*	*n=1.596*	*n=1,578*	
Age (years)	63.0 (9.5)	62.9 (8.9)	62.9 (8.9)	62.8 (8.7)	0.9
Height (cm)	174.5 (6.8)	173.9 (6.5)	173.9 (6.4)	173.4 (6.6)	<0.001
Weight (kg)	71.5 (7.4)	78.5 (7.1)	83.9 (8.1)	92.4 (11.0)	<0.001
BMI (kg/m^2)	23.5 (1.8)	25.9 (1.5)	27.7 (1.7)	30.7 (2.9)	<0.001
Current smoking	175 (10.2%)	119 (7.6%)	105 (6.6%)	115 (7.4%)	<0.001
Alcohol intake (units/wk)*	5.5 (10.5)	6 (11.5)	6.5 (12.5)	6.5 (13.5)	0.004
Past history of fracture	94 (5.5%)	88 (5.6%)	78 (4.9%)	105 (6.7%)	0.2
BUA (dB/MHz)	88.3 (18.5)	90.0 (17.5)	91.3 (16.9)	90.8 (16.8)	<0.001
SOS (m/sec)	1648.2 (41)	1647.5 (40)	1644.8 (39)	1640.4 (38)	<0.001
Incident hip fracture	17 (1.0%)	8 (0.5%)	10 (0.6%)	15 (1.0%)	0.3
Any incident fracture	40 (2.3%)	36 (2.3%)	44 (2.8%)	43 (2.7%)	0.7

Data are mean (standard deviation) or number of participants (percentage)
* Values are median (interquartile range) [Kruskal-Wallis test for P values]
BMI: body mass index; BUA: broadband ultrasound attenuation; SOS: speed of sound

7.4.2. Percentage body fat and heel ultrasound

Figure 7.1 shows the association between %BF and BUA in multivariable-adjusted fractional polynomial models with and without further adjustment for BMI. As depicted in upper left graph, %BF was positively associated with BUA among women which then became a negative linear association after adjustment for BMI (lower left graph, *Figure 7.1*). Before adjustment for BMI among men, there was a non-linear positive association between %BF and BUA with steeper slope among participants with low fat mass (upper right graph, *Figure 7.1*). However, this association also became negative after adjustment for BMI (lower right graph, *Figure 7.1*). Models including BMI for both sexes showed a significant and positive association between BMI and BUA (non-linear among men). This suggests that the positive association observed between %BF and BUA was mainly accounted for by BMI, which is highly correlated with %BF. The residual association between fat and bone ultrasound appeared to be negative after adjustment for BMI.

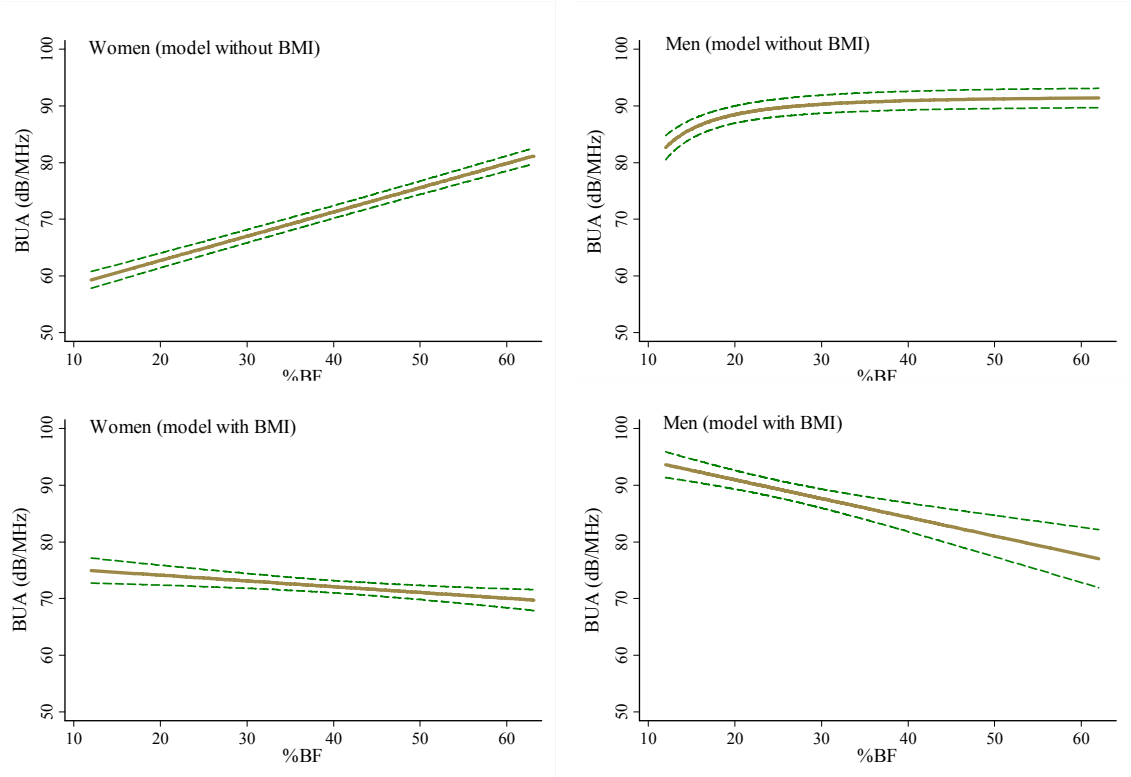

Figure 7.1: Association between percentage body fat and heel BUA among 14,789 EPIC-Norfolk participants
All models are adjusted for age, history of fracture, smoking status and alcohol intake.

7.4.3. Percentage body fat and fracture risk

During 122,330 person-years of follow-up, 556 fractures of any type (163 in men) occurred in EPIC-Norfolk participants of which 184 (50 in men) were hip fractures. Time to fracture from baseline assessment was 5.0 ± 2.5 years for all fractures and 5.4 ± 2.5 years for hip fractures. Average follow-up time was 8.3 ± 1.6 years. *Table 7.1* shows that, in univariate analysis, higher levels of fat mass were associated with lower risk of hip fracture among women. This association was also evident in the multivariable Cox proportional-hazards regression analysis with different levels of adjustment for clinical variables. *Table 7.2* shows that, among women, age-adjusted %BF was significantly associated with lower risk of hip fracture and adding BMI to the model did not change the association. Further adjustment for BUA did not materially change the results (model 3 in *Table 7.2*) indicating that the relationship between fat mass and fracture risk is independent of bone characteristics as measured by heel ultrasound. *Table 7.3* shows the Cox model with all variables (model 4 in *Table 7.2*). The effects of 10% decrease in %BF (which is approximately 1 standard deviation of %BF in women) on risk of hip fracture among women was almost equal to 5 years increase in age and 1 standard deviation (17 dB/MHz) lower BUA. BMI was not a significant predictor of hip fracture for women in this model. There was no significant association between %BF and fracture risk among men in univariate (*Table 7.1*) and multivariable analyses (*Table 7.2* and *Table 7.3*). The best fitting models for both men and women were linear and *Figure 7.2* depicts the linear decrease in hazard of hip fracture attributed to %BF among women but not men.

Table 7.2: Association between percentage body fat and risk of hip fracture with different levels of adjustment for known risk factors
Hazard ratios (HR) and 95% CI are estimated for 10% increase in percentage body fat from Cox proportional-hazards regression models indicated. Details of model 4 are shown in *Table 7.3*.

	Women			Men		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Models with adjustment for:						
1: Age	0.62	0.49-0.77	<0.001	1.00	0.61-1.62	0.9
2: Age and BMI	0.56	0.39-0.80	0.001	0.88	0.35-2.16	0.8
3: Age, BMI and BUA	0.55	0.38-0.78	0.001	0.92	0.39-2.20	0.8
4: Age. BMI, BUA and other clinical factors*	0.56	0.39-0.79	0.001	0.92	0.39-2.21	0.8

*These clinical factors include: history of fracture, smoking status and alcohol intake

Table 7.3: Multivariable Cox proportional-hazards regression model for prediction of prospective risk of hip fracture among EPIC-Norfolk participants
Continuous variables are standardised to make sensible comparisons.

	Women			Men		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Percentage body fat (per 10%)	0.56	0.39-0.79	0.001	0.92	0.39-2.21	0.8
Body mass index (per 4 kg/m^2)	1.24	0.93-1.67	0.14	1.16	0.62-2.16	0.6
Age (per 5 years)	1.69	1.47-1.95	<0.001	1.83	1.48-2.27	<0.001
History of fracture	1.54	0.98-2.44	0.06	1.98	0.83-4.69	0.12
Current smoking	0.97	0.45-2.1	0.9	0.72	0.25-2.02	0.5
Alcohol intake (unit/week)	0.95	0.91-1	0.034	1.01	0.98-1.03	0.5
BUA (per 17 dB/MHz)	0.61	0.48-0.77	<0.001	0.63	0.47-0.86	0.003

HR: Hazard Ratio; CI: Confidence interval; BUA: broadband ultrasound attenuation

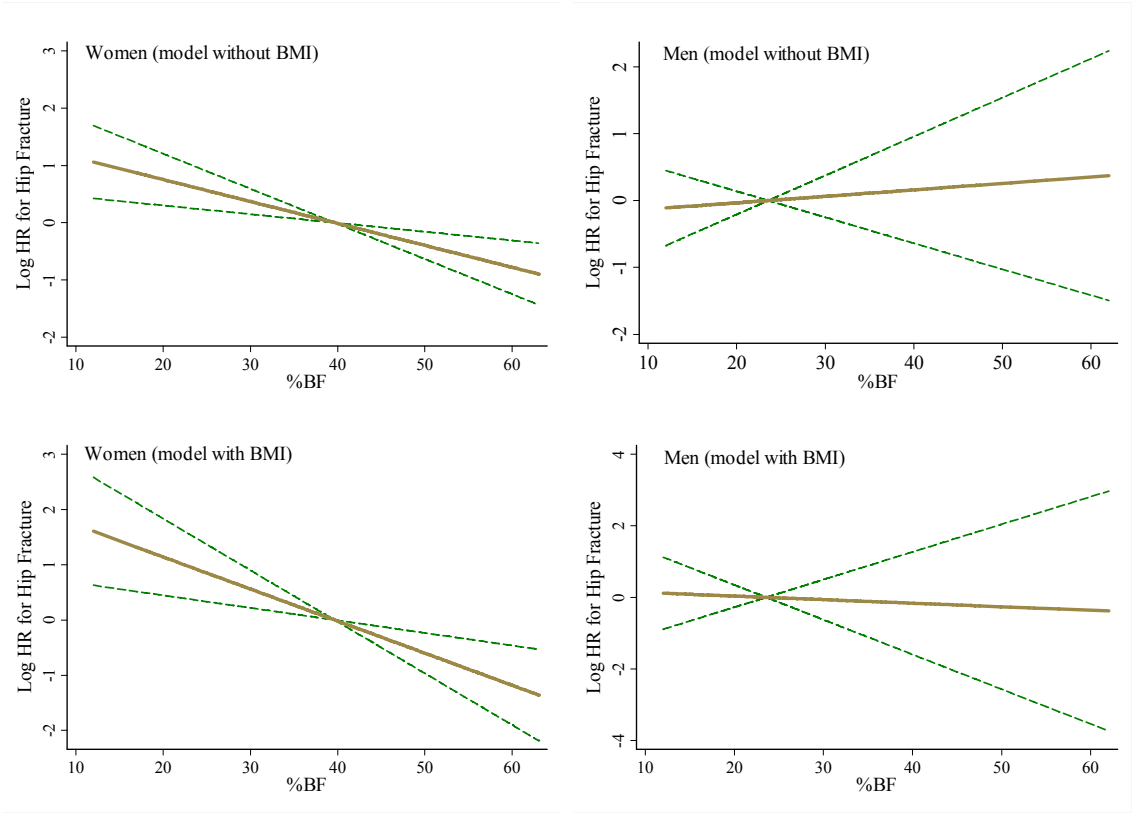

Figure 7.2: Association between percentage body fat (%BF) and risk of hip fracture among participants of EPIC-Norfolk study
Fitted lines (solid) and 95% confidence limits (dashed lines) are from fractional polynomial models with and without adjustment for body mass index (BMI) in women (left graphs) and men (right graphs). All models are adjusted for age, history of fracture, smoking status, alcohol intake and BUA.

The inverse association was also observed between %BF and risk of 'any type of fracture' among women (*Figure 7.3*). Before adjustment for BMI the association appeared to be best modelled by a second-degree fractional polynomial curve with the lowest hazard seen around mean percentage body fat of 40% (upper left graph; p<0.001); after adjustment for BMI, the relationship appeared to be a first-degree fractional polynomial with continuous but decrease in fracture risk with higher %BF (lower left graph, p=0.006). *Table 7.4* shows the hazard ratios for different categories of %BF in comparison to mean fat category (35%-45%). This

Table shows that, while low values of %BF are accompanied with substantially high risk of any fracture (e.g. more than double risk for women with <20% fat mass compared to women with 40% fat mass), higher values of %BF are associated with moderately lower risk of fracture (e.g. women with >55% fat mass had about 20% lower risk of fracture compared to mean). Again there was no significant association among men (*Table 7.4*).

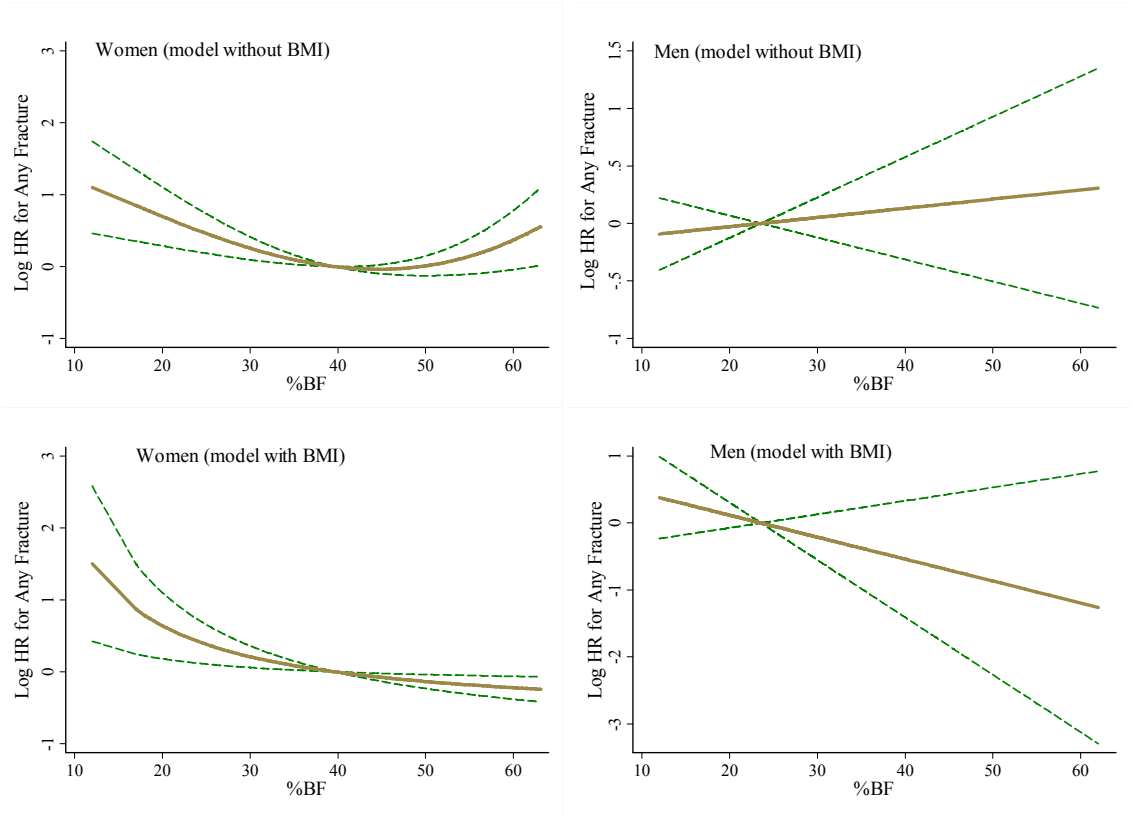

Figure 7.3: Association between percentage body fat (%BF) and risk of any type of fracture among participants of EPIC-Norfolk study
Fitted lines (solid) and 95% confidence limits (dashed lines) are from fractional polynomial models with and without adjustment for body mass index (BMI) in women (left graphs) and men (right graphs). All models are adjusted for age, history of fracture, smoking status, alcohol intake and BUA.

Table 7.4: Hazard Ratios (HR) and 95% CI for different levels of percentage body fat compared to the mean level (35-45%) among female EPIC-Norfolk participants The values are from a Cox proportional-hazards regression model (1st degree fractional polynomial) for prospective risk of any fracture adjusted for age, body mass index, history of fracture, smoking status, alcohol intake and heel broadband ultrasound attenuation.

%BF Range	HR	95% CI	No of Women	No of fractures
<20%	2.30	1.26-4.17	38	5
20-25%	1.57	1.14-2.18	229	23
25-35%	1.20	1.05-1.36	2511	116
35-45%	1.00	-	3502	157
45-55%	0.89	0.81-0.97	1571	68
>55%	0.81	0.69-0.94	468	24

HR: Hazard Ratio; CI: Confidence interval

7.5. Discussion

This study observed an inverse association between body fat mass and risk of fracture among women but not men. Similar to most previous studies, we observed an inverse association between fat mass and bone properties (as measured by heel ultrasound in our study), but this association did not translate into increased risk of fracture as might be expected. In fact, risk of hip fracture among women almost halved with each 10% increase in percentage body fat (*Table 7.3*) and a non-linear reduction in risk was also observed for any type of fracture. Part of the longstanding controversy in the literature about effects of fat on bone might be explained by these opposite relationships with bone measurements and fracture risk. Differences in findings in different studies may also reflect lack of consideration of possible sex difference and variable adjustment for body mass index. Moreover, our study indicates that fat and bone may be non-linearly related. This may also explain the variable relationship observed in different studies between BMI and fracture risk since BMI, which is not associated with fracture risk independently, may be variably related to fat mass in different population groups.

Including both BMI and %BF into the same model may be questioned by some researchers. While both variables share the factor of weight and are correlated, they reflect different aspects of obesity which are of interest both aetiologically and clinically. For example, men and women defined as obese by BMI>30 kg/m^2 might have different contents of fat and muscle in their bodies (fatty obese vs. muscular obese). Body weight and BMI encompass different components including body organs, bone, muscle, and fat mass altogether. It is not clear that the associations observed between BMI and fracture risk, which is not consistent across different studies, is related to the effects of weight (as the big picture comprising all components) on bone or the effects of different components of weight. Including both BMI and %BF into the same regression model in our study showed that fracture risk is related to the fat component of weight but independent of weight itself. This, of course, needs sufficient statistical power to

have a stable model given the correlation between variables, which we achieved using the large number of our participants.

We observed the protective effects of fat mass on hip and other fractures only among women. Although it is possible that lack of significant association among men in our study was due to low power for finding such association, there is no obvious trend towards risk increment or decrement with higher values of %BF in men. It is notable that the range of %BF in men was much narrower than in women. Previous studies have also suggested this sex-specific association between fat mass and BMD [283]. Hormonal differences between sexes are proposed as the mechanism for this effect. Oestrogen reduces osteoclast-mediated bone resorption and stimulates osteoblast-mediated bone formation [295]. After secretion of oestrogen from ovaries ceases in post-menopausal women, extragonadal oestrogen synthesis in fat tissue (mediated by the enzyme aromatase) [296] becomes the dominant oestrogen source and this may lead to the protective effects of fat mass on bone in post-menopausal women. Androgen-deficiency resulted from hypogonadism contributes to bone loss in 20-30% of elderly men, but this association is not affected by the body fat mass in men [297].

Several other mechanisms have been proposed for how fat mass may relate to bone characteristics: these mechanisms may act in both positive and negative directions with respect to bone health. The interplay between these processes in each individual might ultimately determine net beneficial or detrimental effects of fat mass on bone health. Two mechanical explanations for the effect of fat mass on bone are the cushioning effects of fat pads on bony areas, such as the hip [298], and increased bone strength in response to the greater mechanical loading imposed by higher body mass [287]. Meanwhile, adipose tissue is known not to be just an inert organ for energy storage [288]. It expresses and secrets a wide variety of biologically active molecules such as oestrogen, leptin [299, 300], adiponectin [299, 301], resistin [302], and interleukin-6 [303]. The secretion of these hormones as well as bone-active hormones from the pancreas (including

insulin, amylin, and preptin) [304-306] may contribute to the complex relationship between fat mass and bone. Moreover, adipocytes and osteoblasts both originate from a common progenitor, the pluripotential mesenchymal stem cell. These stem cells display an equal propensity for differentiation into adipocytes or osteoblasts, and the balance of the differentiation is regulated by several interacting pathways that may contribute to the final effect of fat mass on bone [289].

An important finding of our study is that fat mass is a protective factor against hip fracture independently of bone density measured using heel QUS. Most cross-sectional studies assessing the relationship between fat and bone have used hip or lumbar DXA with inconsistent findings [279-287]. Few studies have also used heel ultrasound for bone assessment. Kroke et al. [294] used a skinfold thickness method to estimate fat and lean mass and reported a significant association with heel BUA among pre- and post-menopausal women. Assantachai et al. [293] also reported a significant negative association in categorical analysis for BUA. All these studies have used bone measures (either DXA or QUS) to estimate the potential impact on fracture risk. However, our results indicate that the relationship between fat mass and prospective fracture risk is largely independent of bone measurements. In models for prediction of fracture using %BF further adjustment for heel QUS did not materially changed the association (*Table 7.2*). This suggests that simple extrapolation of the relationship between fat mass and bone density to estimate fracture risk is unlikely to be satisfactory. In other words, a single cross-sectional bone measurement (either QUS or DXA) may not represent bone health in the complicated relationship with fat mass and future studies have to use prospective designs with fracture outcomes.

We explored non-linear associations in our study and observed an interesting shape of association between %BF and risk of 'any type of fracture'. Fractional polynomial modelling is an easy and widely-available method from an array of statistical methods recently developed for investigating non-linear associations. Use of this or similar methods (e.g. regression splines) merit a greater role in

epidemiology and future population-based studies evaluating the association between fat and bone health may wish to consider them. Selection of the factors to adjust in multivariable models may also have a significant impact on the final models observed in these studies as, for instance, adjustment for BMI substantially influenced the nature of the association in our study. Whether or not BMI is taken into account may explain some of the inconsistent results for fat mass reported from different studies in the literature [287].

Our study has several methodological strengths, including its prospective design and population-based sample that makes our results more generalisable. A potential limitation of this study is low power to detect associations especially for hip fracture and among men. Although there was virtually complete follow up of the cohort using routine record linkage with national hospitalisation data, only fractures that needed admission to hospitals were ascertained for this study. This might have resulted in underestimation of the rate of fracture in our population. However, hospitalised fractures are arguably the ones with the most clinical impact. We were also not able to exclude fractures due to high trauma such as car accidents; however, it is very hard to distinguish between osteoporotic and non-osteoporotic fractures among the elderly involved in an accident and some researchers recommend considering all fractures in this population as osteoporotic.

In conclusion, our study indicates that higher body fat mass is associated with lower risk of fracture among women but not in men. This relationship appeared to be independent of body mass index, and also of bone characteristics as measured by heel ultrasound. Clarifying the nature of this relationship may help us to understand the different mechanisms involved in fracture risk which can inform preventive strategies in the future.

Chapter 8: Importance and Applications of Absolute Fracture Risk

The work presented in this Chapter has been published in:

Moayyeri A. The importance and applications of absolute fracture risk estimation in clinical practice and research. Bone 2009 Aug;45(2):154-7

Please see Appendix 7.

8.1. Introduction

Currently we are facing a universal shift towards use of absolute fracture risk estimation in the field of osteoporosis research and clinical practice guidelines. Recent attempts by the "World Health Organisation Scientific Group for assessment of osteoporosis at the primary health care level" have resulted in a clinical tool for estimation of 10-year absolute risk of fracture in different populations [24, 162]. This online tool, namely FRAX®, aims to shift the previous clinical practice (which was mainly based on defining osteoporosis using a single bone density assessment) to a more clinically relevant practice, which combines information gained from clinical risk factors and bone mineral density (BMD) measurement to an estimate of absolute fracture risk and categorises patients using this measure. The field is open now to medical researchers working on osteoporosis assessment and diagnosis who can either try to estimate and validate 10-year absolute risk figures in their populations (using various epidemiological study designs and biostatistical approaches) or try to calculate country-specific risk thresholds for patient categorisation (using principles of health economics and mathematical modelling). Clinicians also need to familiarise themselves with the concept and try to utilise the upcoming results in their clinical practice.

10-year absolute risk of fracture is an easily understood measure for most clinicians and patients as it is a direct assessment of the main clinical event at which preventive interventions are aimed. This measure may lie somewhere between about 0-5% for young healthy men and women without fracture risk factors and up to about 50-80% for older women with established osteoporosis. Unlike traditional classification of patients for osteoporosis which only considers BMD testing results, absolute risk charts (like the ones produced by the FRAX® team) can take into account other clinical risk factors known to influence risk of osteoporotic fractures (such as age, sex, past or parental history of fracture, body mass index, smoking, alcohol consumption, medications and comorbidities) [307]. These values can be measured for populations with different characteristics (sex, age, ethnicity, etc). Conventional statistical models such as Poisson or Cox

regression (available via most of statistical packages) or other mathematical modelling approaches have been shown to be efficient tools for pulling together all the available and relevant information for prediction of 10-year absolute risks of fracture [51, 102, 308-310]. Thresholds for categorisation of patients using absolute risk measures may well differ in different countries taking into account cost-effectiveness and affordability of different drug regimens and competing health priorities.

Although the main idea behind absolute risk estimation approach is more systematic management of patients with the use of derived estimates, the value of this approach in clinical practice and research is by no means restricted to this subject. As part of this thesis, I have worked on estimation of 10-year absolute risk of fracture for EPIC-Norfolk participants. Please see Chapter 9 for detailed methods and Chapters 10 and 11 for specific applications of the models. With reference to some of these results, in this Chapter I will review a number of the new applications for and opportunities created by absolute risk measures from an epidemiological perspective.

8.2. Introducing new risk factors

There is a critical distinction in epidemiology between an 'associated factor' and a 'risk factor'. In the osteoporosis literature, there are numerous factors suggested to be associated with the disease (as determined by BMD testing) or osteoporotic fractures and the number of these factors (including biochemical variables, lifestyle factors, anthropometrical or structural characteristics of bone, etc) is increasing. Some of these observed associations are perceived to be etiologically linked with fractures (presumably due to a biological background). However, when assessed in an epidemiological framework, any association, even an etiologic one, should satisfy certain criteria to be accepted as an independent 'risk factor' [201]. The main principles are persistence of the association after adjustment for other known risk factors as well as increase in our predictive power for the outcome by adding the 'new' risk factor to our set of risk factors. While the first principle is usually taken into account with the use of a multivariable regression analysis, the second principle (increase in the predictive power) is generally neglected. Use of absolute fracture risks can help researchers with this issue.

This topic is of vital importance especially for introducing new techniques into clinical practice for assessment of osteoporosis. All the new radiological techniques or biochemical assays need to demonstrate that they add some useful information to the current practice of BMD testing using DXA assessment. In other words, they can predict fractures independently from BMD. We have examined this for quantitative ultrasound (QUS) measurement in the EPIC-Norfolk study. Please see Chapter 11 for details. In summary, two models were constructed for prediction of fractures. One model only used BMD measures and the other used both BMD and QUS measures. After calculation of 10-year absolute risk of fracture using each of these models, participants were categorised into three groups of low-, intermediate-, and high-risk. Groupings based on two models were then compared. *Figure 11.1* shows that, while most of participants were categorised into the same risk groups using both models, there was a

considerable amount of discordance between the results of two models. About 17% of total participants were reclassified to other categories using the model including QUS measure. Comparison of the predicted risks and observed risks further revealed that the predicted values using the model including both BMD and QUS measures were more accurate. Therefore, we were able to confirm that BUA adds useful information to our predictive power.

The method described above can be extended for direct comparison of known risk factors (e.g. can we use BUA in place of BMD for fracture prediction?) or use of surrogate markers (e.g. can we use magnetic resonance imaging [MRI] in place of bone biopsy for the assessment of bone quality?). Statistical methodology supporting the use of absolute risk categorisation is progressing fast and we are now able to compare predictive power of models with different sets of risk factors. Conventional methods such as sensitivity/specificity and receiver operating characteristics (ROC) curves have proved to be incompetent for comparison of discriminative power of models introducing new variables to pre-defined sets of risk factors [311]. Pepe et al. [312] have shown the statistical privileges of an absolute risk-derived curve (named as 'predictiveness curve'). This method increases our power for comparison of two risk factors inside a set of fixed risk factors and needs to be considered more in osteoporosis research.

8.3. Distributions of fracture risk

Having estimated a 10-year probability of fracture for all participants in a prospective study, researchers would be able to look at the distribution of the risk in the populations from different aspects. Careful inspection of the risk scattering in different sub-populations and comparison of risk estimates at different levels of known risk factors would help in acquisition of better understanding of the exposure-outcome relationships. We know that different risk factors may interact with each other in predicting risk of fractures among individuals. The term interaction (or effect modification) in epidemiology describes a situation in which two or more risk factors modify the effect of each other with regard to the occurrence or level of a given outcome [313]. Although these interactions are usually identified using the incidence rates of outcome in different levels of exposures (to estimate attributable risk or relative risk models), distribution of absolute risks at different levels of exposure can provide better alternative to this method as it provides multivariate-adjusted estimates for comparison.

Figure 8.1 shows an example of interaction observed between age and sex for prediction of 10-year absolute risk of fracture among EPIC-Norfolk participants. The effect of age on fracture risk is modified by different handling of sex in the multivariable Cox proportional-hazard models. In the pooled sex-stratified analysis, in which men and women both entered into the same model, 10-year probability of fracture showed a greater proportional increase among men (from 0.6% to 4.4%) and less among women (from 1.2% to 9.5%) in different age groups. However, when estimates were based on two different models for men and women, the increase in fracture risk was steeper among women (from 0.9% to 11%) compared with men (from 1.1% to 3.1%). This shows that the association between age and fracture risk is not identical in different genders. Alongside the biological implications of these sorts of findings, they would be of great importance for the field of risk assessment since generalisation of risk estimates at one level of a contributory variable to other levels would not be justified anymore.

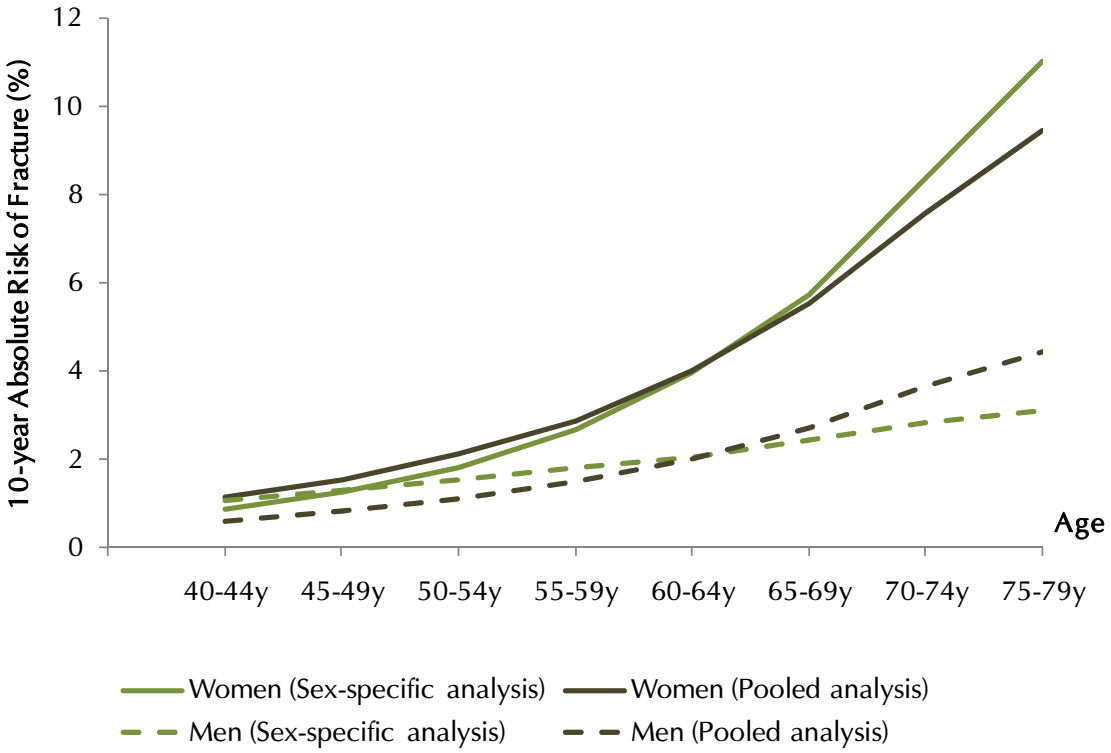

Figure 8.1: 10-year absolute risk of fracture based on sex-specific and pooled (sex-stratified) models in EPIC-Norfolk study

An important point is that, while because of limited data researchers may derive absolute risks for a particular population (e.g., women at age 70 years) and then estimate the absolute risks for other groups (e.g., men at age 60 years) based on the relative risks observed in other studies, these assumptions do not necessarily hold. Therefore, we need more directly observed estimates of absolute risk from real data on populations. This is the rationale for conducting studies in different populations in different countries, and different age and sex groups rather than assuming that the absolute risk estimates derived from a particular population can be modelled appropriately for other populations.

8.4. Public health perspective

Attention to the risk distributions can also help public health agencies consider other aspects of disease burden for estimation of appropriate thresholds. The impact of a health program to prevent fractures in the next 10 years is obviously linked to the risk distribution in the target population. *Figure 8.2* presents this distribution for women of different ages in the EPIC-Norfolk study. In this figure, percentiles of 10-year absolute risk (derived from sex-specific proportional-hazards model with adjustment for all known confounders) have been estimated for women in different age groups. Inspection of both horizontal and vertical axes can provide useful information for economic analysis in order to inform choice of risk thresholds. For instance, a reference line on the horizontal axis marks the absolute risk cut points to identify 5% of women with the highest risk of fracture in each age group (these cut points go up from 1.6% in women aged 40-49 years to 15.7% in women aged 70-79 years).

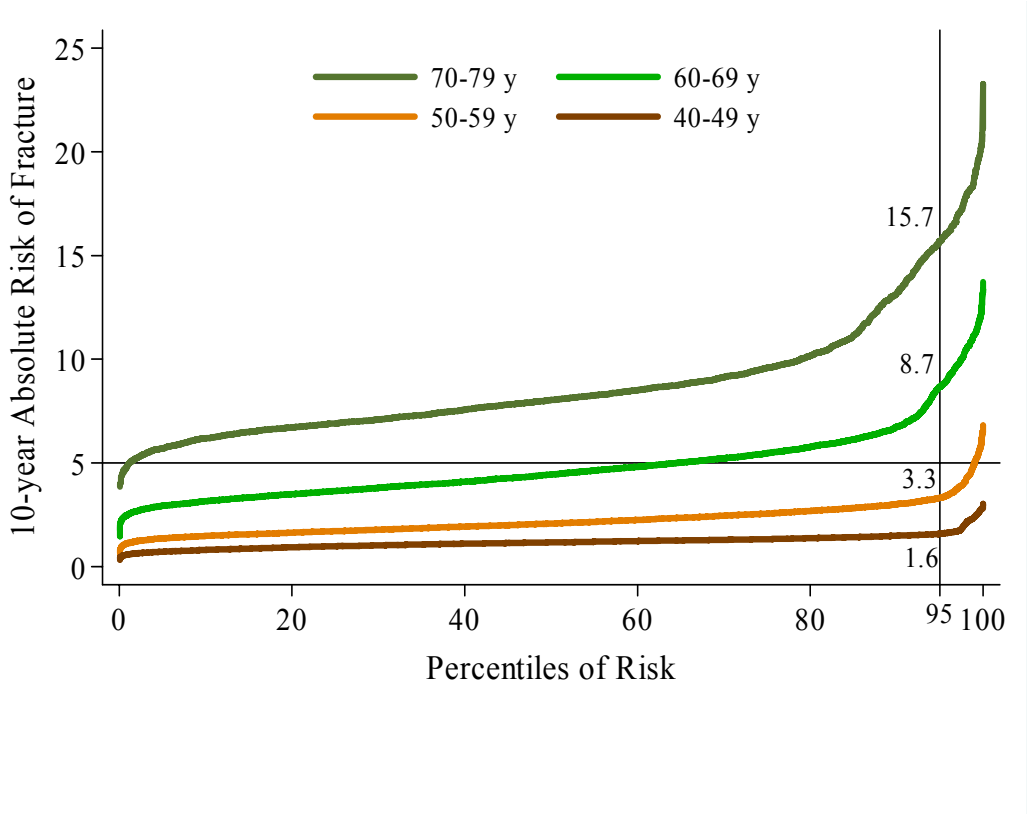

Figure 8.2: Age-specific distribution of 10-year absolute risk of fracture among 14,032 female participants of the EPIC-Norfolk study

The usual question of 'at what absolute risk should patients (of a particular group) be treated?' could be replaced with 'what is the absolute risk level if we choose to treat a certain fraction of high-risk population (in a particular group)?' For instance, health economic studies may suggest that we can only afford to treat 20% of highest-risk women in East Anglia. EPIC-Norfolk study suggests that the 10-year absolute fracture risk corresponding to this number for the whole population of women is about 5%. *Figure 8.2* shows that none of women in the 40-49 year age group and almost all of the women in 70-79 years would be eligible for treatment in this case. About 2% of women aged 50-59 years and 35% of women aged 60-69 years would also be eligible for treatment. This type of questioning is more relevant to national health authorities as they would need a better idea of the impact and potential economic burden of disease outcomes (here fractures) on the community. Presentations like *Figure 8.2* can also be extended to show fracture risk in sub-populations with certain characteristics (such as those with history of fracture or corticosteroid therapy).

8.5. Absolute risk versus relative risk

It is generally accepted that we need to base our clinical actions on absolute risks rather than relative risks (RRs) [314, 315]. We do not treat patients on the basis that they are, for instance, at two fold increased risk of fracture comparing to some other patients. Nevertheless, RR estimates are needed to evaluate the relative importance of different risk factors in inducing future fractures. The problem arises, however, when we want to derive absolute risk estimates from RRs.

The association between fracture risk and known risk factors like age and BMD is commonly expressed in multiplicative measures. RRs of fracture per 5 years increase in age or per 1 standard deviation fall in BMD are typical values reported in the osteoporosis literature. However, this practice assumes that risk increases multiplicatively with advance in age or fall in BMD, which has been shown to be incorrect [315]. Nordin and colleagues [316] showed that it is misleading to express the effect of BMD or any other variable on fracture risk in terms of a simple multiplicative factor. Johnell et al. [46] also showed that RR for 1 SD change in BMD ranged from 1.8 (1.4-2.2) in Z-score of -4 to 1.2 (1.0-1.4) in Z-score of +4. Moreover, translating these RR measures to absolute risk would be more problematic considering the potential interactions between different risk factors (as discussed above). For instance, *Figure 1.6* shows the range of RRs for previous history of fracture across age groups. Hence, estimates of absolute fracture risk directly calculated from prospective studies (and not from RR estimates from different sources) are more accurate and reliable.

8.6. Comparison of drug efficacy

Despite the new advances in the field of methodology and reporting of clinical trials, there are still several difficulties for application of efficacy measures derived from these studies into clinical practice. Traditionally, relative risk reduction (RRR) is the main measure of efficacy reported in clinical trials. Most of the clinical trials now also report absolute risk reduction (ARR) and most clinicians are searching for number needed to treat (NNT; which is the reciprocal of ARR) [317] in their quick glances over trial results. However, it is still unclear which of these measures should be generalised to other patient groups as the current practice still lacks the necessary attention to the absolute risk distribution in the start of the studies.

Clinical trials for new drugs in the field of osteoporosis usually recruit their participants from high-risk populations. Given the obvious constraints from funding sources and considering the overall low incidence of outcomes, trials need to select these populations to reach their results in a shorter timeline. Thus, most trials recruit only women of older ages (usually >65 years old) with history of fracture (clinical or sub-clinical vertebral fractures) or diagnosed osteoporosis (using DXA assessment). Based on these characteristics, most of these participants would have a 10-year fracture probability of more than 20% or 30% [162]. However, we need to generalise the results of these studies to people with lower absolute fracture risk in order to define thresholds for cost-effective treatment initiation. There can be two main assumptions for this generalisation; one is assumption of similarity of RRR and the other is assumption of similarity of ARR (or NNT) across risk distribution. While the first assumption is more backed up by the practitioners in the field, both of these assumptions might be far from reality and can be misleading for calculation of risk thresholds.

Suppose a drug has been studied in people with 10-year absolute fracture risk of 20% and shown to reduce the risk by 5% (ARR=5% so NNT=20). The RRR would be 1 - (15% / 20%) = 25% in this case. The solid line in *Figure 8.3* shows the

distribution of 10-year absolute risk of fracture in a hypothetical population without treatment. This can be considered risk of a major osteoporotic fracture in a relatively young population (50-55 years old) as more than half of population has a 10-year risk of ≤5%. The dashed and dotted lines show the distribution of risk after treatment with the drug assuming a fixed RRR and a fixed ARR, respectively. *Figure 8.3* shows that, although the risk distributions attributed to any of these assumptions are very similar in a high-risk population, there would be a considerable difference in the number of low-risk people who would presumably benefit from this drug. For instance, about 65% of the population would be considered as reaching 10-year absolute risk of ≤5% after treatment given a fixed RRR assumption but this number would be 80% for fixed ARR assumption. This difference could have an immense impact on the cost-effectiveness of the drug.

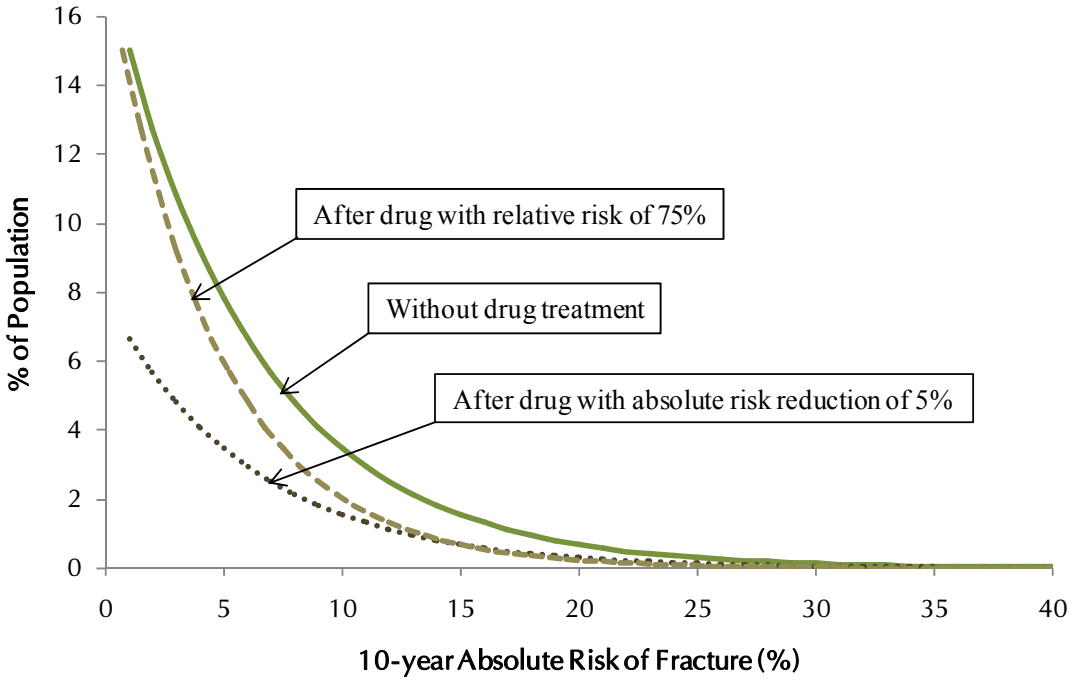

Figure 8.3: Effects of different assumptions for generalisation of drug efficacy measures to populations with lower risk of fracture
The solid line represents risk distribution in a hypothetical population. Each of other lines represents a scenario for the change in the risk distribution after treating all the population with a particular drug.

There are arguments for and against both of these assumptions but it seems that both can be misleading for generalisation of the observed drug effect to other risk bands. Fixed ARR assumption is obviously implausible for low-risk populations since some people would reach an absolute risk of null, which means complete prevention of fractures in the next 10-years [318]. Fixed RRR assumption can also be turned down with some biological reasoning. For instance, if a drug increases femoral neck BMD by 0.01 g/cm^2 (equal to 1.5% of baseline BMD) in a study of high-risk patients, which of these numbers should be generalised to low-risk population (absolute number or percentage)? Moreover, what would be the effect of assumed change in BMD on fracture risk in this low-risk group? It should be noted that different biological pathways may have different impacts on different patient groups and the drugs usually affect only one pathway. Recently, Johnell et al. [46] in a meta-analysis on large prospective studies, showed that the risk gradient (relative risk per SD decrease in femoral neck BMD) for hip fracture decreases from around 3.7 at age 50 to around 1.9 at age 85. In the example above, if the high-risk study patients are very old post-menopausal women, the impact of BMD change on fracture risk might be lower (presumably as a result of increased risk of falls in this population) [319]. If we want to generalise the results to women of age 50-55 years, this much BMD change (either 0.01 g/cm^2 or 1.5%) would have more impact on fracture risk as the role of BMD on fractures would be more prominent in this age group.

This argument supports the idea that clinical trials need to report explicit measures of absolute fracture risk in their recruited populations [320]. This will help clinicians using the FRAX® or other tools assess the generalisability of the results of a clinical trial to a particular patient. Moreover, it would be ideal if researchers consider empowering their studies for further sub-group analysis of the results in different categories of absolute risk. This would enable us to explore the association between effect size of the drugs and baseline risk of populations and to find more accurate measures for generalisation of the results to lower risk populations.

8.7. Conclusion

Different measures of risk (relative risk and absolute risk) may be used for different purposes but they do not always give the same answer. While the conventional practice is based on relative risks for estimation of exposure effects or drug efficacies, absolute risk measures are needed for clinical practice (individual-level) and public health policy-making (population-level). After recent launch of FRAX®, the clinical practice in the field of osteoporosis will be shifting towards more use of absolute risks. Research bodies also need to consider this factor more in their practice. This is particularly important for estimation of distribution of fracture risks in different populations and economic risk-benefit analyses to find intervention thresholds.

In this Chapter, I discussed about several drawbacks of relative risks that support more attention to absolute risk measures as the surrogate. Generalisation of relative risk of fractures for different risk factors might be misleading given the interaction between different risk factors. Relative risk reductions derived from RCTs may not be generalisable to other populations given the impact of baseline fracture risks and the effects of competing factors not affected by the treatment. Absolute risks, on the other hand, may bring new opportunities for introduction of new 'risk factors' as well as for risk categorisation from a public health perspective. All of these arguments suggest that researchers working on diagnosis and prevention of osteoporotic fractures need to be more explicit about the distribution of absolute fracture risk in their study populations. In the next Chapter, I present the results of my work for estimation of absolute risk of fracture in EPIC-Norfolk study.

Chapter 9: Absolute Fracture Risk

The work presented in this Chapter has been published in:

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Please see Appendix 8.

9.1. Abstract

While estimates of relative risks associated with risk factors such as age and bone mineral density (BMD) may be of interest for etiologic and comparative purposes, clinical questions such as who might benefit most from preventive interventions or BMD monitoring depend on estimates of absolute fracture risk. In this study of the original cohort of EPIC-Norfolk cohort including 25,311 participants (11,476 men) aged 40-79 years in 1993-1997, 10-year absolute risk of fracture in men and women were calculated using the baseline survivor function in multivariable Cox proportional-hazards models adjusting for age, sex, history of fractures, body mass index, smoking, and alcohol intake. In comparison of those without history of fracture vs. those with history of fracture, the 10-year absolute risk of any fracture in men ranged from 1.0% vs. 1.2% at age 40 years to 3.0% vs. 4.4% at age 75 years. The respective estimates in women ranged from 0.7% vs. 1.0% at age 40 years to 9.3% vs. 17.2% at age 75 years. Statistically significant interaction between age and sex was found ($p < 0.001$), which contributed to the differences in predicted absolute fracture risks for men and women at different ages. Our study shows the need for population-specific data to develop efficient well calibrated algorithms for assessment of fracture risk. The interaction observed between sex and age points to the need for further prospective studies among men.

9.2. Introduction

There is an emerging consensus that, besides estimating relative risks associated with risk factors for osteoporotic fractures, we also need to express fracture risk using absolute risk estimation [51, 55, 315, 321]. While estimates of relative risks associated with risk factors such as age and bone mineral density (BMD) may be of interest for etiologic and comparative purposes, absolute fracture risk is more relevant for deciding which patients are at the highest priority for preventive interventions. FRAX®, a newly developed fracture risk assessment tool by the World Health Organization (WHO) Scientific Group, has recently become available to help clinicians in their decision-making for middle-aged and older patients [24, 162]. This tool gives estimates of 10-year probability of major osteoporotic and hip fractures using clinical risk factors and BMD measurements in men and women from nine different countries.

Absolute risks of fracture will enable both researchers and clinicians to obtain a better idea about the distribution and magnitude of risk in different age and sex groups. Given the recent methodological advances in the field of epidemiology of osteoporosis and biostatistical modelling, more population-specific estimates of 10-year probability of fracture are expected soon to be available for clinical practice in different countries. Moreover, the estimates of absolute risk of fracture might be highly variable within as well as between countries given the extent of variation in fracture incidence among the elderly in different parts of the world [29, 322, 323]. In the United Kingdom, for instance, uniformly lower rates of hip fracture have been reported in parts of East Anglia compared to other parts of England and Wales [324]. In this Chapter, I report the estimates of absolute fracture risk from EPIC-Norfolk study.

9.3. Methods

The detailed design and procedures for EPIC-Norfolk study have been described in Chapter 2. In this study, 25,639 participants of the baseline health examination (1993-1997) were considered. Anthropometric measures (height, weight, and BMI), smoking status, and alcohol consumption assessed in this health examination were used as fracture risk factors. International Classification of Diseases (ICD) 9 and 10 diagnostic codes were used to ascertain fractures by site occurring in the cohort up to the end of March 2007, an average of 11.3 years (SD=1.5; range 9.2-14.1).

Multivariable Cox proportional-hazard regression models [325] were used to model the association between incident fractures and age, history of fracture, BMI, smoking status, and alcohol intake in both genders. Although likelihood ratio tests and global measures of model fit (Bayesian and Akaike's information criteria) showed that BMI and smoking were not associated with fracture risk in our population, we preferred to keep them in the final models in order to make our models comparable to the clinical risk profile of FRAX® and other studies in the field. Cox models with up to second-degree fractional polynomial terms [326] for age were used to assess potential deviations from the expected log-linear shape of association between age and fracture risk, for which no significant deviations from linear association were found in both men and women. Discriminative ability of the models was evaluated using Harrell's C index [327], a concordance measure for survival data analogous to the area under a receiver operating characteristic (ROC) curve that takes into account censored observations over time in its calculation. The C-index corresponds to the probability that for a randomly selected pair of subjects, of whom at least one is observed to suffer a fracture, the person who fractures first has higher predicted absolute risk of fracture than the other [327]. Departure from the proportional hazards assumption was evaluated by tests based on scaled Schoenfeld residuals for each covariate.

10-year and 5-year absolute risk of fractures for any participant were calculated using the baseline survivor function and the estimated log hazard ratios for the variables in each model. In general, the Cox regression model for the hazard of fracture at time *t* after baseline given k explanatory variables X_1, X_2, ..., X_k included in the model is of the form:

$$h(t \mid X_1, X_2, .., X_k) = h_0(t) \times \exp(b_1X_1 + b_2X_2 + ... + b_kX_k)$$

where $h_0(t)$ is the baseline hazard at time *t* and b_1, b_2, ..., b_k are the log hazard ratios for the k explanatory variables. $h_0(t)$ represents the instantaneous rate of failure expected at time *t* for a person with zero values of all covariates and the cumulative baseline hazard $H_0(t)$ at time *t* is obtained by integrating $h_0(t)$. The baseline survival at time *t*, i.e. $Pr(T > t)$, is then given by:

$$S_0(t) = \exp(- H_0(t))$$

and the survival for a person with covariate values X_1, X_2, ..., X_k is obtained as $S_0(t)$ ^ $\exp(b_1X_1 + b_2X_2 + ... + b_kX_k)$. Hence, our 10 year risk of fracture was calculated as:

$$Pr(T \leq 10) = 1 - S_0(10) \text{ ^ } \exp(b_1X_1 + b_2X_2 + ... + b_kX_k).$$

Values for absolute risks of fracture in men and women at different ages and with or without a history of fracture were calculated and tabulated. We used a split-sample approach for internal validation of our models by designating a randomly

sampled 75% of the participants (10,376 women and 8,607 men) to a derivation set and the remaining 25% (3,459 women and 2,869 men) to a validation set. Sex-specific Cox models were developed in the derivation set and the results were applied to the validation set. Predicted 10-year probabilities of fracture based on these models were compared with the observed risk of fracture in the validation set using the Hosmer-Lemeshow goodness-of-fit test [328]. This test works by partitioning the observations into 10 equal sized groups (deciles) according to their predicted probabilities. Then a test statistic is calculated for each group of observations based on comparison of the observed and predicted risks. Sum of this statistic follows a chi-squared distribution (with 10 degrees of freedom) and a non-significant p value for this test shows the absence of evidence for disparity of observed and estimated probabilities.

We used sex-specific models because the risk profiles in men and women are not similar and gender would not suffice the assumption of proportional hazard to be entered into the models as a simple variable. However, since it is widely claimed that the risks associated with different clinical risk factors are similar among men and women, a sex-stratified model was also used to check out this assumption. In stratified Cox proportional-hazards regression models, each stratum is permitted to have a different baseline hazard function, while the coefficients of the remaining covariates are assumed to be constant across strata [325]. This method can be used to make graphical checks of the proportional hazards assumption for covariates. All database management and statistical analyses were performed using Stata software, version 10.0 (StataCorp LP., College Station, TX, USA).

9.4. Results

9.4.1. Characteristics of the study population

After exclusion of participants with incomplete follow-up data, 25,311 participants (11,476 men) were entered into our analyses. Baseline characteristics of the study population are shown in *Table 9.1*. Participants with fracture were significantly older and had more history of fracture compared to participants without fracture and women with fracture had lower height and alcohol intake compared to other women. There were statistically significant differences between men and women with respect to all baseline factors and number of incident fractures. Out of 925 incident fractures reported, 334 (36%) were hip fractures, 154 (17%) were clinical spinal fractures, and 219 (24%) were wrist fractures. 1,749 of the participants had a past history of fracture at the time of the first visit. As shown in *Table 9.2*, the number of women with a past history of fracture increased with age while the numbers remained fairly steady at around 6% in men aged 45 and above.

Table 9.1: Baseline characteristics of participants in the EPIC-Norfolk study

	Women			Men		
	Fracture	No Fracture		Fracture	No Fracture	
	n=649	n=13,186	P value	n=276	n=11,200	P value
Age (years)	64.7 (8.4)	58.1 (9.2)	<0.001	61.9 (9.7)	59.0 (9.3)	<0.001
History of fracture	117 (11.1%)	936 (7.1%)	<0.001	25 (9.1%)	654 (5.8%)	0.02
Height (cm)	160.2 (6.3)	161.0 (6.2)	0.002	174.4 (6.4)	174.0 (6.6)	0.3
Weight (kg)	67.4 (12.4)	68.0 (11.8)	0.2	80.7 (11.9)	80.4 (11.5)	0.6
Body Mass Index (kg/m^2)	26.2 (4.5)	26.2 (4.3)	0.9	26.5 (3.4)	26.5 (3.3)	0.9
Current smoking	64 (9.9%)	1,508 (11.4)	0.2	38 (13.8%)	1,362 (12.2%)	0.4
Alcohol intake (units/wk)*	1.5 (0.5-4.5)	2.5 (0.5-6.5)	<0.001	7 (2-16.5)	6 (2-14)	0.2

Data are mean (standard deviation) or number of participants (percentage)
* Data are median (inter-quartile range)

Table 9.2: Distribution of participants in different groups of age, sex, and past history of fracture

Age	Women		Men	
	With history of fracture	Without history of fracture	With history of fracture	Without history of fracture
40-44 years	15 (2.5%)	581	15 (3.5%)	417
45-49 years	101 (3.3%)	2,938	129 (5.7%)	2,128
50-54 years	74 (4.1%)	1,744	81 (5.7%)	1,341
55-59 years	143 (5.6%)	2,422	129 (6.0%)	2,020
60-64 years	158 (9.5%)	1,512	87 (6.0%)	1,367
65-69 years	293 (12.1%)	2,138	147 (6.8%)	2,005
70-74 years	207 (15.1%)	1,161	75 (5.9%)	1,190
75-79 years	66 (17.5%)	312	21 (5.7%)	348
Total	1,057 (7.6%)	12,808	692 (6.0%)	10,915

9.4.2. Fitting the models

The results of sex-specific Cox models are presented in *Table 9.3* in terms of hazard ratios and 95% confidence intervals for any incident fracture and hip fractures. BMI and smoking were not significantly associated with fracture risk in any model. History of fracture lost its statistical significance as a predictor of hip fracture in model for men considering the small number of hip fracture outcomes in this group (n=89). As shown in the bottom of *Table 9.3*, the C-index values estimated in the validation dataset were comparable to those estimated in the derivation dataset, which provides reassurance on the internal validity of the risk prediction model. The Hosmer-Lemeshow test for calibration did not show any evidence of statistically significant differences between observed and predicted 10-year risks (p = 0.9 for women and p = 0.08 for men), confirming internal validity of the fitted models. Number of predicted and observed fractures according to deciles of predicted risk of any fracture among men and women are shown in *Table 9.4*.

Table 9.3: Hazard ratios (HR) and 95% confidence intervals (CI) for risk factors to predict prospective risk of fracture in different Cox proportional-hazards models

	Any fracture		Hip fracture	
	Women (649 cases)	Men (276 cases)	Women (245 cases)	Men (89 cases)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age (years)	1.08 (1.07-1.09)	1.04 (1.02-1.05)	1.14 (1.12-1.16)	1.15 (1.11-1.18)
History of fracture	1.92 (1.57-2.36)	1.53 (1.01-2.31)	1.59 (1.14-2.20)	1.73 (0.87-3.45)
Body Mass Index (kg/m^2)	0.99 (0.97-1.01)	0.99 (0.96-1.03)	0.96 (0.93-0.99)	0.95 (0.89-1.01)
Smoking status (current)	1.10 (0.85-1.43)	1.19 (0.84-1.68)	1.19 (0.77-1.83)	1.38 (0.74-2.56)
Alcohol intake (units/wk)	0.98 (0.97-1.00)	1.01 (1.01-1.02)	0.99 (0.97-1.02)	1.01 (0.99-1.03)
C-index (95% CI)				
Derivation dataset	0.70 (0.67-0.72)	0.60 (0.55-0.64)	0.78 (0.75-0.81)	0.79 (0.74-0.85)
Validation dataset	0.72 (0.67-0.76)	0.63 (0.56-0.70)	0.82 (0.78-0.87)	0.79 (0.72-0.86)

Table 9.4: Observed and predicted number of fractures in deciles of predicted risk of any fracture based on sex-specific Cox models

	Women			Men		
Decile of risk	Observed	Predicted	HL	Observed	Predicted	HL
1	14	13.25	0.04	20	11.85	5.67
2	15	17.66	0.41	14	14.04	0.00
3	28	21.50	2.00	21	15.93	1.63
4	28	26.83	0.05	9	17.88	4.48
5	30	34.00	0.48	14	19.90	1.78
6	43	43.21	0.00	24	22.03	0.18
7	58	55.37	0.13	21	24.44	0.50
8	71	71.31	0.00	21	27.26	1.47
9	89	94.07	0.29	31	30.65	0.00
10	141	144.32	0.09	47	40.45	1.10
Total	517	521.53	3.49	222	224.43	16.81

HL: Hosmer-Lemeshow statistic

9.4.3. Estimation of absolute fracture risk

Table 9.5 presents 10-year absolute risks of any incident fracture and incident hip fracture in men and women of different ages. *Figure 9.1* shows the corresponding predicted risks with respect to fracture history. Part A of this *Figure* shows that, while both men and women had a low absolute risk of about 1% below the age of 50 years, women with previous history of fracture experienced a steep increase in fracture risk after this age and their 10-year absolute risk rose to about 17% at the age of 75 years. For men this rise was less steep and reached about 5% at the age of 75 years. Part B of the *Figure 9.1* shows a more steep increase in risk of hip fracture among men in comparison to any incident fracture, although this increase was still lower than age-related increase in risk observed in women. About 85% of women aged ≥ 65 years (3616 out of 4258) had a 10-year fracture risk of less than 10% and 3712 out of 3844 (97%) men aged ≥ 65 years had a 10-year fracture risk of <5%.

Table 9.5: 10-year absolute risk (%) of any incident fracture and hip fracture according to sex-specific Cox proportional-hazards regression models

	Women		Men	
Age (years)	Any fracture	Hip fracture	Any fracture	Hip fracture
40	0.7	0.07	1.0	0.02
45	1.1	0.1	1.2	0.05
50	1.6	0.2	1.4	0.1
55	2.3	0.5	1.7	0.2
60	3.3	0.8	1.9	0.3
65	4.9	1.6	2.3	0.7
70	7.1	3.2	2.7	1.4
75	10.9	6.4	3.1	2.6

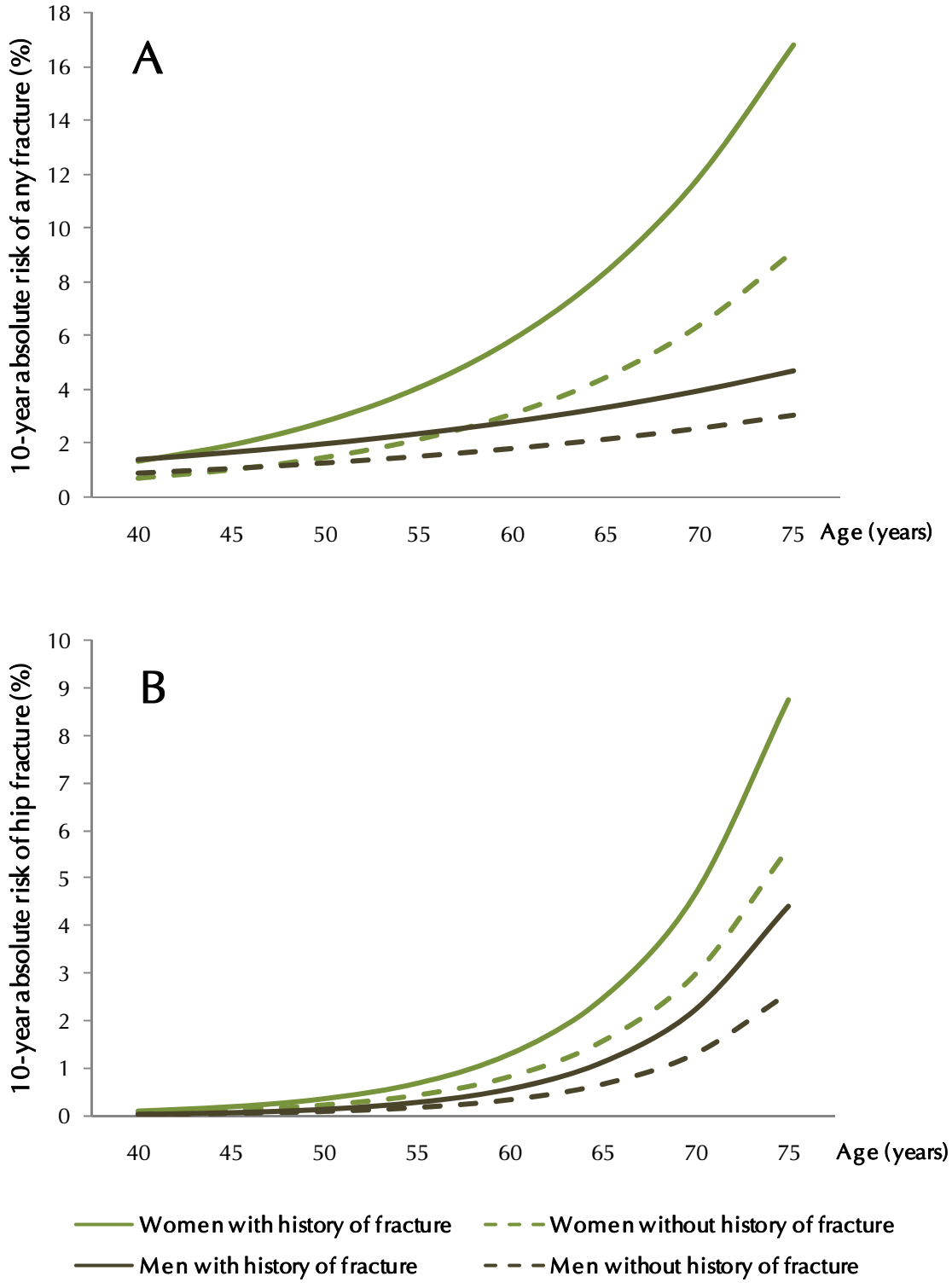

Figure 9.1: 10-year absolute risk of A) any fracture and B) hip fracture among 25,311 men and women in EPIC-Norfolk study

We examined sex-stratified models and compared them to sex-specific models in order to look at the pattern of association between other covariates and risk of fracture in men and women. While in sex-specific models the association between covariates and fracture risk can be different between men and women, in sex-stratified models these associations are considered to be similar (i.e. constant proportional hazards) but with different baseline hazards across strata of men and women. In our analysis, there were noteworthy differences in the risks predicted by sex-stratified vs. sex-specific models for any incident fracture. In general, stratified analysis predicted lower absolute risks for women and higher absolute risks for men compared to the sex-specific models. The C-index for discrimination of any incident fracture from the sex-stratified model was 0.661 (95% CI 0.643 – 0.679), which was intermediate between that seen in sex-specific models for women 0.701 (95% CI 0.681 – 0.722) and men 0.598 (95% CI 0.560 – 0.635). In particular, the pattern of association between age and fracture risk was notably different between the models (as depicted and discussed in *Figure 8.1* and previous Chapter). The interaction term between age and sex included in the stratified model was highly significant (coefficient=0.04, P<0.001). The model with included interaction term outperformed the basic model (confirmed by lower Akaike's information criterion for the first model). The difference between predicted risks using models with and without interaction was more notable especially among older participants. Overall, the comparison between sex-stratified and sex-specific models shows the weakness of the assumption of constant proportional hazards for covariates between men and women. Therefore, separate modelling and analysis for men and women, when possible, is recommended.

9.5. Discussion

This study estimated absolute risks of fracture from a population-based prospective study in England. Using time-to-event data modelled in Cox proportional-hazards regression, we found that 10-year probability of fracture was approximately 1% in both men and women aged 40-45 years rising to about 17% for women and 5% for men aged 75 years with a previous history of fracture. There was a significant effect modification between sex and age of participants in this cohort. This suggests that the association between age and fracture risk is different in men and women. This has a particularly important methodological impact as it suggests that, when estimating absolute risk of fracture among men, it is not reliable to generalise the results of female studies to men. Direct evidence from studies in men is needed for this purpose.

Previous studies have estimated 5-year, 10-year, or lifetime absolute risk of fracture in different populations using different statistical and mathematical modelling approaches [51, 102, 308-310, 329]. The first study to estimate 10-year probability of fracture is based on the Sweden population register of fractures. In that study [51], a mathematical model was devised which combined pooled estimates of relative risk from a meta-analysis [45] with U.S. normative BMD data and Swedish fracture incidence records to provide absolute risk estimates. Comparison of our results with the figures provided by that study shows a considerable difference between the absolute risks in Swedish and British populations. *Figure 9.2* shows that 10-year absolute risk of fracture increases to about 27% in Swedish women ≥75 years (compared to 11% in our population) and men from Sweden are also at higher risk compared to British women in any age group. Although there is a possibility of overestimation of the risk of fracture in the Swedish population (due to several assumption made for computation of fracture and mortality risks) and underestimation of fracture risks in the present study (as a result of potential under-registration of fractures in a healthier population), the considerable difference between the two studies (*Figure 9.2*) points out to the need for population-specific data for calculation of absolute risks

of fracture. Although the estimates of relative risks attributed to different risk factors might be fairly generalisable between populations [307], unknown factors that relate absolute to relative risks vary with age, sex and geography in a way that cannot be predicted. Therefore, clinical and public health authorities need to consider population structure and fracture incidence from direct evidence in their respective communities.

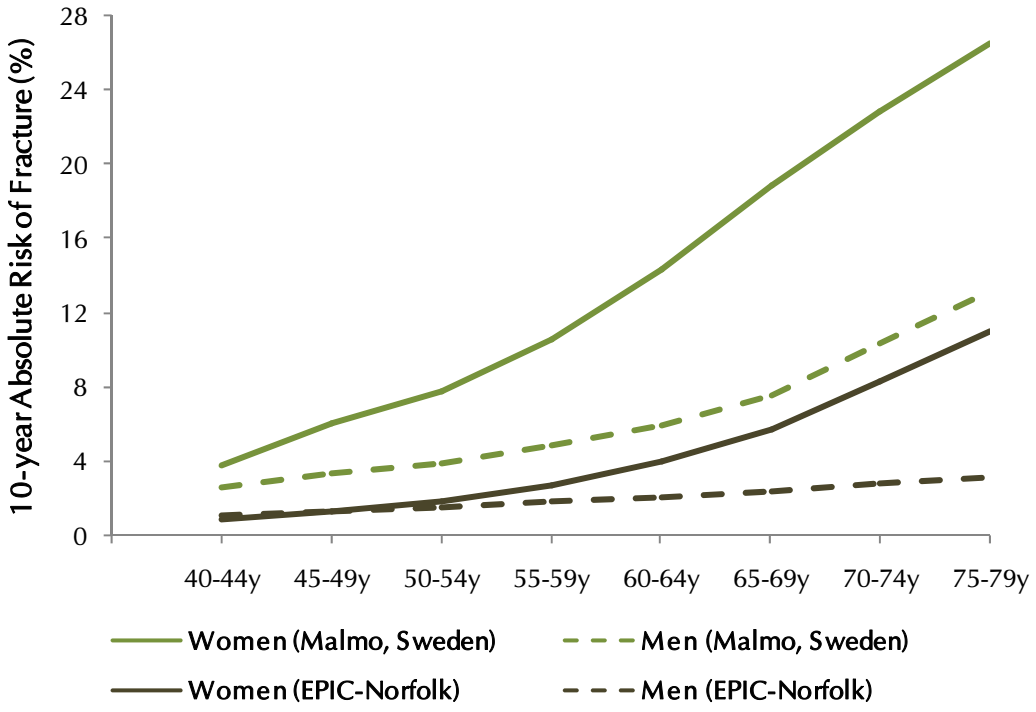

Figure 9.2: Comparison of 10-year absolute risk of fracture estimated in this study with a Swedish population study
Swedish data is reproduced from Reference [51].

This point is particularly important for development of country-specific guidelines for diagnosis of osteoporosis and evaluation of fracture risks. To our knowledge, the only country so far that has tried to shift its practice towards use of absolute risks is Canada. In June 2005, Osteoporosis Canada (OC) and the Canadian Association of Radiologists released their recommendation for BMD reporting in postmenopausal women and older men (please see *Table 1.3*) [91, 321]. These recommendations have altered the fundamental approach to BMD utilisation shifting the emphasis from the relative risk conferred by WHO T-score categories to 10-year absolute risk of fractures. However, the risk estimates and categorisation criteria in this guideline are mainly based on the published Swedish data (with some interpolation of age and T-score groups) [321]. Further studies testing the impact of this guideline on practice of Canadian physicians were also based on the same data [330, 331]. Our study shows that the cut-offs chosen by the Canadian researchers for low and high fracture risk in their population (10% and 20%, respectively) are not applicable to our population (as very few participants had a risk of >20% in our study). Canadian researchers may also need in future to rely more on their population-based studies for estimation of their country-specific absolute risks of fracture.

It should be appreciated that, in order to be used for specific populations, our method for calculation of absolute fracture risk (Cox regression) requires time-to-event data derived from prospective population-based cohort studies with more than 10 years of follow-up for at least a part of the population. This is demanding and few studies so far have used this method [329]. Cox regression as a semi-parametric method has some advantages compared to parametric statistical methods like Poisson regression, which is the method utilised by the WHO Scientific Group to develop FRAX® tool [24, 162]. Because of lack of BMD measurements in 90% of participants in the EPIC-Norfolk study and some differences between variables entered into models we cannot directly compare our model with the FRAX® estimates for UK. With the growing awareness in the research community about the burden of osteoporotic fractures and because of

ongoing prospective studies, it would be reasonable to anticipate population-specific absolute risk measures becoming available for individual countries.

For the purpose of clinical practice, absolute fracture risks in individual patients have to be categorised as high-risk (indicated for treatment), medium-risk (suggested for further evaluation), or low-risk (lifestyle and dietary advice). Thresholds for this categorisation may vary greatly depending on several factors like effectiveness and affordability of treatment regimens as well as patient characteristics and preferences. It is expected that these thresholds should be calculated from population-specific cost-effectiveness models that incorporate measures of absolute risk for individuals with the costs and benefits of treatment, willingness-to-pay of the healthcare funders and individual preferences.

The main limitation of this study is the lack of BMD assessment at the beginning of follow-up. This was mainly related to the primary health outcomes in the initial plan for EPIC-Norfolk study, which were cardiovascular events and cancers. However, a small fraction of participants (about 1,500 men and women aged 65-76 years) underwent BMD assessment using dual-energy X-ray absorptiometry (DXA) as well as quantitative ultrasound (QUS) of the heel. A majority of participants who attended the second health check about 4 years later underwent QUS, which was highly predictive of future fractures in this population [77]. Due to the small number of participants with BMD measurement, we have not entered BMD as a variable into our models. However, the lack of assessment for BMD does not diminish the validity of the methods and results of this study although these additional measures are likely to improve the power of the models to predict fractures in individuals.

Other limitations of this study are the potential for under-registration of fracture outcomes in the cohort population (due to fractures not necessarily being managed in hospitals, emigration of participants, miscoding or misclassification of fractures and other problems inherent to automated linkage programs like ENCORE), inclusion of healthier population for follow-up, and not including older people (>80 years) in the cohort. In particular, although the study

population resembles the UK population in general characteristics, participants in such a study are likely to be healthier and have lower fracture rates. Nevertheless, a previous study also suggested that the incidence rates of fracture among the elderly residents of East Anglia is lower compared to other parts of the UK [324]. The results of this study, therefore, need validation before generalisation to other parts of UK for clinical practice.

There are several points of strength with the methodology used in this study. Cox proportional-hazard modelling is a powerful and precise method that is easily available to all researchers via several statistical packages. Models can be adjusted for different risk factors as well as mortality in the cohorts and there is a potential for meta-analysis of prospective studies (using individual-level data) within countries and populations. Moreover, our large number of male participants followed for a long period of time enabled us to look for the interaction between sex and age as major determinants of fracture risk.

In conclusion, this study showed a lower absolute risk of fracture for the elderly population of East Anglia compared to other northern European populations. This urges further attention to population-specific estimates for clinical applications. Additionally, the interaction observed between sex and age in this study suggests that more prospective studies among older men are required to achieve more reliable estimates of fracture risks in this group. In order to clinically apply the results of this study and other similar estimates of fracture probability (e.g. FRAX® tool), we need population-specific thresholds (or absolute risk cut-offs) using cost-effectiveness models of the current available treatments of osteoporosis. The field is highly open to future research.

Chapter 10: Heel QUS vs. Hip DXA for Absolute Fracture Risk Estimation

The work presented in this Chapter has been published in:

***Moayyeri A**, Kaptoge S, Dalzell N, Luben RN, Wareham NJ, Bingham S, Reeve J, Khaw KT.* Is QUS or DXA better for predicting the 10-year absolute risk of fracture? Journal of Bone and Mineral Research 2009 Jul;24(7):1319-25

Please see Appendix 9.

10.1. Abstract

Although quantitative ultrasound (QUS) is known to be correlated with BMD and bone structure, its long-term predictive power for fractures in comparison to dual-energy X-ray absorptiometry (DXA) is unclear. We examined this in a sample of men and women from EPIC-Norfolk study who had both heel QUS and hip DXA between 1995 and 1997. From 1,455 participants (703 men) aged 65-76 years at baseline, 79 developed a fracture over 10.3±1.4 years of follow-up. In a sex-stratified Cox proportional-hazard model including age, height, body mass index, prior fracture, smoking, alcohol intake and total hip BMD, 1 SD decrease in BMD was associated with a hazard ratio (HR) for fracture of 2.26 (95% CI 1.74-2.95). In the multivariable model with heel broadband ultrasound attenuation (BUA) in place of BMD, HR for 1 SD decrease in BUA was 2.04 (95% CI 1.55-2.69). Global measures of model fit showed relative superiority of the BMD model whereas the area under the ROC curve was slightly higher for the BUA model. Using both Cox models with BMD and BUA measures, we calculated exact 10-year absolute risk of fracture for all participants and categorised them in groups of <5%, 5% to <15%, and ≥15%. Comparison of groupings based on two models showed a total re-classification of 28.8% of participants with the greatest re-classification (about 40%) among the intermediate- and high-risk groups. This study shows that the power of QUS for prediction of fractures among the elderly is at least comparable to that of DXA. Given the feasibility and lower cost of ultrasound measurement in primary care, further studies to develop and validate models for prediction of 10-year risk of fracture using clinical risk factors and QUS are recommended.

10.2. Introduction

Many trials have been conducted in the field of osteoporosis over the last decade and several treatments have proven efficacy for reduction of fracture risk. Today, a major challenge is to better identify individuals at high risk of fracture who would benefit from intervention. To identify patients at high risk of fractures, dual X-ray absorptiometry (DXA) is widely accepted as the reference method for measuring bone mineral density (BMD) [81]. At the population level, a decrease in BMD is associated with a significant increase in fracture risk. However, at the individual level, BMD assessment is quite sensitive but not specific for prediction of fractures. This is explained partly by the fact that DXA measures BMD only, a surrogate of bone strength that is also influenced by bone architecture and hip geometry, and partly by the fact that the occurrence of fracture depends on other clinical risk factors [332].

Quantitative ultrasound (QUS) of the calcaneus, developed in the past two decades, is expected to provide information on bone structure and density [117, 333]. Previous studies suggest that QUS parameters are influenced by the mechanical properties of bone, which in turn are determined by the amount of bone, the bone's material properties (e.g., bone mineralisation and elasticity), and its structural properties (e.g., bone architecture) [140, 334-336]. The pattern of absorption of a range of wavelengths of sound is called the broadband ultrasound attenuation (BUA; expressed in dB/MHz) and transmission of sound through bone can be quantitatively assessed by the speed of sound (SOS; expressed in m/s). Recent research has shown that ultrasonic assessments of the calcaneus are significantly discriminative and predictive of osteoporotic fractures independently of hip BMD [337-343]. In fact, major prospective studies have shown that QUS measurements are predictors of hip fracture with a similar performance to hip DXA measurements [344-349].

The significant growth in use of QUS has been based on the affordability of the technology and the potential of sound waves to probe multiple bone properties

such as bone density, microarchitecture, and elasticity. The cost of the devices is much lower compared to DXA scanners and, hence, QUS might be more appropriate compared to DXA assessment for use in primary care. This, however, depends on the performance of QUS for prediction of osteoporotic fractures in the long term. Several studies have tried to compare the predictive power of QUS and DXA for various types of fractures, but they have used different methods of comparison and the overall results are still inconclusive [335, 350].

Currently, the use of absolute fracture risk estimation in the field of osteoporosis research and clinical practice guidelines has come to the forefront since that is what matters to the patients and the health care providers. The 'World Health Organization (WHO) scientific group for assessment of osteoporosis at the primary health care level' have developed the FRAX® tool (based on DXA and clinical risk factor) for estimation of 10-year absolute risk of fracture in different populations [24, 162]. Similar methods can now be applied for comparison of different radiological techniques or clinical risk factors to predict long-term absolute risk of fracture. We aimed in this study to compare models based on clinical risk factors and DXA with those using QUS measures obtained simultaneously for estimation of 10-year absolute risk of fracture in elderly men and women.

10.3. Methods

This study has been done on a subset of 1,511 men and women aged ≥ 65 years from EPIC-Norfolk study who collaborated with the European Prospective Osteoporosis Study (EPOS) [108]. Full details of participant recruitment and study procedures for EPIC-Norfolk have been described in Chapter 2. A subset of participants in the original EPIC-Norfolk study (≥ 65 years of age and without DXA-confirmed diagnosis of osteoporosis) was invited to a bone densitometry study about 18 months after the baseline visit. An information sheet detailing the purpose of the study was sent to eligible subjects. Over the period of May 1995 to January 1998, 1,511 participants underwent hip BMD measurements using a Hologic 1000 W bone densitometer (Hologic Inc, Bedford, MA). BMD (in gr/cm^2) of the total hip region was used for this study. All measurements were done by the same operator and an experienced independent operator reviewed all scans to ensure consistency of positioning of the hip regions [351, 352]. In the same day, 1,458 of these participants also had a QUS assessment in the heel by a CUBA sonometer (McCue Ultrasonics, Winchester, UK). The means of at least two measures of BUA and SOS (on left or right calcaneus) were used for analysis in this study. Demographic, anthropometric and lifestyle variables were collected at the time of bone measurements. Detailed procedures are described in Chapter 2. For this study, participants were followed up to the end of March 2007, an average of 10.3 years (SD=1.4; range 8.2-13.1).

Multivariable Cox proportional-hazard regression models were used to model the association between incident fractures and potential risk factors. Two separate models, one including total hip BMD and the other including BUA of the heel, were constructed with age, past history of fracture, BMI, smoking status, and alcohol intake as the covariates in both models. Both models were stratified for sex. For comparison of performance of models, different global measures of model fit were used. These measures included Bayesian information criterion (BIC) [353], Akaike's information criterion (AIC) [354], deviance information criterion (DIC) [355], likelihood ratio chi-squared statistic, Nagelkerke's and Cox-

Snell R-squared [356], and D-statistic [357]. Lower values for the three information criteria and higher values for other measures indicate better fitness of the proportional-hazard models. Harrell's C-index (which is equivalent to area under the ROC curve for survival data) was used as the measure of discrimination [327]. Calibration, which refers to the ability of a model to match predicted and observed outcome rates across the entire spread of the data, were compared between two models using the Hosmer-Lemeshow chi-squared statistic [328]. This measure compares observed and predicted outcomes over deciles of risk and higher values for its p value indicate better calibration of the model (i.e., a less significant difference between expected and observed rates).

For further comparison of the two models, 10-year absolute risk (probability) of fractures for each participant was calculated using the baseline survivor function and the estimated log hazard ratios for the variables in each model. Please see Chapter 9 for detailed methods for calculation of these absolute risks. All participants were assigned to two different 10-year probabilities of fracture using Cox models including hip BMD or heel BUA as covariates. Participants were then categorised into three groups with absolute risks of <5%, 5% to <15%, and ≥15% based on these two models. Unlike other ultrasound devices that report combined measures of BUA and SOS (namely, quantitative ultrasound index [QUI] for Sahara and Stiffness Index [SI] for Achilles devices), there is no combined measure for CUBA sonometer. Substitution of SOS for BUA resulted in poorer prediction in all models (BIC = 995.3 vs. 991.9) and inclusion of SOS with BUA did not result in better prediction (BIC = 992.4 vs. 991.9). Hence, only the models including BUA are reported here as representative of QUS measures.

10.4. Results

10.4.1. Characteristics of the study population

In sum, 1,455 participants aged 65-76 years (703 men, mean age 69.5 ± 3 years) were entered into the analysis. Three participants were excluded due to incomplete data. The characteristics of study participants are summarised in *Table 10.1*. Bone characteristics were higher on average among men. Mean total hip BMD was 0.944 ± 0.140 gr/cm^2 among men and 0.767 ± 0.125 gr/cm^2 among women. Mean BUA of the calcaneus was 88.3 ±18.2 dB/MHz among men, which was significantly higher than the mean 63.5 ± 15.4 dB/MHz for women. During 15,567 person-years of follow-up, 79 participants (61 women) developed a fracture. The Pearson correlation coefficient was 0.47 for total hip BMD and heel BUA.

Table 10.1: Characteristics of the study population

	Men *n=703*	Women *n=752*
Age (years)	69.6 (3.1)	69.4 (2.9)
Height (cm)	172.8 (6.3)	159.5 (5.8)
Body Mass Index (kg/m^2)	26.5 (3.1)	26.5 (4.1)
Past history of fracture	40 (5.7%)	109 (14.5%)
Current smoking	62 (8.8%)	48 (6.4%)
Alcohol intake (units/week)*	5 (10.5)	1.5 (5)
Total hip BMD (g/cm^2)	0.944 (0.140)	0.767 (0.125)
Heel BUA (dB/MHz)	88.3 (18.2)	63.5 (15.4)
Heel SOS (m/s)	1668.4 (44.5)	1631.4 (38.4)
Follow-up time (years)	10.4 (1.1)	10.2 (1.6)
Any incident fracture†	18 (2.6%)	61 (8.1%)

Data are mean (standard deviation in parenthesis) or number of participants (percentage in parenthesis); BMD = bone mineral density, BUA = broadband ultrasound attenuation, SOS = speed of sound

* Median (inter-quartile range in parenthesis)

† Number of incident fractures up to March 2007

10.4.2. Comparison of heel QUS and hip DXA by model performance

Two sex-stratified proportional-hazard models including BMD and BUA are shown in *Table 10.2*. Most of the variables entered into the models were significant predictors of fractures. *Table 10.2* shows that the hazard ratio (HR) for a 1 standard deviation (SD) decrease in total hip BMD was 2.3 (95% CI 1.7-3.0) compared with 2.0 (95% CI 1.6-2.7) for a 1 SD decrease in BUA. *Table 10.3* compares the performance of two models. Global measures of model fit (including different information criteria, likelihood ratio test, R-squared estimates and D-statistic) showed relative superiority of the BMD model while the area under the ROC curve was 0.6% higher for the BUA model (*Table 10.3*). High Hosmer-Lemeshow p values confirmed that both models were adequately calibrated (distribution of expected and observed fractures are shown in *Table 10.4*). In general, performances of both models were fairly similar.

Table 10.2: Sex-stratified multivariable Cox proportional-hazard models using total hip BMD or heel BUA included in the predictors

	BMD Model		BUA Model	
Variable	Hazard Ratio	P value	Hazard Ratio	P value
Age (year)	1.13 (1.05-1.22)	0.001	1.12 (1.04-1.21)	0.003
Height (cm)	1.04 (1.00-1.08)	0.051	1.04 (1.00-1.08)	0.084
Body mass index (kg/m^2)	1.05 (0.99-1.12)	0.096	1.02 (0.96-1.09)	0.432
Past history of fracture	2.24 (1.34-3.73)	0.002	2.31 (1.40-3.84)	0.001
Current smoking	2.15 (1.09-4.24)	0.027	2.18 (1.11-4.29)	0.024
Alcohol intake (units/week)	1.03 (1.00-1.06)	0.048	1.02 (0.99-1.05)	0.132
Total hip BMD (per SD decrease)	2.26 (1.74-2.95)	<0.001	-	-
Heel BUA (per SD decrease)	-	-	2.04 (1.55-2.69)	<0.001

Table 10.3: Measures of model fit for comparison of the Cox models including total hip BMD and heel BUA as predictors

	BMD Model	BUA Model
Global measures		
Bayesian Information Criterion (BIC)	981.6	991.9
Akaike's Information Criterion (AIC)	944.7	955.1
Deviance Information Criterion (DIC)	930.7	941.1
Likelihood ratio chi-square (df)	69.2 (7)	58.8 (7)
Nagelkerke's R^2	9.4%	8.0%
Cox-Snell R^2	4.7%	4.0%
D-statistic	1.63	1.50
Discrimination		
C-index (area under ROC curve)	67.9%	68.5%
Calibration		
Hosmer-Lemeshow P value	0.46	0.62

Lower values of the BIC, AIC, and DIC and higher values of all other statistics, including the calibration P values, indicate better fit of a model.

Table 10.4: Observed and predicted number of fractures in deciles of risk based on Cox models including total hip BMD and heel BUA as predictors

	BMD Model			BUA Model		
Decile of risk	Observed	Predicted	HL	Observed	Predicted	HL
1	0	0.71	0.71	0	1.09	1.09
2	3	1.43	1.75	0	2.07	2.10
3	1	2.15	0.62	2	2.96	0.32
4	3	2.91	0.00	4	4.04	0.00
5	1	3.96	2.27	5	5.38	0.03
6	7	5.34	0.53	7	6.91	0.00
7	7	7.47	0.03	6	8.92	1.02
8	10	10.26	0.01	10	11.69	0.27
9	18	14.86	0.74	12	17.04	1.69
10	24	32.82	3.07	28	35.63	2.17
Total	74	81.92	9.74	74	95.73	8.68

HL: Hosmer-Lemeshow statistic

10.4.3. Comparison of heel QUS and hip DXA by absolute fracture risk

For the next stage of the analysis, two new variables containing estimated 10-year absolute fracture risk using the BMD and BUA models were generated. The estimated fracture risks using the BUA model (median 4.2%, interquartile range [IQR] 2.0%-8.0%) were higher than estimated risks using the BMD model (median 3.1%, IQR 1.5%-7.1%; Wilcoxon signed-ranks test p value < 0.001). *Table 10.5* compares the classification of participants based on two models into three risk categories (10-year risk of <5%, 5% to <15%, and ≥15%). Most of the participants were classified into the same category of risk using each model. However, 419 participants (28.8%) were re-classified using different models. 45 out of 112 participants (40%) assigned to the high-risk group (10-year risk of ≥15%) using the BMD model were re-classified to a lower risk group according to the BUA model. The greatest re-classifications (about 40%) were observed among the groups with intermediate and high risk of fracture. While most of the participants were re-classified to adjacent categories, 10 participants categorised as low-risk (<5% risk) using the BMD model were re-classified to high-risk (≥15% risk) according to the BUA model and 6 of high-risk participants based on the BMD model were re-classified as low-risk using the BUA model (*Table 10.5*). The distribution of the participants in different categories based on the two models is shown graphically in *Figure 10.1*.

Table 10.5: Observed and expected risks of fracture using Cox proportional-hazard models based on BMD or BUA

10-year fracture risk in BMD model	10-year fracture risk in BUA model			
	0 to <5%	5% to <15%	≥15%	Total re-classified
0 to <5%				
Number of participants, n	728	201	10	
Participants classified in each stratum by the BUA model, %	77.5	21.4	1.1	22.5%
Observed 10-year risk, %	1.2	4.0	10.0	
5% to <15%				
Number of participants, n	99	241	64	
Participants classified in each stratum by the BUA model, %	24.5	59.7	15.8	40.3%
Observed 10-year risk, %	6.1	7.5	17.2	
≥15%				
Number of participants, n	6	39	67	
Participants classified in each stratum by the BUA model, %	5.4	34.8	59.8	40.2%
Observed 10-year risk, %	0	15.4	22.4	

Each stratum of risk according to the Cox model with BMD is categorised according to the stratum of risk predicted by the Cox model with BUA

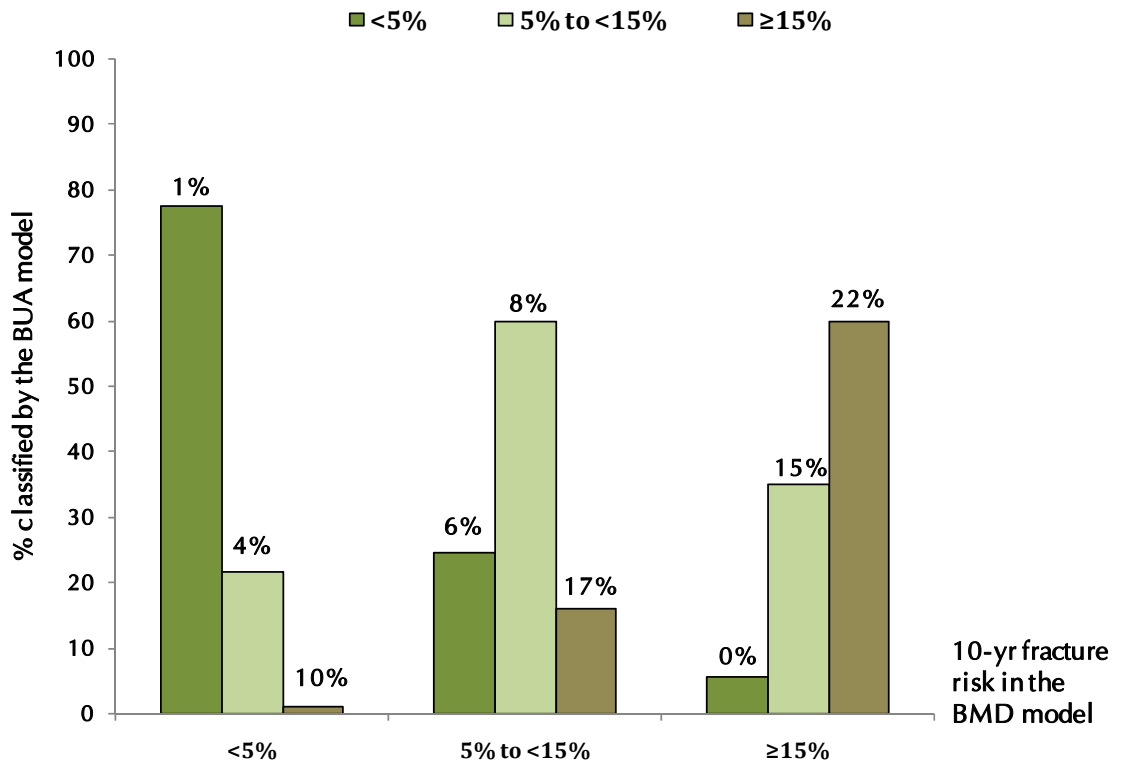

Figure 10.1: Distribution of 10-year absolute fracture risk based on two Cox proportional-hazard models among 1,455 EPIC-Norfolk participants
Bars show the percentage of participants categorised to the specific risk bands using the BUA model. The numbers on top of each bar show the observed 10-year fracture risk during the study period for that particular population.

As we had followed up most of the participants for more than 10 years, we were able to calculate observed 10-year fracture risk (which is the incidence rate of fracture in the first 10 years of follow-up). *Table 10.5* and *Figure 10.1* also report the observed fracture risks for different categories. These numbers show that the estimated fracture risks based on the BUA model were relatively more compatible

with the observed risks particularly in the intermediate- and high-risk groups. For instance, the right side of *Figure 10.1* shows that none of participants categorised as high-risk based on the BMD model but as low-risk using the BUA model experienced a fracture during follow-up. Similarly, 17% of those categorised as intermediate-risk based on the BMD model but re-classified as high-risk using the BUA model developed a fracture. In general, observed risks were closer to the estimated fracture risks using the BUA model for participants with higher risks of fracture based on any model.

10.5. Discussion

To our knowledge, this is the first study that uses calculated 10-year absolute risks of fracture for comparing QUS with DXA for their ability to predict fractures. Our results indicate that, while the conventional statistical methods show a relatively similar performance for both BMD and BUA models, there is a significant difference between two models regarding categorisation of patients to different risk bands. Global measures of model fit showed relative superiority of the model based on clinical risk factors and BMD whereas the area under the ROC curve was slightly higher for the model with clinical risk factors and BUA. Nevertheless, almost one in three of the participants (28.8%) were re-classified to a different category when 10-year absolute risk of fractures was considered. Estimated fracture risks based on the BUA model were closer to the observed fracture risk compared to the BMD model particularly for participants with higher risks of fracture. These findings suggest that QUS and DXA measure somewhat different aspects of bone strength and, suggest that hitherto QUS measurement has been under-rated for the prediction of long-term risk of fractures among the elderly.

Since 1984, when QUS measures began to be applied in bone research [358], it has been hypothesised that ultrasound may give information not only about the bone density but also about architecture and elasticity [333]. A growing number of researchers have used QUS to assess bone status for prediction of osteoporotic fracture risk and various studies have found a lower [337], an equal [339-341, 344, 345, 348], or a higher [342] prediction value than the one obtained with DXA. Relative risks or hazard ratios have been the most widely-used measures of association in prospective studies to compare predictive power of QUS and DXA [344-349]. However, these measures may not be perfect for comparison of these methods as they may only reflect the superiority of one method for estimation of short-term risk of fractures. Five out of six major prospective studies in this field have followed their participants for less than 3 years [344-348] and the only long-term study showed similar hazard ratios for BUA and femoral neck BMD [349]. Moreover, generalisation of relative risks derived from prospective studies that

only used QUS measurements might be problematic since we need to consider the effect of clinical risk factors and their potential interactions with these measurements.

It has been recently appreciated that the clinical practice should be founded on the estimation of absolute fracture risk in long term and using a multitude of risk factors. The measurement of a single risk factor can only capture one aspect of the likelihood of the outcome when the disease is multifactorial, and in osteoporosis for instance, assessment with BMD captures a minority of the fracture risk. The increase in risk with age is approximately sevenfold greater than that can be explained on the basis of BMD alone [359]. This has been the basis for development of the FRAX® tool by the WHO scientific group. This online program for estimation of 10-year absolute fracture risk for individuals currently considers several clinical risk factors and BMD in the femoral neck [24, 162]. FRAX® is likely to be a basis for future routine clinical practice in the field of osteoporosis. While the FRAX® methodology is the current best choice as it captures all the relevant information and summarises it to a single sensible measure for clinicians (i.e., 10-year probability of fractures), other potential risk factors (including clinical, radiological and biochemical factors) can be added to or replaced with the current set of risk factors. Our results suggest that BUA can be considered as a suitable alternative to BMD in such models.

Glüer and Hans [360] have suggested four potential strategies on how to use ultrasound clinically. The first strategy, the estimated BMD approach, suggests use of QUS for estimation of BMD and then use of that BMD estimate for fracture risk assessment. This approach is unsatisfactory due to low coefficients of correlation observed in different studies (including our study) between heel ultrasound and axial DXA as well as the poor predictive power of peripheral DXA [360]. Another strategy, the 'prescreening' approach, uses a threshold for QUS (presumably derived from a cross-sectional study) so that all subjects with a QUS result below this threshold would be referred for DXA assessment. This is particularly problematic given the extent of assumptions for derivation of the

threshold as well as the view to BMD as the gold standard for fracture risk estimation [360]. The third strategy, the composite approach, categorises subjects as high-, intermediate-, and low-risk and subjects with intermediate risk would be referred for further assessment (DXA, bone biomarkers, or second independent QUS at a different site). This strategy depends greatly on identification of other diagnostic techniques that add predictive power to QUS. The fourth strategy, the stand-alone approach, therefore seems to be optimal among these approaches. It considers replacement of BMD with a QUS measure for fracture risk prediction [360]. Considering the advances put forward by the FRAX® method, and given the results of our study which shows a similar performance of the models based on QUS and DXA for risk prediction, similar models can be built using clinical risk factors and QUS measures for estimation of 10-year absolute fracture risk and application in clinical practice.

It should be noted that ultrasound devices have some technological drawbacks that have precluded their widespread utilisation in bone assessment hitherto. An important factor is the precision of the devices. The short-term in vivo precision of BUA varies between 2.0 and 3.5%, depending upon the device and the site of measurement. Since a 2–3% precision of calcaneal BUA generates a least significant change that is about 6–9 times larger than the average annual loss rate in postmenopausal women [361], QUS devices cannot be good candidates for monitoring response to therapy. Moreover, there are no criteria for diagnosis of osteoporosis using QUS measurements. It has been shown that the -2.5 SD criterion for osteoporosis cannot be applied to many QUS devices [362] and, because of the technological differences between devices, results cannot be extrapolated from one device to another [361]. However, QUS instruments have some advantages: they are radiation-free, portable, and inexpensive [350]. Therefore, given the predictive power of QUS compared to DXA observed in this study, using a stand-alone approach may be the most cost-effective approach for fracture risk assessment [360]. This issue needs further attention of researchers working in this field.

This study has some limitations. The most important one is the choice of thresholds for categorisation of participants. We acknowledge that these thresholds must ideally come from population-specific cost-utility or cost-effectiveness studies that combine absolute risk measures, age structure of the population, cost and efficacy of the therapies, and the value (or utility) of fractures in the community. Currently, however, there is no such study using absolute risk estimates in the UK (as for other parts of the world) and we had to rely on arbitrary thresholds. We considered the distribution of incident fracture cases in our study population and the estimated fracture risks using both models in this study. Given the low incidence of fractures in our population, we chose to consider about 10% of participants as high-risk and about 30% as intermediate-risk. This translated to cut points of 5% and 15%. If we were to use previously suggested thresholds (such as the thresholds of 10% and 20% for risk categorisation suggested by Siminoski et al.) [363], we would have only 4% of participants as high-risk and about 11% as intermediate-risk based on both models.

The other potential limitation of this study is the representativeness of the study population. Although it was population-based, there is a potential for `healthy participant' recruitment into the EPIC-Norfolk study as well as this particular analysis [352]. Healthy participants are more likely to complete food diaries and questionnaires and consent to undergo several diagnostic procedures. The incidence rate of fractures was very low according to UK norms in our participants (about 5 per 1000 person-years). However, it should be noted that previous studies from East Anglia have shown that the rate of fracture in this region is considerably lower compared to other parts of UK [324]. Given the follow-up procedure in the EPIC-Norfolk study, only fractures that needed admission to hospitals or recorded in the general practices were considered for this study. This may have led to an underestimation of fracture rate in our study compared to other populations, although only minor fractures (e.g., of digits or ribs) are thought not to attract clinical attention. Nevertheless, this is not likely to have confounded the comparison of the results for models based on BUA and

BMD unless there was an independent interaction with the composition of the sample. In any case, the results of this study need validation in other settings before generalisation to other populations.

In conclusion, we estimated 10-year absolute risk of fracture for comparison of models based on BMD and BUA as fracture predictors. We found that, while the conventional statistical methods showed a similar performance for both models, almost one in three participants were re-classified to a different risk band using different models. Although individuals were categorised to different risk bands, both models classified a similar fraction of participants to each risk band. Interestingly, estimated fracture risks based on the BUA model were closer to the observed fracture risks. These results suggest that QUS has at least a similar performance compared to DXA in prediction of long-term fracture risk among elderly men and women. Given the lower cost and affordability of ultrasound measurement in primary care, further studies to develop and validate models for prediction of 10-year risk of fracture using clinical risk factors and QUS are recommended.

Chapter 11: Heel QUS as a 'Risk Factor' for Fracture

The work presented in this Chapter has been published in:

***Moayyeri A**, Kaptoge S, Dalzell N, Luben RN, Wareham NJ, Bingham S, Reeve J, Khaw KT.* The effect of including quantitative ultrasound assessment in models for estimation of 10-year absolute risk of fracture. Bone 2009 Aug;45(2):180-4

Please see Appendix 10.

11.1. Abstract

The role of quantitative ultrasound (QUS) in clinical practice is debatable. An unanswered question is that whether combining QUS and BMD measurements could improve the prediction of fracture risk. We examined this in a sample of men and women from EPIC-Norfolk study who had both heel QUS and hip DXA between 1995 and 1997 and were followed for any incident fracture up to 2007. From 1,455 participants (703 men) aged 65-76 years at baseline, 79 developed a fracture over 10.3 ± 1.4 years of follow-up. Two separate sex-stratified Cox proportional-hazard models were used including clinical risk factors and total hip BMD. Heel broadband ultrasound attenuation (BUA) was also included in the second model. Global measures of model fit, area under ROC curve, and the Hosmer-Lemeshow statistic showed relative superiority of the model including BUA. Using each model, we calculated 10-year absolute risk of fracture for all participants and categorised them in groups of <5%, 5% to <15%, and ≥15%. Comparison of groupings showed a total re-classification of 16.6% of participants after inclusion of BUA with the greatest re-classification (30.7%) among the group with intermediate risk. Adding a QUS measurement to models based on clinical risk factors and BMD improves the predictive power of models and suggests that further attention should be paid to QUS as a clinical tool for fracture risk assessment.

11.2. Introduction

Quantitative assessment of osteoporosis and estimation of fracture risk relies mainly on bone mineral density (BMD) measurements using radiologic methods such as dual-energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT). A limitation of these techniques is that BMD measurements are dependent on the amount of mineral in the bone and not on bone structure and bone tissue quality. However, trabecular architecture is an important parameter in assessing bone strength. Although it turned out to be a modest predictor of bone architecture, this encouraged the development of quantitative ultrasound (QUS) techniques in the past years [117, 118].

Several studies have documented the ability of QUS measurements to discriminate between individuals with or without fractures and to predict fracture risk independently of hip BMD. In cross-sectional studies, calcaneal QUS significantly differentiates women with hip fracture from controls [338, 339, 341, 343, 364-367] and major prospective studies have concluded that QUS measurements are predictive of osteoporotic fractures [344-347, 349]. A recent large-scale prospective study showed that the combined use of clinical risk factors and QUS measures is a promising tool to assess hip fracture probability in elderly women [368]. QUS prediction was found to be partly independent of hip DXA measurements and similar in the magnitude of the association [335, 350, 361]. However, despite these advances QUS has not yet been included in the routine assessment of osteoporotic patients. As Durosier et al. [335] have pointed out, a major problem that precludes comparison of most published studies and interpretation of their results is that they use different measures of association (such as relative risks, odds ratios, and absolute risks) and performance of the tests (i.e., sensitivity/specificity or area under receiver operating characteristics [ROC] curve).

There is an emerging consensus among researchers that fracture risk assessment needs to shift toward estimation of long-term absolute risk of fracture for

individuals. It is necessary to consider the effects of including QUS measures into models for estimation of 10-year absolute fracture risk and observe whether QUS can add useful information to the current models based on DXA measures. As discussed in Chapter 8, adding new information to prediction models is a necessary principle for accepting a measure as a 'risk factor'. In this Chapter, this will be evaluated for heel QUS. I compared models based on clinical risk factors and BMD for estimation of 10-year absolute risk of fracture with and without QUS measures included in the models.

11.3. Methods

This study was done in the group of EPIC-Norfolk participants who underwent hip DXA and heel QUS measurements on the same day. Please see Chapters 2 and 10 for full details of participants' recruitment and health examination procedures. Demographic, anthropometric and lifestyle variables of 1,511 participants were collected at baseline examination (1993-1997). Participants were followed up to the end of March 2007 for different fracture outcomes (excluding fractures of skull, face, metacarpals, metatarsals, and phalanges).

Two separate multivariable Cox proportional-hazard regression models stratified by sex [325] were used to model the association between potential risk factors and incident fractures. The first model included age, past history of fracture, BMI, smoking status, alcohol intake, and total hip BMD as predictors. The second model included BUA in addition to these variables. For comparison of performance of models, different global measures of model fit including Bayesian information criterion (BIC), Akaike's information criterion (AIC), deviance information criterion (DIC), likelihood ratio chi-squared statistic, Nagelkerke's and Cox-Snell R-squared, and the D-statistic were used. Interactions (effect modifications) between different factors entered into both models were sought and verified using the AIC and BIC of the models and likelihood ratio tests. Discrimination was measured by Harrell's C-index (which is the equivalent of an area under ROC curve for survival data). Calibration, which refers to the ability of model predictions to match the observed outcome rates across the entire spread of the data, was compared between two models using the Hosmer-Lemeshow chi-squared statistic. This measure compares observed and predicted outcomes over deciles of risk and a significant p value for this statistic shows lack of calibration of the model (i.e., there exists a significant difference between expected and observed rates). Generally p values >0.1 can be considered as satisfactory for calibration of the models [328].

In the next stage of analysis, 10-year absolute risk of fractures for any participant was calculated using the baseline survivor function and prediction coefficients for different models (details are described in Chapter 9). Every participant was assigned to two different 10-year fracture risk using models with and without BUA. Predicted risks based on two models were compared using the non-parametric Wilcoxon signed-ranks test. Participants were then categorised into three groups with absolute risks of <5% (low-risk), 5% to <15% (intermediate-risk), and ≥15% (high-risk) based on these two models and compared. These cut-offs were chosen according to the distribution of fracture risk in our population and a priori to the analysis. Inclusion of SOS measures into the models did not materially change the results of BUA models and we chose not to include them in this study. All database management and statistical analyses were performed using Stata software, version 10.0 (StataCorp LP., College Station, TX, USA).

11.4. Results

11.4.1. Characteristics of the study population

After exclusion of those with incomplete data, 1,455 participants aged 65-76 years (703 men) contributed to the analysis. The characteristics of study participants are summarised in *Table 11.1*. As expected, the three bone characteristics (BMD, BUA and SOS) were higher on average among men compared to women. During an average of 10.3 years of follow-up (SD=1.4; range 8.2-13.1) for all participants, which accounted for 15,567 person-years, 79 participants suffered a fracture, of whom 61 were women.

Table 11.1: Characteristics of the study participants

	Men *n=703*	Women *n=752*
Age (years)	69.6 (3.1)	69.4 (2.9)
Height (cm)	172.8 (6.3)	159.5 (5.8)
Body Mass Index (kg/m^2)	26.5 (3.1)	26.5 (4.1)
Past history of fracture	40 (5.7%)	109 (14.5%)
Current smoking	62 (8.8%)	48 (6.4%)
Alcohol intake (units/week)*	5 (10.5)	1.5 (5)
Total hip BMD (g/cm^2)	0.944 (0.140)	0.767 (0.125)
Heel BUA (dB/MHz)	88.3 (18.2)	63.5 (15.4)
Heel SOS (m/s)	1668.4 (44.5)	1631.4 (38.4)
Follow-up time (years)	10.4 (1.1)	10.2 (1.6)
Any incident fracture†	18 (2.6%)	61 (8.1%)

Data are mean (standard deviation) or number of participants (percentage); BMD = bone mineral density, BUA = broadband ultrasound attenuation, SOS = speed of sound
* Median (inter-quartile range)
† Number of incident fractures (including hip, spine, wrist, and shoulder) up to March 2007

11.4.2. Fitting the models including heel QUS

Table 11.2 shows the results of sex-stratified Cox proportional-hazard regression models with and without BUA included as a covariate. Most of the variables entered into the models were significantly associated with fracture risk. The hazard ratio (HR) for any fracture per standard deviation decrease in total hip BMD was 2.3 (95% confidence interval 1.7-3.0) without BUA in the model and it reduced to 1.9 (95% CI 1.4-2.5) after inclusion of BUA. *Table 11.2* also shows that BUA was significantly associated with fracture risk even with BMD in the model (HR=1.6, 95% CI 1.2-2.1).

Table 11.2: Sex-stratified multivariable Cox proportional-hazard models with and without BUA included in the predictors

	Model with BUA		Model without BUA	
Variable	Hazard Ratio	P value	Hazard Ratio	P value
Age (year)	1.12 (1.04-1.21)	0.002	1.13 (1.05-1.22)	0.001
Height (cm)	1.05 (1.01-1.09)	0.019	1.04 (1.00-1.08)	0.051
Body mass index (kg/m^2)	1.07 (1.00-1.13)	0.040	1.05 (0.99-1.12)	0.096
Past history of fracture	2.07 (1.25-3.44)	0.005	2.24 (1.34-3.73)	0.002
Current smoking	2.12 (1.08-4.18)	0.029	2.15 (1.09-4.24)	0.027
Alcohol intake (units/week)	1.03 (1.00-1.06)	0.055	1.03 (1.00-1.06)	0.048
Total hip BMD (per SD decrease)	1.91 (1.43-2.54)	<0.001	2.26 (1.74-2.95)	<0.001
Heel BUA (per SD decrease)	1.59 (1.18-2.13)	0.002	-	-

Table 11.3 compares the performance of the models with and without BUA on three major aspects. All of the global fit measures (including different information criteria, likelihood ratio, R-squared estimates, and the D-statistic) showed enhanced model fit, although of a small magnitude, for the model including BUA. Discrimination was also improved in the model with BUA, with C-index being larger by about 2% (*Table 11.3*). Both models were adequately calibrated as shown by high p values from the Hosmer-Lemeshow test in *Table 11.3*. Details of estimated Hosmer-Lemeshow statistics have been shown in *Table* **11.4**.

Table 11.3: Measures of model fit for comparison of the Cox proportional-hazard models with and without BUA

	Model with BUA	Model without BUA
Global measures		
Bayesian Information Criterion (BIC)	979.7	981.6
Akaike's Information Criterion (AIC)	937.6	944.7
Deviance Information Criterion (DIC)	921.6	930.7
Likelihood ratio chi-square (df)	78.4 (8)	69.2 (7)
Nagelkerke's R^2	10.6%	9.4%
Cox-Snell R^2	5.3%	4.7%
D-statistic	1.81	1.63
Discrimination		
C-index (area under ROC curve)	69.8%	67.9%
Calibration		
Hosmer-Lemeshow P value	0.62	0.46

Lower values of the BIC, AIC, and DIC and higher values of all other statistics, including the calibration P values, indicate better fit of a model.

Table 11.4: Observed and predicted number of fractures in deciles of risk based on Cox models with and without BUA as predictor

	Model with BUA			Model without BUA		
Decile of risk	Observed	Predicted	HL	Observed	Predicted	HL
1	0	0.79	0.80	0	0.71	0.71
2	1	1.54	0.19	3	1.43	1.75
3	1	2.33	0.77	1	2.15	0.62
4	3	3.27	0.02	3	2.91	0.00
5	6	4.49	0.53	1	3.96	2.27
6	4	5.81	0.59	7	5.34	0.53
7	8	7.74	0.01	7	7.47	0.03
8	4	10.90	4.72	10	10.26	0.01
9	19	16.56	0.40	18	14.86	0.74
10	28	36.77	2.80	24	32.82	3.07
Total	74	90.20	10.83	74	81.92	9.74

HL: Hosmer-Lemeshow statistic

11.4.3. Impact of heel QUS on absolute fracture risk estimation

For the next stage of our analysis, two new variables containing predicted 10-year absolute risk of fracture using models with and without BUA were created. Wilcoxon signed-ranks test showed that the estimated fracture risks using the BUA model (median 3.5%, interquartile range [IQR] 1.6%-7.4%) were higher than estimated risks using the model without BUA (median 3.1%, IQR 1.5%-7.1%; p value = 0.039). The difference between two models does not necessarily show more accurate estimates for the model including BUA.

Table 11.5 compares the classification of participants based on two models into three risk categories. Most of the participants were classified into the same category of risk using both models. However, one in six participants (16.6%) were classified to a different category according to the model used. About 22% of participants assigned to the high-risk group (10-year risk of ≥15%) using the model without BUA were re-classified to a lower risk group after inclusion of BUA into models. The greatest re-classification (30.7%) was observed among the group with intermediate risk. Most of the participants were classified to adjacent categories; only one participant with 10-year fracture risk of ≥15% based on model without BUA was categorised to <5% risk category after inclusion of BUA (*Table 11.5*).

Table 11.5: Observed and expected risks of fracture using Cox proportional-hazard models with and without BUA as a predictor

10-year fracture risk in model without BUA	10-year fracture risk in model with BUA			Total re-classified
	0 to <5%	5% to <15%	≥15%	
0 to <5%				
Number of participants, n	847	92	0	
Participants classified in each stratum by the model including BUA, %	90.2	9.8	0.0	9.8%
Observed 10-year risk, %	1.4	6.5	-	
5% to <15%				
Number of participants, n	77	280	47	
Participants classified in each stratum by the model including BUA, %	19.1	69.3	11.6	30.7%
Observed 10-year risk, %	5.2	8.6	14.9	
≥15%				
Number of participants, n	1	24	87	
Participants classified in each stratum by the model including BUA, %	0.9	21.4	77.7	22.3%
Observed 10-year risk, %	-	12.5	20.7	

Each stratum of risk according to the Cox model without BUA is categorised according to the stratum of risk predicted by the Cox model with BUA

The distribution of the participants in different categories based on the two models is shown graphically in *Figure 11.1. Table* **11.5** and *Figure 11.1* also report the observed fracture risks for different categories. As we had followed up most of the participants for more than 10 years, we were able to calculate observed 10-year fracture risk (which is the incidence rate of fracture in the first 10 years of follow-up). These numbers show that the estimated fracture risks based on the model with BUA were more compatible with reality. For instance, the left side of *Figure 11.1* shows that the observed risk for participants categorised to <5% risk based on model without BUA and 5% to <15% based on model with BUA was about 7%. The same is true for the right hand side of the *Figure 11.1* as the observed risk for the participants categorised to intermediate risk band was 13%. Models including BUA showed a marginal superiority as the observed risks among reclassified participants within the intermediate risk group were close to the risk thresholds (5% and 15%).

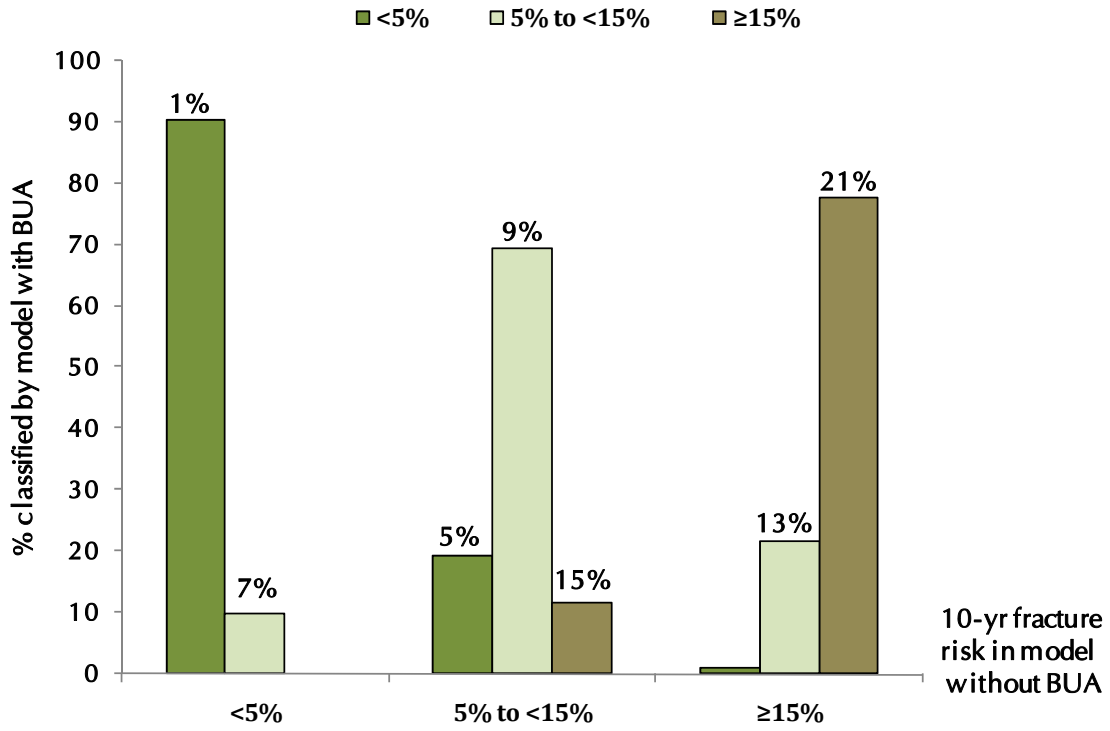

Figure 11.1: Distribution of 10-year absolute fracture risk based on Cox proportional-hazard models with and without BUA among 1,455 EPIC-Norfolk participants
Bars show the percentage of participants categorised to the specific risk bands using the model including BUA. The shading of the bars refers to the fracture risk from the model including BUA. The numbers on top of each bar show the observed fracture risk during the study period for that particular population.

11.5. Discussion

To our knowledge, this is the first study that evaluates the effects of inclusion of QUS measurements in prediction models for incident fracture risk using prospective data for 10-year absolute risk of fracture. We found that, while there is a small difference with regard to conventional statistical measures between prediction models with and without BUA, the resulting change in the estimates of 10-year fracture risk would be of sufficient magnitude to re-classify one in six of participants to other risk categories. Area under the ROC curve increased by 2% for the model including BUA and global measures of model fit showed relative superiority of the model with BUA. However, categorisation of participants to three risk bands showed a discordance of 16.6% between two models and the risk estimates in the re-classified groups were closer to the observed risks in our population.

Recently, due to increased public awareness and the introduction of novel and effective treatments for osteoporosis, there has been a raise in the demand for bone densitometry services. QUS has been introduced in the past two decades as an alternative technology to DXA and a large body of evidence supports the idea that QUS measurements can discriminate patients with fracture and predict incident fracture risk independently and similarly to BMD measurements [343, 345, 346, 348, 349, 365, 368]. The widespread availability of both QUS and DXA equipments raises the question of whether a combination of QUS and BMD measurements could improve the prediction of fracture risk [360]. The answer to this question, however, remains uncertain as different studies have reached different conclusions hitherto [350]. The EPIDOS study supported this combination as the incidence of hip fracture among women with values above the median for both calcaneal BUA and femoral neck BMD was 2.7 per 1000 person-years compared with 19.6 per 1000 person-years for those with values below the median for both measures [345]. The Study of Osteoporotic Fractures (SOF), on the other hand, suggested that BUA may be a reasonable surrogate for BMD to screen for high-risk older women, but the utility of BUA to define further

a group of individuals at a very high risk for fracture is modest [344]. The debate on this issue continues in smaller cross-sectional studies [337, 340, 369, 370].

An important drawback common to all these reports is the retrospective or short follow-up design of the studies that compared QUS and DXA for fracture prediction. Most of the prospective studies have followed their participants for less than 3 years [344-347]. However, it seems necessary to compare the long-term predictive power of different technologies for prediction of fractures in order to have a better estimate of their performance. Moreover, clinical practice is currently shifting towards considering these long-term estimates. The FRAX® tool is likely to be a major resource for use in routine clinical practice in this field [24, 162]. This tool currently considers several clinical risk factors and BMD measurements in the femoral neck. The results of this tool can be replicated for different populations using prospective studies with long follow-ups. Moreover, other potential risk factors (including clinical, radiological and biochemical factors) can be added to these estimations. In the current study, we examined the effects of inclusion of BUA into models for calculation of 10-year fracture risk when all models contain clinical risk factors and BMD measures. Our results confirm that combining QUS measures with clinical and BMD measures can have an impact as it re-classifies about 17% of participants to other risk categories.

Our study has some limitations. The main limitation, which applies not only to this study but also to the whole osteoporosis risk-assessment field, is the choice of thresholds for categorisation of participants. We know that these thresholds must come from population-specific cost-utility or cost-effectiveness studies that combine absolute risk measures, age structure of the population, cost and efficacy of the therapies, and the value (or utility) of fractures in the community. Currently, there is no such study using absolute risk estimates in the UK (as well as other parts of the world) and we had to rely on some arbitrary thresholds. We considered distribution of incident fracture cases in our study population as well as the estimated fracture risks based on both models in this study. Given the low

incidence of fractures in our population, we chose to consider about 10% of participants as high-risk and about 30% as intermediate-risk. This translated to cut points of 5% and 15%. Choosing other previously suggested thresholds [363] yielded similar results (data not shown) as, for instance, thresholds of 10% and 20% for risk categorisation showed about 14% total re-classification between two models.

The other potential limitation of this study is the representativeness of the study population. There is a potential for healthy subject recruitment of participants into the EPIC-Norfolk study as well as this particular analysis since healthy subjects are more likely to participate in long-term prospective studies and consent to undergo several diagnostic procedures. The incidence rate of fractures was low according to the UK norms (about 5 per 1000 p-y in our participants compared to about 20 per 1000 p-y in other parts of UK [4, 371]). About 85% of our participants had an estimated 10-year fracture risk of less than 10% based on either model. However, it should be noted that previous studies from East Anglia have shown that the rate of fracture in this region is much lower compared to other parts of UK for unknown reasons, possibly related to a healthier lifestyle and higher levels of physical activity [324]. Given the follow-up procedure in the EPIC-Norfolk study, which is based on surveillance of hospital admissions throughout England and Wales for all participants, only fractures that needed admission to hospitals were considered for this study. This may have led to an underestimation of fracture rate in our study population compared to other populations, even though only minor fractures (e.g., of digits or ribs) are thought likely to avoid hospital attention. Nevertheless, the association found in this study between BUA and fracture risk as well as its impact on re-classification of participants is unlikely to change with recruitment of higher risk individuals unless there was an independent interaction between these factors and the composition of the sample. In any case, the results of this study need to be validated in another study setting before generalisation to other populations.

In conclusion, we estimated 10-year absolute fracture risk for comparison of models with and without QUS measures included as a predictor of fractures. Our method of comparison can be regarded as a new application for absolute fracture risk calculation and may be used with other presumably important risk factors (such as clinical, radiological and biochemical risk factors) to assess whether they can add useful information to the current risk prediction models. Our results show that combining QUS measures into models based on clinical risk factors and BMD provides useful information that helps to more accurately categorise patients according to their risk of fracture. This suggests that further attention should be paid to QUS as a useful clinical tool for prevention of fractures.

Chapter 12:Discussion

12.1. Interpretation of the main findings

Various projects of this thesis have contributed to the field of epidemiology and risk assessment of osteoporotic fractures. The first part of the thesis looked at different risk identifiers for fractures. These included clinically-applicable `measured height loss' and `respiratory function' measures. Non-linear associations between physical activity as well as body fat mass with osteoporotic fractures were also assessed in this part. The second part of the thesis dealt with absolute risk of fracture and the methods and applications of it in the field of fracture risk assessment, which is a really hot topic in the current research world. We developed a method for estimation of absolute fracture risk using individual-level prospective data and applied it for comparison of two radiological measures of bone and then showed the independent contribution of bone ultrasound for improvement of absolute risk measures.

Currently, measuring changes in height over time is not a routine practice among clinicians caring for the elderly. Creating charts with detailed measurements of height in consecutive visits is easily applicable in all general and geriatric clinics throughout the world. Our study shows that a rapid loss of height (e.g. >2 cm over a period of 4 years) can be an indicator of osteoporosis and increased risk of fracture. This may also be an indicator of frailty and susceptibility to other morbid outcomes in this older population and needs verification in other studies. Similarly, assessment of respiratory function using a simple and inexpensive device can inform the clinicians about the risk of osteoporotic fractures in their patients. FEV_1 may also be an indicator of general health status of individuals as another EPIC-Norfolk analysis showed that it independently predicts self perceived physical well-being across the whole normal distribution of respiratory function [372].

Physical activity by nature is a difficult exposure to measure, especially in a prospective setting. My review on the associations between physical activity and different fractures or surrogate bone outcomes showed a complex, and sometimes

conflicting, relationship. While moderate physical activity is surely protective against hip fractures, it may act differently or in opposite direction on other fractures or in higher intensities. Moreover, its impact on bone density and bone quality seems to be of a questionable magnitude and, therefore, most of it effects of fracture risk might be related to muscle functions and reduced risk of falls among the elderly. It is important to notice that a physically active lifestyle includes assessment of activities in all domains of life, which has been considered in the EPAQ2 questionnaire. Our study showed different patterns of association between physical activity in different domains of life and prospective risk of fractures among men and women. Alongside direct information derived from our findings, non-linear associations observed in our study will inform researchers about the factors to consider when designing future trials on this subject.

Inter-relationships between bone and fat tissues have recently taken attention of researchers in the field of bone research. Most of previous epidemiological studies considered obesity indices like weight or body mass index as their covariate for assessment of fracture risk. However, it is now shown that fat mass as a lively tissue may have different effects on the function and properties of bone in cellular and tissue levels. In this sense, consideration to the risk of fracture attributed to the fat content of individuals may have a great impact on our understanding about these mechanisms. Meanwhile, the association between body fat mass and fracture risk does not follow a linear trend and adjustment for BMI changes the association noticeably. These impose immense problems for analysis of data in epidemiological studies and have resulted in challenging controversies in the literature. Use of fractional polynomial modelling in our study empowered us to assess the non-linear association between fat mass and fracture risk considering its independence from body mass index.

Estimation of 10-year absolute risk of fracture is gradually becoming the routine practice for clinicians in this field. This practice is recommended by the WHO and many other academic and clinical societies across the world. Consequently, the field of research on fracture risk is also changing direction towards use of

these measures. As one of the first studies in this field, we developed a model for prediction of 10-year absolute risk (or probability) of fracture using long-term follow-up data available in EPIC-Norfolk study. This method needs follow-up of more than 10 years for at least a subset of participants as it uses the semi-parametric Cox proportional-hazards regression modelling. However, the method can be extended to parametric methods such as Poisson regression to use in cohorts with shorter follow-ups. I have also applied this method for comparison of two bone measurement modalities and for assessment of independent power of bone ultrasound measures for fracture risk prediction. Our method has already attracted large attention and I am collaborating now with a team of experts from the International Society for Clinical Densitometry to develop guidelines for inclusion of bone ultrasound into FRAX®.

12.2. Strengths and limitations of the study

Studies presented in this thesis have several strengths and advantages related to the design and methodological subtleties contemplated in EPIC-Norfolk study. The long follow-up and large number of participants from both sexes are the obvious strengths. Participants have been examined for a thorough list of health measures related to a variety of outcomes and this enabled me to consider a number of them in this thesis. Although the cohort was not originally designed for assessment of osteoporotic fractures, participants in the second health examination of EPIC-Norfolk underwent measurement of heel QUS that, as shown in this thesis also, is a powerful predictor of risk of fractures. Designing and validating a detailed questionnaire for assessment of physical activity in different domains of life is another strength point of EPIC-Norfolk study. In all chapters of this thesis, I have used robust statistical tests with consideration to sex differences and adjustment for known risk factors of fracture. Large number of participants enabled us to look at the non-linear associations between some of

the complex exposures and risk of fracture. Use of these methods alongside with longitudinal design of EPIC-Norfolk makes a distinction between our findings and other studies previously reported in this field.

Our studies have also some limitations that have been mainly discussed in each chapter. EPIC-Norfolk was not originally designed for assessment of osteoporosis and bone fractures and this put some restraints for exploitation of its findings in the field of bone research. The main limitation pointed out by several reviewers of our papers is the lack of DXA assessment in our studies. Although we have shown in Chapter 10 that heel QUS can predict fracture as efficiently as DXA, most of the researchers in this field do trust in DXA measures in a much respected way. The reason usually mentioned is that the output of DXA, which is mineral content and density of the bones, is obvious and sensible, while the output of QUS measures, which is change in the characteristics of the sound waves passing the bone, is not clear. In this sense, not using DXA in EPIC-Norfolk might be considered as a weakness. However, the expense and applicability of measurement techniques should also be considered in running a large population-based prospective study. This also should be noted for risk assessment of fracture in clinical practice. Moreover, associations observed in this thesis for different risk identifiers, which are all independent of heel BUA measures, are unlikely to be dependent on bone density and use of DXA measures would not change most of our findings.

The other limitation of EPIC-Norfolk with respect to fracture risk assessment is the age structure of participants. EPIC-Norfolk can be considered as a young population compared to most of other cohorts in the field of osteoporosis. Given the exponential increase in fracture rate with age, most cohorts include participants older than 70 years, which are a minority in EPIC-Norfolk. This is especially true for the male population. There is also a potential for `healthy participant' bias in our study. However, characteristics of EPIC-Norfolk study population are shown to be comparable with the Health Survey of England and this population can be considered representative of the UK population [107]. The

method of assignment of fractures is another potential limitation of our study. Although we can be sure that we have captured all the fractures with high health impact that demanded hospitalisation, the shape of distribution of different fracture types indicates that we might have lost some minor fractures (for instance in distal forearm). Lack of radiological assessment for potential vertebral fractures is another constraint. Active follow-up of participants and asking directly and frequently about different health outcomes including fractures is not practical in the settings of a large population-based study like EPIC-Norfolk and we had to put up with this limitation. However, we can be sure that we have covered for almost all of the high-impact clinical consequences of osteoporosis in our study for a long period of follow-up.

12.3. Future works

The findings of studies carried out in this thesis may be applied in clinical settings and may serve as a basis for future research in related topics. Results of first part of the thesis, after validation in independent populations, can be used in clinical practice for better estimation of fracture risk in patients. Currently, I have started collaboration with two cohorts (Canadian Multi-centre Osteoporosis Study and TwinsUK study) to validate these findings. Both cohorts are long-term prospective studies and have baseline and follow-up data available on measured height, respiratory function and percentage body fat. Unfortunately the method of assessment of physical activity is different in other cohorts and needs specific methods for analysis in each cohort.

An important research question that can be considered as an extension to the works of this thesis is concerning the role of muscle function in prediction of fracture risk. The term sarcopenia, or reduced muscle mass and strength, is suggested to be the starting point for physical frailty process among the elderly

[373]. While the biological mechanisms underlying sarcopenia remains elusive, there is growing evidence for the link between sarcopenia and osteoporosis [374]. Several factors that play a role in the origin of osteoporosis are thought to contribute in causing sarcopenia. These putative causal factors include a decreased level of physical activity, hormonal changes, a reduction in dietary protein, and catabolic stimuli from chronic inflammation [375]. Furthermore, a role of genetic factors in linking muscle and bone mass has been advocated [376]. Sarcopenia may also be a risk factor for fracture as it increases the hazard of falling [377]. However, there is a lack of large-scale epidemiological studies focussing on the predictors and functional consequences of sarcopenia and its connection with osteoporotic fractures. Several methods can be considered for assessment of sarcopenia including measurement of muscle mass (using DXA, CT scan, or bio-impedance), muscle strength tests (such as handgrip test and knee flexion/extension test), physical performance tests (such as Short Physical Performance Battery [SPPB], gait speed, and timed get-up-and-go test), and balance tests [375]. Most of these tests are being performed for participants of the 3rd health examination of EPIC-Norfolk.

Future works for finding new risk identifiers or determinants of osteoporotic fractures inside EPIC-Norfolk study can be more focused on the measures of muscle strength or physical performance. Unfortunately, the length of follow-up for these variables is short and prospective analysis with the fracture outcomes is unlikely to be fruitful at this stage. However, as we are aware of the link between these measures and risk of osteoporotic fractures, we may consider them (or sarcopenia as a clinical entity) as a separate outcome and try to find predictors and determinants of them in EPIC-Norfolk population. The other option is collaboration with long-term prospective studies with data available in this field. Currently, I am applying for funding to start a collaborative project for working on the determinants and markers of sarcopenia in older men and women. This project will be based on four prospective cohorts: EPIC-Norfolk study, TwinsUK study, Hertfordshire Cohort study, and Framingham Osteoporosis study. We aim to understand the contribution of lifestyle, biological, and genetic determinants of

muscle strength and performance and to examine the association between sarcopenia and the prospective risk of development of physical frailty and its adverse outcomes including falls, fractures, increased medication, hospitalisation, institutionalisation and death.

Works done in the second part of this thesis may also be applied in different ways. Methods developed for comparison of different risk factors using estimated absolute risks of fracture may be applied to other clinical and radiological tests. The method of evaluation of independent `risk factors' (such as heel QUS in Chapter 11) can also be applied to other risk identifiers. I have also used the method for calculation of 10-year probability of fracture in the Canadian Multi-centre Osteoporosis study (CaMos) for about 7,500 men and women aged > 50 years. The estimated 10-year probabilities are being compared with the newly developed FRAX® for Canada and the results will be published in collaboration with CaMos researchers.

Another important point of application for our method of estimation of fracture probability is related to the length of follow-up required to achieve an accurate estimate of 10-year fracture risk. These estimates should ideally come from population-specific prospective studies that follow representative members of the community for a sufficiently long time. However, given practical and resource constraints, cohort studies usually follow their participants for a shorter interval (typically 4-7 years) and extrapolate their results to generate 10-year predictions. The most widely used statistical methods for extrapolation are based on exponential distribution of fracture risk and using Poisson regression. This is also true for the FRAX® estimates since they are based on modelling in 59,644 individuals followed for 252,034 person-years in 9 cohorts (follow-up average of 4.2 years in the development set) [24]. I extended the method described in Chapter 9 to compare fracture probabilities derived from models with different length of follow-up.

For this purpose, I employed sex-specific Poisson regression models adjusting for age, history of fracture, height, body mass index, smoking and alcohol

consumption in the original cohort of EPIC-Norfolk. 10-year absolute fracture risks were calculated in 10 different sub-cohorts with one year added interval of follow-up (i.e., the original cohort was re-arranged to produce 10 cohorts with follow-up period of 1, 2, 3, …, and 10 years; incident fractures after the follow-up period were censored for each cohort). While 758 fractures were observed in the first 10 years of follow-up among EPIC-Norfolk participants, models with 5, 6, 7, 8, 9, and 10 years of follow-up, respectively, predicted this number to be 423, 491, 569, 638, 685, and 761 fractures. This shows a strong trend towards underestimation with more censoring in shorter studies. When compared to sex-specific Cox model with 10 years of follow-up, estimates derived from Poisson models with follow-up of 7 years or less showed significantly lower area under the ROC curve (AUC for Cox model = 0.700; AUC for Poisson models ranging from 0.670 to 0.696; P values < 0.05). I have also used this method in the CaMos dataset and found quite similar results. This suggests that short-term studies systematically underestimate long-term risks of fracture and might not be suitable for this purpose.

In summary, various projects of this thesis have contributed to the field of epidemiology and risk assessment of osteoporotic fractures. The findings of our studies need verification in independent cohorts and methods used for analysis can be applied to other settings and other variables. The perspective of works in EPIC-Norfolk are being extended to include risk of muscle wasting and strength as a potential contributor to osteoporotic fractures and collaborations are underway for application of our absolute risk estimation method in other cohorts.

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Appendix 1: Health and lifestyle questionnaire in the EPIC-Norfolk study

Appendix 2: EPIC Physical Activity Questionnaire (EPAQ2)

Appendix 3: Measured height loss predicts fractures in middle aged and older men and women: the EPIC-Norfolk prospective population study

Appendix 4: Respiratory function as a marker of bone health and fracture risk in an older population: the European Prospective Investigation into Cancer-Norfolk Study

Appendix 5: The association between physical activity and osteoporotic fractures: A review of the evidence and implications for future research

Appendix 6: The association between physical activity in different domains of life and risk of osteoporotic fractures

Appendix 7: The importance and applications of absolute fracture risk estimation in clinical practice and research

Appendix 8: Estimation of absolute fracture risk among middle-aged and older men and women: the EPIC-Norfolk population cohort study

Appendix 9: Is QUS or DXA better for predicting the 10-year absolute risk of fracture?

Appendix 10: The effect of including quantitative ultrasound assessment in models for estimation of 10-year absolute risk of fracture