**Fracture prediction, imaging and screening in osteoporosis**

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**Abstract [Au: I’ve edited the abstract (which can be up to 200 words long) to increase the number of key terms included. This will improve the searchability of your article on web databases. Please be aware that BMD and CT are terms that we use without definition in our journal.]**

Osteoporosis is a condition that is associated with increased fragility of bone and a subsequent increased risk of fracture. The diagnosis of osteoporosis is intimately linked with the imaging and quantification of bone and BMD. Scanning modalities, such as dual-energy X-ray absorptiometry or quantitative CT, have been developed and honed over the last half century to provide measures of BMD and bone microarchitecture for the purposes of clinical practice and research. Combined with fracture prediction tools such as FRAX (which use a combination of clinical risk factors for fracture to provide a measure of risk), these elements have led to a paradigm shift in the ability to diagnose osteoporosis and predict individuals who are at risk of fragility fracture. Despite these developments, a treatment gap exists between individuals who are at risk of osteoporotic fracture and those who are receiving therapy. In this Review, we summarise the epidemiology of osteoporosis, the history of scanning modalities, fracture prediction tools and future directions, including the most recent developments in prediction of fractures.**[Au: Edits OK?]**

**Key points:**

* The WHO defines osteoporosis as a BMD that is at least 2.5 standard deviations less than the mean BMD for a 30 year old man or woman.**[Au: You can have up to 6 key points associated with your article and I thought the current operational definition of osteoporosis by the WHO might be a good one.]**
* Dual-energy X-ray Absorptiometry provides a measure of BMD that can be used to diagnose osteoporosis.
* Central and peripheral quantitative CT can be used to provide measures of bone microarchitecture within a research setting.
* BMD, combined with clinical risk scores, including FRAX®, can be used to predict individuals at who are at high risk of fracture.
* A gap exists between individuals who are at risk of fracture and those who are receiving treatment and requires closing as a matter of paramount importance.

**[H1] Introduction [Au: Hx heading markers have been added in to keep track of the heading levels. Please leave them in for now.]**

Osteoporosis is a disorder associated with a decrease in BMD, low bone mass and increased bone fragility; individuals with osteoporosis have increased risk of fragility fractures.**[Au: The introduction should contain enough information to set up the narrative and to allow a non-specialist reader to follow the rest of the text. As such, I’ve suggested that you add a couple of introductory sentences on osteoporosis here, please amend as necessary.]** The economic and societal burden of fragility fractures is huge and is set to rise due to an increasing skew towards an older population [1](#_ENREF_1), [2](#_ENREF_2)**[Au: It might be nice to specify why the burden of fragility fractures is set to rise. Please also reference this statement.]**. Importantly, the ability to predict those at risk has developed enormously over the last 20 years through the use of fracture prediction tools and an increasing understanding of scanning modalities, such as dual-energy X-ray absorptiometry (DXA). Despite this, a treatment gap exists between those at risk of fracture and those receiving treatment to prevent fragility fractures.**[Au:OK? I feel like it is important for the introduction to make this important point.]**

**[Au: Our journal style is that the last paragraph of the introduction always begins ‘In this Review’… and then sets out what the Review will cover.]**In this Review, we expand on the current epidemiology of fragility fractures, the up-to-date**[Au:OK? To avoid use of current twice in 1 sentence.]** definition of osteoporosis and we cover the widening gap in treatment for those at risk. We also highlight the development of fracture prediction tools and the benefits they have brought in identifying those at risk, with particular focus on the recent SCreening Of Older women for the Prevention of fractures (SCOOP) trial. We discuss the role of DXA in enhancing the identification of individuals at risk of fracture and examine more recent imaging modalities and analyses.

**[H1] The epidemiology of fractures [Au: Level 1 headings may be up to 39 characters long including white spaces.]**

Fractures are a major concern for the health of individuals and the population at large, with common fragility fracture sites**[Au: common fragility fracture sites, or do you refer to all fractures in this first sentence?]** being found in the hip, spine and wrist. In 2010, in Europe there were 22 million women and 5.5 million men with osteoporosis, accounting for 2% of the overall burden of non-communicable diseases [3](#_ENREF_3)**[Au: Please reference this statement.]**. This population experienced an estimated 3.5 million fragility fractures with 610,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1.8 million ‘other fractures’ (comprising fractures of the pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum and other femoral fractures)[3](#_ENREF_3). In the United States (US), one in two women experience osteoporosis-related fractures post-menopause[4](#_ENREF_4). In the United Kingdom (UK), there are an estimated 200,000 osteoporosis-related fractures per year [5](#_ENREF_5) **[Au: Please include the RCP guidelines as an entry in the reference list and cite a number here.]**, which severely effect quality of life, with 50% of patients with hip fracture losing the ability to live independently [6](#_ENREF_6). In the US, fragility fractures are responsible for over 432,000 admissions to hospital and 180,000 admissions to nursing homes each year [7](#_ENREF_7).

*[H2] Incidence, mortality and economic cost.* **[Au: Subheadings should be used to break up the text and guide non-specialist readers through the narrative. Level 2 headings can be up to 70 characters long including white spaces. New subheading, OK?]**

The incidences of age-specific vertebral, forearm and hip fractures are increasing due to the elderly population being the fastest growing age demographic **[Au: It might be nice to add a few words to explain why this is so.][Au: As Figure 1 has been updated to show** **secular changes in hip fracture worldwide, I’ve removed the reference to figure 1 from this particular sentence. In this main section (epidemiology of fractures), please can you add a sentence referring to this new figure, to put it into context?]** [3](#_ENREF_3), [8](#_ENREF_8), [9](#_ENREF_9). Although the incidence of fragility fractures**[Au:OK?]** continues to rise in transitioning populations, notably, the rate of hip fracture has stabilized in many resource-rich countries [10](#_ENREF_10) (seen in Figure 1) and wide global variation exists by geography[11](#_ENREF_11), ethnicity and socioeconomic status [12](#_ENREF_12).

The mortality associated with major osteoporotic fractures (those affecting the hip, forearm, humerus or clinical spinal fractures) **[Au: Please clarify what is meant by major fracture in this context (perhaps you could include it as a glossary term). In addition, does this statement refer to the general population, or perhaps the elderly and/or osteoporosis populations?]** is substantial with 20% mortality from hip fractures within the first year[13](#_ENREF_13), [14](#_ENREF_14). Moreover, hip fractures result in 20% of orthopaedic bed occupancy in the UK and the mean in-hospital stay is 27 days. **[Au: Paragraphs merged.]** The annual economic cost **[Au: Globally or in a specific region?]** of fragility fractures in Europe**[Au: Please clarify these fractures. Do you mean hip fractures specifically or all fragility fractures.]** was estimated at €37 billion [3](#_ENREF_3) with 66% of the cost attributable to incident fractures, 29% to prevalent fractures and 5% to associated pharmacological costs. In the US alone, the cost of fragility fractures has been previously estimated to be $17 billion (in 2005) with a subsequent increase**[Au: What is the cost in the US currently? A comparator is required here.]** to $25.3 billion by 2025[15](#_ENREF_15). A shift in the demographic landscape of fractures has occurred, which is associated with the increasingly elderly skew of the population[16](#_ENREF_16), therefore the above costs might increase further**[Au: Edits OK? To improve the flow and break up a long sentence.]**. As such, more recent health economic analyses are required to elucidate the modern day financial impact of fragility fractures.

*[H2] Medical interventions for osteoporosis.* **[Au: New subheading, OK?]**

The last 20 years have seen marked developments in medical interventions for osteoporosis including calcium and vitamin D supplementation, hormonal replacement therapy**[Au: in post-menopausal women?]** and bisphosphonates[3](#_ENREF_3), [17](#_ENREF_17). These pharmaceutical therapies reduce the incidence of osteoporotic fractures [18-22](#_ENREF_18), for example, bisphosphonates decrease all fractures by 35%, non-vertebral fractures by ~25% and vertebral fractures by 50%**[Au:OK? For consistency, I’ve used percentage values throughout the sentence.]**[20](#_ENREF_20), [23](#_ENREF_23). In addition, denosumab **[G] [Au: I have highlighted suggestions for glossary terms throughout your manuscript. Please provide succinct, one-sentence definitions for these specialist terms.]** has been shown to reduce fracture rates after 10 yearsof treatment**[Au:OK? Or do you mean after 10 years of treatment? Please clarify.]** [24](#_ENREF_24). Notably, in this trial,**[Au:OK? Are you still referring to reference 21 here?]** vertebral fracture yearly incidence in the denosumab treatment group (females aged 60-90 years) **[Au:OK? The patient population here required clarification.]** remained at a similar rate during the trial extension (to 10 years) to that seen in the original trial (3 years) **[Au: Please clarify the length of the original trial.]**; vertebral fractures at 0.9–1.9% and non-vertebral fractures at 0.8–2.6%. This yearly incidence**[Au:OK? House style does not allow a hanging this.]** was lower than that observed in a virtual placebo group and both efficacy and safety surveillance is on-going. Since 2015**[Au:OK? For date context as the Review ages.]** , bone-forming agents such as teriparatide [25](#_ENREF_25), [26](#_ENREF_26) and abaloparatide [27](#_ENREF_27), [28](#_ENREF_28) have shown good efficacy in randomised controlled trials.

**[Au: I’ve moved this sentence down to the start of the next section.]**

*[H2] The osteoporosis treatment gap.****[Au:OK? For consistency with the first reference to the term.]***

**[Au: Green text moved down from above and edited here.]**A major concern in management of osteoporosis is that only a minority of patients receive treatment[3](#_ENREF_3), [29](#_ENREF_29) and this untreated population is referred to as ‘The Osteoporosis Treatment Gap’[30](#_ENREF_30). This term refers to the difference between the number of individuals who are at high risk of fracture and the proportion of these people who receive fracture preventative interventions. An unfortunate reality of this treatment gap**[Au:OK? Edit to remove passive language and break up a long sentence.]** is that of individuals who sustain a fragility fracture, less than 20% receive secondary preventative treatment [31](#_ENREF_31), [32](#_ENREF_32) with this proportion being even lower in older females and patients in long-term care. Fracture assessment tools, which utilise clinical variables to provide a measure of fracture risk, have therefore been developed and will be discussed later.

Globally, marked variation exists in the use of fracture assessment tools with 1000-fold variation in tool use**[Au:OK?]** worldwide, despite far lower variation in fracture rates[33](#_ENREF_33). This paucity of tool use could be attributable to a lack of coherent local guidelines or difficulty accessing the tools online or even in paper format [34](#_ENREF_34). **[Au: Paragraphs merged.]** Beyond the variation in assessment of fracture risk, some resource-rich countries, including UK and US, have shown a concerning downward trend in treatment of osteoporosis**[Au: Edits OK? Edited for style and flow.]** [35](#_ENREF_35), [36](#_ENREF_36). In the US, this observation might be due to changes in the provision of medical reimbursement. Moreover, in the UK and US**[Au:OK? To clarify both cases]** increasing concern exists regarding adverse events related to bisphosphonates, which have been hyped in the lay-media[37](#_ENREF_37). This latter concern is countered by a Danish study, which demonstrated that even in individuals who were ‘over-treated’ with 10 years of the bisphosphonate**[Au:OK?]** alendronate the fracture risk was lower than in age-matched controls[38](#_ENREF_38), [39](#_ENREF_39).

Progress in the effective identification of ‘high risk’ individuals has depended upon the definition of osteoporosis, the development of fracture risk prediction tools and an understanding of imaging modalities for assessing bone parameters, all of which are discussed below**[Au:OK?]**.

**[H1] Diagnosis of osteoporosis**

A step-change in the assessment of bone fragility occurred with the advent of non-invasive methods for determining BMD, the most prominent of which is DXA**[Au: This abbreviation is now defined at first use.]** [40](#_ENREF_40). Historically**[Au:OK? For clarity]**, the lumbar spine or proximal femur were sites that were considered, however, since 2013**[Au:OK? Date context was required here, please check for accuracy.]** the femoral neck has been recognised as the reference site for epidemiological studies[41](#_ENREF_41).

DXA provided a homogenized, widely-utilizable method for calculating BMD as a T-score that measures the number of standard deviations from the mean BMD for a 30 year old man or woman**[Au:OK? I feel like we should introduce the concept of T-scores for our non-specialist readers, as they are a key concept in the article. Please check my definition for accuracy.]**. As a result, in 1994 the WHO produced an operational definition of osteoporosis based on a BMD T-score of –2.5 or lower [42](#_ENREF_42). This score has since become the diagnostic criterion for osteoporosis **[Au: In every global region?]**. A 2006 study**[Au:OK?]** showed that there is a 1.5–2.5 fold increase in fracture risk per standard deviation decrease in BMD[21](#_ENREF_21). Thus, BMD is a good**[Au:OK?]** predictive measure of future fractures. By contrast, another measure with equal predictive power is blood pressure as a predictor of future stroke. Both measures have more predictive power than serum cholesterol levels have for cardiovascular disease risk [43](#_ENREF_43). **[Au: I edited this sentence as it could currently be intepreted as BMD being a predictor for future stroke. Edit OK? Please can you provide a reference for these statements?]**.

Although BMD is a good specific predictive measure,**[Au:OK? I felt the narrative here required a few lead in words, please feel free to edit.]** the sensitivity for BMD alone in predicting future fractures is <50%, and those in an osteopenic range (T-score between -1.0 and -2.5) are still at risk of fracture. The Rotterdam study[44](#_ENREF_44) demonstrated that 44% of women with non-vertebral fractures over a follow-up of 6.8 years had a BMD T-score between 0 and –2.5**[Au:OK? Less than –2.5 is slightly confusing.]** and 12% had a completely normal BMD. Another study from the US showed that only 46% of women who sustained a hip fracture during a 5 year follow-up period had a T-score of ≤-2.5 for BMD at baseline **[Au: Please clarify when the measurement of BMD was made; at the start of the follow up period, during follow up or after hip fracture?]** [45](#_ENREF_45). **[Au: It might be nice to include a sentence in this paragraph that mentions osteopenia.]**

For the above reasons, 2019 European clinical guidelines**[Au:OK?]** have repeated the recommendation of using fracture risk factors (such as fall risk, and age[46](#_ENREF_46))**[Au:OK? Moved up these examples and the reference from below for flow.]** for identifying those at risk of fracture, as well as a thoracic kyphosis **[G]** and loss of height of >4cm (to identify subclinical vertebral fractures) [47](#_ENREF_47).**[Au: Paragraphs merged.]** The low sensitivity of BMD is of high clinical importance**[Au: Just to let you know, our journal style is to only use significance in the context of statistical significance.]** and emphasizes that BMD does not take non-skeletal determinants of fracture risk into account. As such, assessment modalities and particularly DXA have a crucial role in identifying ‘at risk’ individuals **[Au: Edits OK? To remove passive language and break up a long sentence.]**.

**[H1] Dual energy X-ray Absorptiometry**

Absorptiometry generally relies upon an energy source (for example, photon or X-ray) passing through a test material and a detector that is used to measure the degree of attenuation. This measurement can be compared to a standard, control material to calculate the density of the test material. Depending on the properties of a tissue, it will attenuate radiation differently, which allows quantification and separation of different tissues (for example, fat, muscle, bone) from one another.**[Au: Paragraphs merged]** DXA was first described by Mazess in 1981 [48](#_ENREF_48). This method uses two different energy sources (at ~40 KeV and >70 KeV) to allow discrimination between soft tissues and bone and provides increased resolution, precision **[Au: this figure is slightly unclear, please can you add some extra words to put it into context?]** [49](#_ENREF_49) and a shorter scan time than previous modalities.

DXA has since become the gold-standard measure for BMD due to the scientific demonstration of a strong correlation with biomechanical bone strength via finite element analysis [50](#_ENREF_50), a correlation with the clinical outcome of fracture risk [51](#_ENREF_51) and the relatively low radiation burden [52](#_ENREF_52). Moreover, DXA is also a viable measure for muscle mass in the assessment of sarcopenia[53](#_ENREF_53). Notably, DXA measurements alone may be more advantageous than using clinical risk factors (and the related prediction tools) alone, when identifying individuals with rare conditions that increase the risk of fracture. However, DXA can be used in conjunction with clinical risk tools (for example, Fracture risk assessment tool (FRAX) **Au: Abbreviation for FRAX now defined at first use, OK?]** as described later) in order to more accurately identify those at risk of future fracture.

*[H2] Quantitative measures derived from 2D densitometry.* **[Au: New subheading to break up the text, OK? ]**

DXA is a form of 2D densitometry**[Au:OK? Something to this effect is required for the narrative flow.]** and the quantitative measurements that can be derived from this method include bone area (cm2), bone mineral content (BMC) (grams) and areal BMD (g/cm2)**[Au: I suggest omitting this figure as there are currently too many display items associated with the manuscript and the elements of the figure are well enough described in the main text.]**. Areal BMD is calculated using pixel by pixel attenuation values of a test material (in this case bone) against a control phantom[54](#_ENREF_54). Bone area is calculated by summing the pixels that lie within the bone edges and bone mineral content (in grams) is calculated by multiplying areal BMD (g/cm2) and bone area (cm2). In 2001,**[Au: I’ve edited these names out as per our journal style.]** a model was proposed to enhance the comprehension and interpretation of bone densitometry measures in children and adolescents [55](#_ENREF_55), although this model**[Au:OK? Or did you mean bone densitometry measures here? Please clarify]** can also be employed in the understanding of adult bone physiology. The model focuses on three key areas: material BMD, compartmental BMD and total BMD.

Material BMD refers to the mineralization of a small volume of organic bone matrix. A small volume is necessary to exclude marrow, lacunae, canaliculi and osteonal canals from the sample. This measurement can be performed invasively via bone biopsy, or, since 2000**[Au: Please specify the year this technique was developed as ‘more recently’ loses relevance as the Review ages.]** (for cortical bone), via a virtual bone biopsy afforded by high resolution peripheral quantitative computed tomography (HRpQCT)[56](#_ENREF_56)**[Au: Please reference this statement.]**, which will be described further below. **[Au: Paragraphs merged]** Compartmental BMD refers to the amount of mineral in the cortical and trabecular compartments and can be assessed by QCT methods (central, peripheral and HRpQCT). DXA does not provide measures of compartment BMD as it is a 2D method. Instead, DXA provides an integrated measure of total BMD, which refers to the entire density of the material within the periosteal envelope **[G]**.

A limitation of DXA is the aforementioned 2D image that it provides, which limits the ability to measure density (mass per volume), as the depth of the bone cannot be accounted for. This limitation creates a size-dependence to measurements, which is problematic in children. Several methods exist to account for these inaccuracies in the use of DXA in children. The methods include calculation of a size-corrected total BMD from the DXA image, bone mineral apparent density (BMAD) **[G]** [57](#_ENREF_57), [58](#_ENREF_58) or regression methods to take into account the size of the child[59](#_ENREF_59), [60](#_ENREF_60).

Over the past decade, developments in DXA scanning include: vertebral fracture assessment using lateral views of the thoracolumbar spine [61](#_ENREF_61); hip structural analysis, which utilizes hip cross-sections to ascertain bone strength; and trabecular bone scoring (TBS)**[Au: Abbreviation now defined at first use.]**, which provides a measure of bone ‘quality’ (rather than the ‘quantity’ supplied by BMD) and is a surrogate of bone microarchitecture.

*[H2] Trabecular bone score*

TBS**[Au: Abbreviation now defined at first use.]** is an analytical tool that is used on data acquired using DXA**[Au:OK?]** to provide a surrogate measure of bone microarchitecture, providing information on bone structure above and beyond areal BMD[62](#_ENREF_62). The tool uses a sequence of experimental variograms **[G]** to quantify variation in grey-level texture between pixels [63](#_ENREF_63) and generate a value that**[Au:OK?]** is strongly related to experimental trabecular separation, trabecular number and connective density [64](#_ENREF_64), [65](#_ENREF_65). The region of interest is usually an anterior-posterior view of the lumbar spine on DXA; a higher TBS is consistent with fracture-resistant bone and a lower score with weaker bone[66](#_ENREF_66). **[Au: Paragraphs merged.]** Seemingly, there is an age-dependent variation in TBS, with a relative plateau in mid-life (aged 30–45) and a gradual reduction with age[67](#_ENREF_67).

A point of interest is whether TBS provides any information for the effective prediction of fractures independently of clinical risk factors**[Au: FRAX hasn’t been discussed yet, and so the non-specialist reader might be confused by FRAX clinical risk factors here, so I’ve removed it.]** and areal BMD**[Au:OK? If not, please define ‘aBMD’.]**. A study in a cohort from Manitoba attempted to address this question in women [68](#_ENREF_68) and men[69](#_ENREF_69) and found that, in women, TBS predicted incident fractures (HR: 1.36, 95% CI 1.30–1.42, *p*<0.001). After adjustment for clinical risk factors and femoral neck areal BMD**[Au:OK?]**, the associations were attenuated, although a hazard ratio of 1.18 (95% CI 1.12–1.23) remained for a major osteoporotic fracture[68](#_ENREF_68)**[Au: Ref 63 OK here?]**. In males, the area under the curve for the prediction of incident major osteoporotic, hip and clinical vertebral fractures was better than that expected by chance alone[69](#_ENREF_69)**[Au: Ref 64 OK here?]**.

 **[Au: Please reference this statement.]**. In 2016,**[Au:OK? Deleted the original text as I’m not sure to which study you refer.]**a meta-analysis of 14 cohorts was performed to assess the triangular relationship between clinical risk factors, TBS and areal BMD with regard to fracture prediction. This meta-analysis found that TBS was partially independently predictive of future major osteoporotic and hip fractures and concluded that the score may have some utility in clinical practice[70](#_ENREF_70). Through this analysis, a low risk of fracture was defined as a lumbar TBS score >1.31 **[Au: Lumber spine TBS? Please clarify the site of TBS that was used for these definitions.]** and a high risk of fracture with a score of <1.23.

Although TBS has been demonstrated to respond to fracture prevention therapy, including bisphosphonates and raloxifene, the percentage change is generally less than that observed in areal BMD [71](#_ENREF_71), [72](#_ENREF_72). **[Au: Paragraphs merged.]** An advantage of TBS is that the tool can be applied to DXA, radiographs, CT and QCT and at any skeletal site, although DXA of the lumber spine is the most common modality**[Au: Edits OK? Edited for style and flow.]**. A potential disadvantage of areal BMD is the artefact caused by degenerative disease (particularly in the spine), which leads to falsely raised BMD levels. However, due to the methodology, TBS is not affected by degeneration or osteophytes[73](#_ENREF_73). In addition, TBS is available as a modifier to the FRAX risk assessment tool online. Potential clinical and technical issues with the accuracy of TBS exist, including artefact generated from image resolution, noise and soft tissues**[Au: The punctuation here was a little odd. OK to put a comma before noise? As image resolution, noise and soft tissues are all indendent things that might cause artefact? Or did you mean something else? Please bear in mind that we don’t use the oxford comma at Nature Reviews.]**, including adipose tissues [74](#_ENREF_74). As such, the most accurate measures of TBS will be obtained from individuals with a BMI between 15–37 kg/m2 **[Au:OK? Edited to remove passive language, improve clarity and break up a long sentence.]**.

In summary, TBS provides additional information regarding bone quality beyond the quantitative measures provided by 2D densitometry**[Au:OK?]**. Although DXA is the clinical leader in the image assessment of bone, other scanning modalities have been developed and are used in the research context.

**[H1] Research scanning modalities**

As previously attested, DXA is the current gold standard for predicting those at high risk of fragility fractures**[Au:OK? I felt the narrative required a few extra words here.]**, though this method does have some issues and limitations. These issues include the lack of estimates**[Au:OK?]** of compartmental and material BMD, the fact that BMD measurements are size dependent (as they are calculated using a 2D projection of a 3D structure with no adjustments for object depth) and that the measures of BMD are susceptible to changes in body composition[75](#_ENREF_75" \o "Ward K.A., 2007 #232) **[Au: Please add a reference for these statements.]**.

In order to counter these issues and to provide additional measures of bone structure, morphometry and biomechanics, other, non-DXA scanning techniques have developed and are employed, largely in the research setting. Indeed, elements of bone microarchitecture have been shown to be predictive of incident fracture independent of BMD[76](#_ENREF_76). These scanning modalities**[Au:OK? To clarify the hanging ‘these’]** include central quantitative QCT**[Au: CT doesn’t require definition in our journal.]**, peripheral QCT (pQCT) and HRpQCT**[Au: HRpQCT was defined at first use.]**.

*[H2] Central QCT.*

Central QCT**[Au: Does this modality also take 2D slices, like peripheral QCT? Please clarify.]** was first developed in the 1970s [77](#_ENREF_77) but came to wider usage in the 1980s [78](#_ENREF_78). Central QCT is a modality which uses multiple 2D slices and the‘central’ description of the modality refers to the fact the regions of interest are the lumbar spine (particularly the L1–L3 vertebrae), the proximal femur and peripheral sites, and central QCT also provides a measure of muscle mass[79](#_ENREF_79)**[Au:OK to move ref to the end of the sentence? If not, please add references for the other parts of the sentence.]**. The advantages of central QCT over DXA include the ascertainment of mean volumetric BMD (**[Au: I removed the abbreviation for accessibility]** measured in mg per cm3. This measurement is less sensitive to changes in bone size than areal BMD **[Au: I combined all the brackets into one large bracket, OK?]**), compartmental BMD, bone geometry and biomechanical measures of bone strength[79](#_ENREF_79)**[Au: Please reference this statement.]**. Compared to DXA, the main disadvantages of central QCT are the increased burden of ionizing radiation[80](#_ENREF_80) and potential issues exist with confounding by changes in bone marrow fat owing to the majority of scanners being single-energy devices[81](#_ENREF_81)

*[H2] Peripheral QCT.*

The next scanning modality in the QCT family is peripheral QCT, which became commercially available in the 1990s[82](#_ENREF_82), with the most common model being the XCT 2000 (Stratec, Pforzheim, Germany). This method takes 2D slices (1–2mm thick) of the radius and tibia, which (owing to the very low radiation burden) can be performed at multiple sites along the bone.**[Au: Paragraphs merged.]** Not only does this modality provide valuable data on volumetric BMD, compartmental BMD, bone geometry and bone strength but peripheral QCT also provides muscle measures including cross-sectional area and muscle density[83](#_ENREF_83" \o "Griffith, 2008 #231)**[Au: Please reference this statement.]**. Measurements of muscle provide the opportunity to calculate a bone to muscle ratio, which is relevant when considering some hypotheses for bone strength and loading (for example, the ‘mechanostat theory’[84](#_ENREF_84)).

*[H2] High-Resolution peripheral QCT.* ***[Au: Is this a 2D or a 3D scanning modality? Please clarify this somewhere in the paragraph.]***

The most recently developed QCT scanning modality is HRpQCT (XtremeCT, Scanco Medical, Bruttisellen, Switzerland) which allows multiple 2D slices (most commonly of the radius or tibia) to be recreated into a 3D ‘virtual bone biopsy’. The enhanced spatial resolution afforded by this modality is in excess of that provided by standard peripheral QCT, QCT or MRI**[Au: We can use this abbreviation without definition in our journal.]**[85](#_ENREF_85). HRpQCT imparts a low dose of radiation (<3 microSv) and owing to semi-automated contouring and segmentation of tissue**[Au: of tissue? Please clarify for non-specialists]** this method provides data**[Au:OK?]** on densitometry, morphometry and biomechanical measures (including stiffness and elastic modulus)**[Au:OK? Sentence restructured for clarity]** through finite element analysis)[86](#_ENREF_86), [87](#_ENREF_87).

*[H2] Non-DXA scanning in clinical practice.* ***[Au: Removed the question mark from the heading as per our journal style.]***

A recent prospective study by the Bone Microarchitecture Consortium**[Au: Abbreviation removed as it’s only used once in the article.]** found that HRpQCT measurements (particularly peripheral skeleton failure load, which is the prediction of the external force required to cause failure of the bone) **[Au: Please clarify peripheral skeleton failure load for non-experts.]**) were statistically significantly**[Au: statistically significant or substantial?]** associated with future risk of fracture over ~4.5 year follow-up after adjustment for BMD [76](#_ENREF_76). However, it should be emphasized that although the above ‘non-DXA’ scanning modalities provide valuable data to drive forward densitometric research, they are not currently used in clinical practice due to a lack of routine accessibility. Whilst quantitative ultrasonography was used extensively, particularly in the 1990’s, the practical limitations of this technology and inferior ability to predict individual fracture status (compared to DXA) led to diminishing use and application **[Au: The meaning of the highlighted text is currently unclear. Do you mean, use of DXA to predict individual fracture status led to diminishing use of ultrasonography?]**. Quantitative ultrasonography**[Au:OK?]** also lacks a coherent standardization across different models and instruments of algorithmic data resolution and resultant reported parameters[88](#_ENREF_88). This method does, however, have a potential utility in low-resource settings where DXA is unavailable. Interestingly, MRI has also been used to assess bone densitometry and has future potential **[Au:OK? If not, please clarify ‘above’.]** in terms of usage in the clinical or research settings[89](#_ENREF_89)**[Au: Please reference this statement.]**.

**[H1] Fracture prediction tools [Au: I moved the heading up, as this sentence makes a nice lead in for this main section, before the first subsection starts.]**

In clinical practice, imaging (particularly DXA) is used not in isolation but together with clinical risk factors for fractures[47](#_ENREF_47)**[Au: Please reference this statement.]**. These risk factors can each be assessed in isolation, but have also been incorporated into usable ‘tools’ for assessing fracture risk.

*[H2] FRAX.*

The WHO definition of osteoporosis was used to determine the threshold for treatment, but, although the definition held at a population level, many individuals sustain fractures with BMD T-scores that are closer to 0**[Au:OK?]**. This observation has led to the development of fracture risk prediction tools, including FRAX**[Au: Abbreviation now defined at first use, OK?]**, QFracture and Garvan.

The first clinical risk score**[Au: Was the first tool named? If it was, it might be nice to add the name in here.]** was developed as a proof of concept**[Au: colleague names removed as per our journal style.]** in 2006 [90](#_ENREF_90).This algorithm was produced from data on the General Practitioner Research Database**[Au: This abbreviation is only used twice so I edited it out, OK?]** and provided a measure of future fracture risk. However, there are two important limitations in the use of this tool that are both based around the absence of BMD from the algorithm (due to the primary care nature of the data collected). The first limitation is that it seemed counterintuitive to exclude BMD as an important parameter in the prediction of fracture. The second limitation is that the medical trials designed to prevent fragility fractures**[Au:OK?]** had been performed in individuals with low BMD and, thus, it seemed a non-sequitur to ask clinicians to base their decision to treat on an alternative yard-stick.

The next (and now most widely adopted) of the fracture prediction tools was FRAX, which was published in 2008 [91](#_ENREF_91). The FRAX tool was developed via systematic meta-analyses of primary data from 9 global, geographically-spread cohort studies and then validated on data from a further 11 cohort studies. **[Au: Paragraphs merged.]**Key principals in the development of the FRAX tool were that any variable included in the algorithm (and thus the clinical tool) should be intuitively linked to fracture, readily clinically available, at least partly independent of BMD and be associated with a fracture risk that might be reversible through pharmacological treatment. [92](#_ENREF_92)

The clinical parameters incorporated into the FRAX tool include; age, sex, weight, height, previous fracture, parental hip fracture, current smoking status, glucocorticoid usage, the presence of rheumatoid arthritis, secondary causes of osteoporosis, alcohol consumption and BMD (though the latter can be excluded in resource settings which preclude the use of DXA). These clinical parameters**[Au:OK?]** are used to provide a separate 10-year probability of any osteoporotic fracture and hip fracture. **[Au: Paragraphs merged.]**The tool, which is available in over 30 languages, has been made freely available via the FRAX website and is used for an estimated 225,000 calculations per month[93](#_ENREF_93), although paper formats are available in under-resourced settings. **[Au: Paragraphs merged.]**Fracture incidence is known to differ across the globe [11](#_ENREF_11)and FRAX has the ability to adjust according to global region; in 2006, 80% of the global population were covered by the FRAX tool**[Au:OK?]**[93](#_ENREF_93).

The limitations of FRAX include the unquantified glucocorticoid exposure, which is recorded as a binary ‘yes/no’, and the omission of lumbar spine BMD, TBS, hip axis length and falls history. Methods to account for some of these considerations have now been documented, or implemented through adjunctive algorithms or national guidelines[93](#_ENREF_93). **[Au: Paragraphs merged.]**For example, diabetes mellitus increases the risk of fracture but is not directly included in the FRAX tool. Different approaches have been used to circumvent the limitations of the tool**[Au:OK?]** including incorporation of TBS, ticking the rheumatoid arthritis ‘button’ (on the FRAX website)**[Au: Please clarify ‘using the ‘rheumatoid arthritis button’. RA was already included as a parameter in the paragraph above]**, increasing the age input by 10 years and reducing femoral neck BMD**[Au:OK?]** T-score by 0.5 standard deviations (for example, a T-score of -1.75 became -2.25)**[Au: Please clarify this last point. Do you mean the threshold for osteoporosis was reduced by 0.5 SD to be -2.0 for femoral neck BMD?]** [94](#_ENREF_94).

A further example of FRAX tool refinement**[Au:OK?]** is that of ‘spine-hip discordance’, which uses the difference between lumbar spine and femoral neck BMD**[Au:OK?]** T-scores to improve fracture prediction by using the following rule: “increase or**[Au:OK?]** decrease the FRAX estimate for major osteoporotic fracture by one tenth for each rounded BMD T-score difference between lumbar spine and femoral neck” [95](#_ENREF_95).

*[H2] Q-fracture.*

The QFracture tool was published in 2009[96](#_ENREF_96). This tool was derived using Cox proportional hazards models on the data of 2 million individuals aged between 30 and 85 on the General Practitioner Research Database in the UK. The same dataset was then used to validate the tool. Consequently, QFracture is primarily applicable to the UK population and, although it is only calibrated on hip fracture, the tool does provide estimated**[Au:OK? Or predicted?]** incidences of hip, forearm, spinal and shoulder fracture. As in the 2006 tool, BMD is not included and QFracture is therefore subject to the same limitations. The number of risk factors was extended in 2012, on the basis of National Institute for Health and Clinical Excellence**[Au: Abbreviation only used once so I removed it.]** guidance on the risk assessment for osteoporosis, to include history of previous fracture, presence of epilepsy (or anticonvulsant use), ethnicity and the presence of type 1 diabetes mellitus.

The current list of clinical parameters included in the QFracture tool**[Au:OK?]** includes: age; sex; ethnicity; smoking status; alcohol use; type 1 or type 2 diabetes mellitus; parental history of hip fracture and/or**[Au:OK?]** osteoporosis; nursing or care home residence; history of prior osteoporotic (wrist, spine, hip, or shoulder) fracture; history of falls; dementia; cancer; obstructive airways disease (asthma or Chronic Obstructive Pulmonary Disease); cardiovascular disease; chronic liver disease; chronic kidney disease; Parkinson's disease; rheumatoid arthritis or systemic lupus erythematosus; gastrointestinal malabsorption; epilepsy (or use of anticonvulsants); use of antidepressants; use of corticosteroids; BMI**[Au: We can use BMI without definition in our journal]** (QFracture.org). The following additional factors are only used for women: oestrogen only hormone replacement therapy; endocrine problems (including thyrotoxicosis, primary or secondary hyperparathyroidism and Cushings syndrome) (QFracture.org).

*[H2] Garvan.*

The Garvan fracture prediction tool was developed based on ~2500 members of the Australian Dubbo Osteoporosis Epidemiology Study (DOES)[97](#_ENREF_97)**[Au: Please reference this statement]**. This tool does not include rheumatoid arthritis, secondary osteoporosis, steroid use, smoking, alcohol, parental hip fracture or secondary osteoprorosis in the parameters that are entered into the risk calculation. However, the Garvan tool does provide a novel angle through the inclusion of the number of fractures since the age of 50 and the number of falls in the previous year. The tool previously provided a risk of fracture at a large number of sites (including distal femur, pelvis, patella, proximal and distal tibia and fibula, patella, ribs and sternum, hands and feet) but has now focused down to a 5 and 10 year percentage risk of hip fracture and any osteoporotic and/or fragility fracture [97](#_ENREF_97)**[Au: Please reference this statement]**. The potential disadvantages of the Garvan risk score are that it is based on a single Australia cohort (which could limit its wider applicability) and it does not take the competing hazard of death into account.

*[H2] Prediction tools worldwide.*

FRAX has been more widely adopted globally than Q-Fracture or Garvan and, in 2016, had been incorporated into 120 guidelines worldwide and is widely incorporated into DXA software and primary care computer systems [98](#_ENREF_98)**[Au: Please add a reference to support this statement]**. When incorporated into these recommendations, FRAX is either used with a fixed FRAX intervention threshold (with or without BMD) or as a gateway to an assessment that includes age-dependent intervention thresholds[93](#_ENREF_93).

The use of fixed thresholds for intervention is usually incorporated with a measure of BMD and a history of prior fragility fracture and is very simple to use in a clinical setting. **[Au: Paragraphs merged.]**However, the simplicity of the use of fixed thresholds for intervention masks the issue demonstrated in figure 2, which depicts the FRAX percentage 10-year risk of major osteoporotic fracture against age for men and women with a history of prior fragility fracture and individuals with a BMD T-score of -2.5. Notably, the fixed threshold for BMD T-score results in a minimal proportion of women aged between 80 and 90 being treated and in under-treatment of the whole population**[Au: Edits beginning ‘and in under-treatment…’ OK? Was this what you meant here?]**[93](#_ENREF_93).

The above observation is clearly unsatisfactory and counterintuitive to good clinical practice. For this reason, in the UK, the National Osteoporosis Group Guidelines**[Au: Abbreviation removed as only used once in main text.]** employs a combination of age-dependent and fixed thresholds**[Au: Are these thresholds employed by NOGG based on BMD or a particular clinical score? Please clarify.]** to guide further investigation (via DXA) and intervention[99](#_ENREF_99), [100](#_ENREF_100). To expand on this, the intervention thresholds for the initiation of pharmacologic therapy are, for women with a history of prior fragility fracture (with no requirement for further assessment), age-dependent thresholds until the age of 70 years and fixed thresholds thereafter.

**[Au: New paragraph.]**The National Osteoporosis Foundation**[Au: abbreviation removed as only used once in the main text.]** guidelines in the United States suggest that pharmacological therapy should be initiated in those with a prior history of hip or vertebral fracture and in individuals with a T-score ≤ -2.5 [101](#_ENREF_101). Additionally, postmenopausal women and men ≥50 years with T-scores in an osteopenic range (that is, -2.5 to -1.0) and a US-adapted FRAX score of ≥3% risk of hip fracture and ≥20% of major osteoporotic fracture should receive treatment. Here, the reference to a US-adapted FRAX indicates that NOF guidelines**[Au:OK? To clarify ‘it’]** have been calibrated according to US fracture and mortality rates. The American College of Rheumatology (ACR) [102](#_ENREF_102) and Scottish Intercollegiate Guidelines Network (SIGN) guidance use FRAX risk to direct BMD screening and intervention thresholds[103](#_ENREF_103). Notably, the SIGN guidelines use fracture clinical risk factors**[Au:OK?]** as an initial assessment, followed by BMD assessment;**[Au:OK?]** a BMD T-score of less than or equal to -2.5 is the gateway to treatment, which is an approach that could potentially widen the treatment gap [103](#_ENREF_103).

European guidance regarding thresholds for pharmacological intervention in postmenopausal women recommend the use of a FRAX-based approach to clinical decision-making**[Au: incorporating BMD or without BMD?]** and that women over the age of 65 years with a history of prior fragility fracture are considered for treatment without any further assessment[47](#_ENREF_47). Younger postmenopausal women should undergo an additional assessment of BMD. This recent guideline also recommended that age-dependent thresholds are clinically appropriate and cost-effective in their identification of those requiring treatment**[Au:OK? To add citation to ref 42 here?]** [47](#_ENREF_47).

After FRAX was devised and validated, it was important to examine whether the test had a discernable effect on fracture rates within the context of a RCTs, which are described below.

**[H1] The SCOOP trial**

The WHO recommendations for screening for fragility fractures**[Au:OK?]** include the assessment of fracture risk into high, medium or low risk groups; high-risk individuals are considered for treatment, low-risk individuals are not recommended for treatment and medium-risk individuals are further assessed with a measurement of BMD [104](#_ENREF_104).

The SCreening Of Older women for the Prevention of fractures (SCOOP) trial was designed as a pragmatic, unblinded, randomised controlled trial of women aged 70–85 years. It was based in seven centers in the UK including Birmingham, Bristol, Manchester, Norwich, Sheffield, Southampton and York, from which 12,483 participants were recruited.

*[H2] Aims and rationale.* ***[Au: New subheading OK? This main section is quite long, so I have suggested a few subheadings to break up the text and guide non-expert readers through the narrative.]***

The aim of the study was to examine the effectiveness and cost effectiveness of a community-based screening programme to decrease fragility fractures in older women and thereby address the aforementioned ‘Treatment Gap’ in this population. The structure of the study is depicted in figure 3 **[Au: Figure number updated.]**.

Previous trials of population screening for osteoporosis have been undertaken, including one based in a population of post-menopausal women, which was started in the 1990s and reported in 2010[105](#_ENREF_105), and reported that screening marginally increased the usage of osteoporosis treatments and reduced fracture incidence.**[Au: It might be nice to add a few words of the conclusions of this trial.]** **[Au: Paragraphs merged]** In addition, a more recent RCT of primary-care based screening was reported in 2012[106](#_ENREF_106), which found that screening for osteoporosis increased prescription of osteoporosis medication at 6 months (OR 2.24, 95% CI 1.16 to 4.33).**[Au: Again, it might be nice to add a few word on the conclusions of this trial here.]** The primary difference between these studies and SCOOP is that, with SCOOP the that the primary outcome was fracture incidence and not treatment uptake**[Au: the primary outcome of SCOOP was treatment uptake or of the older trials was treatment uptake? Please clarify.]**.

*[H2] Results.*

 **[Au: I’ve moved down this detailed text on methods and study design into the figure legend, OK?]** The study population comprised women aged between 70 and 85, who were assigned to either a screening arm (those found to have moderate or high risk of fracture by FRAX underwent further assssment of BMD) or a control arm (receiving usual care, provided in a primary care setting**[Au: please specify what this usual care is]**) (Figure 3)**[Au: I’ve condensed the cut text down into one sentence and moved the detail into the figure 3 legend. This will improve the narrative flow. Please check for accuracy.]**. The key effectiveness findings of the SCOOP study were published in 2018[107](#_ENREF_107), although there were no significant differences in the primary outcome measure of all osteoporosis-related fractures between the screening arm and control arm (*p*=0.178; HR 0.94; CI, 0.85–1.03) or the rate of all clinical fractures (*p*=0.83; HR 0.94; CI 0.86–1.03), as shown in table 1. However, in a pre-specified analysis, the rate of hip fracture was statistically significantly lower in the screening arm (*p*=0.002; HR 0.72; CI, 0.59–0.89).

In terms of numbers needed to treat, the absolute size in hip fracture rate reduction was 0.9%, which means that 111 women aged 70–85 would need to be screened in order to avert a single hip fracture. Notably, the reduced risks that were observed in SCOOP were strongly affected by the efficacy of the currently available treatments and as the efficacy of treatments rise, the risk of fracture will probably reduce. **[Au: Paragraphs merged.]** Osteoporosis medication use was higher in the screening group compared to controls at the end of year one (15% vs 4%), with medication use being particularly high in the high risk group at the 6 month time point (78%). **[Au: Paragraphs merged.]** There was no difference in mortality, anxiety or quality of life outcomes between the two groups.

Of the 6,233 participants randomised to the screening arm, 3,049 (49%) reached criteria for subsequent DXA assessment of BMD and 898 (14%) received treatment with osteoporosis medication by 6 months. At 1 year, 953 (15%) of individuals in the screening arm had received at least one treatment with**[Au:OK?]** osteoporosis medication and this proportion remained relatively stable, between 13% to 15% over the course of the 4 years of follow-up. In the control arm, 264 (4%) received an osteoporosis medication by 1 year but this proportion steadily rose to 633 (10%) at 4 years. **[Au: Paragraphs merged]** In terms of the fractures, across both arms**[Au:OK?]** there were 1,975 fragility fractures which affected 1,657 participants (13% of those randomised). The most common sites were distal forearm and hip. **[Au: Paragraphs merged.]** The qualitative work performed as part of the SCOOP study demonstrated that the screening was acceptable to women[108](#_ENREF_108).

*[H2] Trial limitations.*

The limitations of the SCOOP study include that of the eligible population, only a third of individuals participated and there appeared to be selection bias towards healthy individuals**[Au:OK?]**, with mortality lower than expected (9% observed versus 19% expected) and higher educational and socioeconomic status. Relatively few participants were at high risk of fractures (14% observed versus 20–40% expected) however, the rates of fracture were higher than predicted. It is also possible that general practitioners may have been more likely to treat individuals in the control arm due to the ‘contamination’ of their involvement in an osteoporosis-related study.

Whether this model of population screening is eligible for national roll-out depends not only on efficacy but also on cost-effectiveness and the feasibility within the constraints of the public purse.

**[H1] Cost-effectiveness analysis**

Since the advent of the SCOOP study there have been two helpful systematic reviews of cost effectiveness in the field of fragility fractures. The first found that health economic models have recently evolved in terms of their complexity and emphasis[109](#_ENREF_109), whereas the second purports to the cost-effectiveness of drug therapy for osteoporosis in post-menopausal women[110](#_ENREF_110). The latter review found that osteoporosis medications were cost-effective in women aged 60 years and over, particularly if additional risk factors for fracture were present[110](#_ENREF_110)**[Au:OK?]**.

Given that the SCOOP study **[Au:OK?]** was performed in the UK, the subsequent health economic analyses **[Au: do you mean health economic analyses in references 99 and 100? Or the cost effectiveness analysis performed in the SCOOP study?]** were performed according to this geography. A 3 level EQ-SD (an instrument used to assess health-related quality of life) **[Au: please define this term.]** assessment provides a measure of quality-adjusted life-years (QALY) [111](#_ENREF_111). The costs of DXA scans, clinical review, primary care consultations and written notifications in SCOOP**[Au: Are you still referring to the SCOOP study here?]** were calculated locally through dialogue with the general practice surgeries involved. In-patient, out-patient and emergency department datasets were run though HRG4+ (Healthcare Resource Group 4+) reference costs grouper [112](#_ENREF_112" \o ", 2019 #229)**[Au: Please clarify what this means for non-specialist readers.]** **[Au: Please reference these statements.]**.

The key heath economic finding from the SCOOP study was that the screening model trialed was cost-effective. There was an increase of 0.0237 QALYs for participants in the active arm of the trial with an £2,772 incremental cost per QALY in the screening arm versus the control arm[113](#_ENREF_113). The screening intervention also reduced fractures with a cost per osteoporosis-related fracture prevented was £4,478 and a cost per hip fracture prevented via the screening programme was £7,694. **[Au: Does this mean that the mean cost of a hip fracture to the NHS is £7,694? If not and I’ve misinterpreted the numbers, please can you specify the mean cost of a major osteoporotic fracture to the NHS.]** The cost-effectiveness acceptability curves suggested that there was a 93% probability of the screening intervention being cost-effective, at a value of >£20,000 per QALY, concluding that the screening programme was a highly cost-effective strategy**[Au: Please reference this statement.]** [113](#_ENREF_113" \o "Turner, 2018 #2)(FIG.4).

A post-hoc analysis focusing on those who are at high risk of fracture was published in 2018,[114](#_ENREF_114) **[Au: Please reference this statement.]** which aimed to examine possible interactions between screening efficacy and baseline FRAX 10 year risk of fracture and fracture outcomes. **[Au: Paragraphs merged.]** Interactions were observed between history of prior fracture, parental fracture history, smoking and the efficacy of screening[114](#_ENREF_114). Importantly, in individuals at highest risk of fracture the estimated reduction in hip fracture risk was greater than 50% (FIG.5, FIG.6)[114](#_ENREF_114" \o "McCloskey, 2018 #1)**[Au: Please reference this statement.]**. **[Au: Paragraphs merged.]** Despite the limitation that not all participants included in the SCOOP trial had BMD measurements at baseline or during follow-up **[Au: do you mean at baseline, or if identified as high risk during study follow up, please clarify]**, the conclusion of the post-hoc analysis was that those women who are at high risk of hip fracture based on FRAX probability are responsive to appropriate osteoporosis management[114](#_ENREF_114)**[Au: Please reference this statement.]**. The greater reduction in hip fracture risk in those who had higher baseline risk strongly suggests that treatment rather than other factors explained the observed effect.

The effect of screening was greatest in those with the risk factors of prior history of fracture and parental history of fracture[114](#_ENREF_114)**[Au: Please reference this statement.]**. These two groups represent that most relevant clinical risk factors**[Au: Is this statement based on data from any other studies or just the SCOOP trial? If so, please cite them here.]**. These factors might have had some bearing on persistence and uptake of medications by study participants**[Au:OK?]**. The presence of these two factors might also have driven increased treatment rates in the screening arm.

In summary, if the SCOOP screening strategy is adopted in the UK**[Au:OK? Or do you mean globally?]** for 70–85 year old women (assuming the size of this population is similar to that estimated in 2016 of 3.7 million), it could prevent 8,000 hip fractures each year, would be cost-effective in doing so and result in considerably better treatment adherence at 5 years of follow-up.

**[H1] Conclusions**

The last 20 years has seen a concerted shift from the definition of osteoporosis based on BMD**[Au:OK?]**, to the effective identification (and therefore treatment) of individuals at risk of fracture. Fracture prediction algorithms such as FRAX**[Au:OK? So the focus is not just on FRAX]** and imaging modalities such as DXA present usable and highly effective tools to identify individuals at risk. Moreover, developments in research scanning have enhanced our scientific understanding of bone microarchitecture. As recent trial evidence clearly shows **[Au: Please cite the relevant studies at the end of the sentence]** , primary prevention of osteoporotic fragility fractures is not only effective but also cost-effective[107](#_ENREF_107), [113](#_ENREF_113), [114](#_ENREF_114). Despite this, there is still a concerning majority of at risk individuals who are missed through a lack of assessment and there must therefore be a concerted effort to address this issue if we are to close the ever-widening treatment gap. In the future, novel methods of fragility assessment (Box 1 and Box 2) might go some way to address this need.**[Au:OK? I thought it might be nice to refer the reader back to the boxes containing the novel methods in the concluding statements. Please feel free to edit.]**

**References [Please ensure that references are cited sequentially in the following order: main text, boxes, figure legends and then tables. The numbered references should be listed at the end of the article in the format: 1. Author, A. B. & Author, B. C. Title of the article. Nat. Cell Biol. 6, 123–131 (2001). (with journal abbreviation italic, and volume bold). If there are six or more authors to a reference, only the first author should be listed followed by ‘et al.’ (italic). For more details on reference format please consult the Guidelines to Authors.**

**Please make sure that you use your reference management software to update the order of the reference list after making revisions, as some references may have been moved around during editing.]**

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**[Au: Please check reference 4, as it seems incomplete.]**

**[Au: Please check reference 24, as it seems incomplete.]**

**[Au: Please check reference 50, as it seems incomplete.]**

**[Au: Please check reference 94, as it looks a little odd. There is no title.]**

**[Au: For references that are particularly worth reading (5-10% of the total), please provide a single bold sentence that indicates the significance of the work.]**

 **Ref 24:** Denosumab is safe and effective for use after 10 years follow-up

**Ref 34:** The use of the FRAX prediction tool across the globe

**Ref 47:** The latest guideline for the management of osteoporosis in post-menopausal females

**Ref 64:** Trabecular bone score is a predictor of fracture independent of BMD

**Ref 70:** Meta-analysis which details the potential adjustments of FRAX for TBS

**Ref 93:** A systematic review of global guidelines and the intervention thresholds utilised

**Ref 97:** Description of the Garvan tool

**Ref 103:** A comparison of the available fracture prediction tools

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Competing interests

The authors declare no competing interests.

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**DISPLAY ITEMS: 3 boxes; 5 figures; 1 table. [Au: I’ve suggested including an additional box (see below)]**

**Box 1: Microindentation [Au: This box is currently 488 words. I’ve made edits to streamline it and bring it closer to our 300 word text box limit.]**

Stiffness is the ability of a structure to resist deformation. When subjected to a particular load, a stiffer bone will deform less than a softer, more compliant bone. The increasing porosity of bone with age leads to reduced stiffness and, thus, increased risk of fracture[115](#_ENREF_115)**[Au: Please reference this statement.]**. Measurements of BMD do not capture bone porosity and so other methods have developed to assess this element of fracture risk.

Microindentation is novel methodology that involves inserting a probe through the skin and down onto the bone surface at a particular anatomical site (for example, the anterior midtibia) to measure the stiffness and toughness **[Au: The paragraph above refers to stiffness. Is there a difference between stiffness and hardness, as biomedical properties?]** of a bone. Bone Material Strength Index (BMSi) is measured by comparing the indentation distance of the bone to a reference standard calibration material. On the surface of the bone, the probe induces microfractures; the weaker the bone is, the greater the distance that the probe extends into the bone and the lower the BMSi[116](#_ENREF_116)**[Au: Please add a reference for these statements.]**.

Microindentation has been shown to distinguish between degrees of fracture risk [116-118](#_ENREF_116), between individuals with osteoporosis and controls [119](#_ENREF_119), and individuals at risk of atypical femoral fracture [120](#_ENREF_120). However, the technique has also been associated with areal BMD in isolation**[Au: Do you mean that Microindentation only provides a surrogate measure of areal BMD and does not directly assess fracture risk? Please clarify.]** without associations with fracture risk [121](#_ENREF_121).

This method has limitations, as it tests the tibia, which is an uncommon site of fragility fracture. Moreover, the invasive nature of microindentation means that it might be less likely **[Au: Edits OK? For clarity.]** to be tolerated in clinical practice than imaging modalities. Regarding the latter, a 2018**[Au:OK?]** study has sought to address this in a large cohort of 345 Australian males, in whom the procedure was well tolerated, although 56 individuals were contraindicated by the presence of excessive soft tissues in the midtibial zone [122](#_ENREF_122). Overall, it is estimated that approximately 1,500 individuals have had the procedure globally**[Au:OK? Is this what you meant?]**, with two reported episodes of adverse events; one was a mild skin infection and one was a reaction to local anaesthetic [122](#_ENREF_122).

 **[Au: Paragraphs are duplicated. I deleted them to avoid repetition.]** In summary, microindentation is a technique that shows promise and seeks to identify individuals who are at risk of fracture due to bone weakness, who are potentially missed by measurement of BMD alone [123](#_ENREF_123).

**Box 2: Biochemical markers of bone turnover**

Bone turnover is characterised by bone formation and bone resorption. Biochemical Bone Turnover Markers (BTMs) have been discovered and developed to capture measurements of these two activities. International expert groups in the field of clinical chemistry and osteoporosis have come to a consensus that N-terminal propeptide of type I procollagen (PINP)**[Au:OK?]** and C-terminal telopeptide of type I collagen (CTX-I)**[Au:OK?]** **[Au: Plasma levels of these markers? ]** should be the markers for bone formation and bone resorption respectively [124](#_ENREF_124).

CTX-I is a product of the breakdown of type I collagen and has a strong circadian rhythm, which necessitates early morning blood collection. PINP is formed from the post-translational cleavage of type 1 procollagen and has no circadian rhythm, however, owing to obvious practicalities, it is usually collected contemporaneously with CTX-I**[Au: Please reference these statements.]**.

Pre-analytical variability of BTMs is an important consideration, with circadian variation, seasonal variation, physical activity and food intake being examples of modifiable determinants [124](#_ENREF_124)**[Au: Please reference this statement.]** . The latter is due to the intestinal induction of glucagon-like peptide 2 which stimulates a post-prandial decrease in CTX-I. Less modifiable determinants include age, sex, hormones (including menopausal changes and endocrine disorders) and the effect of certain medications (for example, corticosteroids, anti-epileptics and heparin)[124](#_ENREF_124)**[Au: Please reference this statement.]**.

BTMs appear to be predictive of fracture (independently of age, BMD and prior fracture) in particular demographic groups, including postmenopausal women and elderly women[125-127](#_ENREF_125). Moreover, they are associated largely with major osteoporotic fractures and can be predictive over a relatively short follow-up period (<5 years) (as opposed to 10 year prediction probabilities by FRAX)**[Au:OK? A comparator was required.]**. The association with future fractures is probably due to the link between a high turnover state and lower BMD and poor quality bone microarchitecture [128](#_ENREF_128).

BTMs can be employed to monitor the response to fracture protective therapies, and are often used in the context of bone-forming agents such as teriparatide [27](#_ENREF_27)**[Au: Please reference this statement.]** . 2019 guidelines have also noted their potential utility in predicting fractures when BMD is unavailable [47](#_ENREF_47).

In conclusion, BTMs appear to be a useful adjunct to traditional methods of identifying those at risk of fracture (in particular post-menopausal women) and may have an additional role in monitoring response to treatments.

Box 3: Osteoporosis as a case study of the Wilson-Jungner criteria **[Au: One of the referees made the following comment: Given the title ‘Diagnosis and imaging in osteoporosis’ the lengthy discussion of the SCOOP study seems out of place. If the title is changed to cover screening for osteoporosis, more studies should be mentioned and the ten WHO-criteria for screening programs should be discussed. You mentioned in the referee rebuttal that you were in discussions with the editor about adding in a text box to address this comment. I have removed one of the figures to allow you space for this box. Text boxes can be up to 300 words in length and may be accompanied by a small figure or table.]**

In order to contextualize the developments in osteoporosis and fragility fracture, it is interesting to review the condition as a case study, in light of the Wilson-Jungner Criteria for the validity of screening[129](#_ENREF_129).

These criteria state that for a screening programme to be valid, the condition to be screened should be an ‘important health problem’, and with the increasing prevalence, associated mortality and substantial financial costs[3](#_ENREF_3), [13](#_ENREF_13), it can be concluded that osteoporosis qualifies.

The second criterion ‘natural history of the disease’ is increasingly well understood in the field of osteoporosis with mapping of BMD and fracture prevalence across the lifecourse.

‘Treatment at an early stage must be more beneficial than at a later stage’ and this is confirmed by the reduction in fracture risk afforded by anti-osteoporosis interventions, with the clear benefit being a reduction in the risk of fracture, which is a substantially morbid event.

The criteria of ‘a detectable early stage’ and ‘a suitable test for the early stage’ are important to consider in the case of osteoporosis and are accounted for by the pre-fracture measurement of fracture risk, using BMD and clinical fracture risk assessment tools. The ‘acceptability of the screening approach’ and ‘physical and psychological risk’ in osteoporosis screening are confirmed by the fact that performing a fracture risk assessment, and even DXA, is low risk, low radiation and low cost approach. Indeed, the ‘cost-benefit’ analysis required for a valid screening programme has been supported by the findings of the SCOOP study and assists with the calculation of ‘adequate health service provision’ both the in UK and across the globe.

The ‘intervals between testing’ are defined according to clinical guidelines.

As demonstrated above, osteoporosis, and the subsequent screening for the condition, are a valid approach, when measured against these rigorous criteria.

**Figure 1:** **Secular changes in hip fracture worldwide. [Au: Please provide a legend of 100–150 words that fully describes all elements of the figure in isolation from the main text. Our figures are often downloaded as powerpoint slides and so must contain enough information to interpret the figure away from the main body text. In addition. Please make sure that the main text has a sentence that refers to this new figure, as currently the main text refers to the old figure 1.]** This figure demonstrates the secular trends in hip fracture across the globe. Geographical regions are divided by dotted lines and countries are shown in differing bars with labels including the country name and the years between which the secular trend was measured. Annual percentage change is shown on the x-axis with a percentage rise being positive and a percentage decrease being negative. The general trend for European, Australasia and North American countries is an increase in hip fracture rates in the latter quarter of the 20th century with a plateau as they near the year 2000. In Asia, the general trend is towards a continued increase in rates approaching the year 2000 threshold. Figure reproduced with permission from reference[10](#_ENREF_10). **[Au: Please make sure that you return us a complete third party rights form in good time, so that we will be able to start applying for all the relevant figure permissions.]**

 **[Au: I suggest omitting this figure for brevity, as there are too many display items associated with the manuscript and we can well enough describe the message of this figure in the main text.]** **Figure 2: The pitfalls of a fixed FRAX threshold for intervention.** **[Au: This legend requires more information so that the figure may be interpreted in isolation from the main text. Please check my edits for accuaracy.]** The graph plots 10 year probability of major osteoporotic fracture (MOF; calculated using FRAX) against age**[Au:OK?]**. The dotted line**[Au: should this read dotted line?]** depicts the treatment threshold**[Au:OK?]** based on history of prior fracture **[Au:OK?]** (left panel) and a BMD**[Au:OK?]** T-score of –2.5 (right panel)**[Au: Currently the dotted line doesn’t extend over to the right panel so please make sure that you mark up the figure with the appropriate place for the dotted line.]**. A substantially undertreated population is evident, as only individuals whose 10-year probability of MOF falls**[Au:OK?]** above the line receive treatment. Figure is reproduced with permission from Ref.[93](#_ENREF_93)

**[Au: In figure 3, the flowchart shows that FRAX questionnaire was part of the baseline information. Does this mean that FRAX information was already available for some participants before they were randomized to the screening arm or the control arm? This should be made clear in the main text.]**

**Figure 3 Participant flow for the SCOOP study.[Au: Title OK?]** . **[Au: Moved down green text from above to form this figure legend and then edited here to streamline. Please check my edits for accuaracy, OK? The figure legend shoud be no longer than 250 words. Please make sure the ‘usual care’ that the control arm receives is specified in the main text.]**

The inclusion criteria for the SCOOP trial were female sex, age (70–85) and ability to provide informed consent. The exclusion criteria were individuals on osteoporosis treatment, individuals with substantial comorbidity and other factors (for example, recent bereavement). After completing a FRAX questionnaire, participants underwent block randomisation stratified by age (70–74; 75–79; 80–85) and general practice. Owing to the pragmatic study nature, double-blinding was not feasible, however, research staff acquiring hospital fracture data were blinded to participant study arm. A total of 12,483 participants were randomised to either the control arm or the screening arm, constituting 59,401 person-years of observation. The control arm comprised individuals receiving ‘usual care’ (provided in primary care); individuals in the screening arm had their 10 year probability of fracture calculated using FRAX. Those at moderate to high-risk underwent DXA to calculate BMD. Treatment decisions were made in primary care based on the above findings. In SCOOP, the primary outcome measure was the proportion of individuals sustaining fragility fractures (that is, not excluding fractures of the skull, hand, foot and nose) in each group. Secondary outcomes included: the proportions of all fractures, hip fracture rate, cost-effectiveness, mortality and EQ-5D in each group, and a qualitative evaluation of participant acceptability. Effectiveness data analysis was performed using Cox’s proportional hazards models. Linear models were used for quality of life analyses and all relevant analyses were performed on an intention to treat basis. Economic analyses were obtained from a tax payer’s perspective according to the costs to the NHS. A qualitative exploration of acceptability and adherence was performed.

DXA, dual-energy X-ray absoptimetry; SCreening of Older wOmen for Prevention of fracture, SCOOP; EQ-5D, a healthcare quality assessment tool **[Au: Please define EQ-5D in the footnote.]**. Figure reproduced with permission from reference[130](#_ENREF_130).

**Figure 4: Cost-effectiveness acceptability curves from the SCOOP study.[Au: Title OK?]** The graph depicts cost-effectiveness acceptability curves for cost per quality adjusted life year (QALY)(blue line), per osteoporotic fracture prevented (OFP) (in orange), and per hip fracture prevented (HFP) (green line) from the Screening of older women for prevention of fracture (SCOOP) study. The figure is reproduced with permission from Ref. [113](#_ENREF_113).

 **[Au: I suggest removing this figure as it is difficult to interpret in this context and it will allow you space for an additional box (see above).]**

**Figure 5: The effect of screening on hip fracture rates in the SCOOP study[Au: Title OK?].** The graph shows the effect**[Au:OK?]** of screening on hip fracture risk**[Au:OK? Or hip fracture rate?]** compared with the control arm, expressed as a hazard ratio, across a range of FRAX 10-year hip fracture probabilities calculated at baseline without BMD. An interaction is observed between effectiveness of screening **[Au: effectiveness of screening? ]** and baseline probability of fracture(p=0.021). The range of baseline probabilities are indicated by symbols in the total study population (darker**[Au:OK?]** symbols) and in the high-risk group who were identified by screening (lighter**[Au:OK?]** symbols) [114](#_ENREF_114)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcome** | **Control arm (*n*=6,250)** | **Screening arm (*n*=6,233)** | **Hazard ratio (95% CI)** | ***p* value** |
| **Osteoporosis-related fractures** |
| No Fracture | 5398 (86.4%) | 5428 (87.1%) | NA | NA |
| Fracture | 852 (13.6%) | 805 (12.9%) | 0.94 (0.85–1.03) | 0.178 |
| **Hip fractures** |
| No Fracture | 6032 (96.5%) | 6069 (97.4%) | NA | NA |
| Fracture | 218 (3.5%) | 164 (2.6%) | 0.72 (059–0.89) | 0.002 |
| **All clinical fractures [Au: should this be All clinical events? Please clarify ‘all clinical’.]**  |
| No Fracture | 5248 (84.0%) | 5282 (84.7%) | NA | NA |
| Fracture | 1002 (16.0%) | 951 (15.3%) | 0.94 (0.86–1.03) | 0.183 |
| **Mortality** |
| Survived | 5725 (91.6%) | 5683 (91.2%) | NA | NA |
| Died | 525 (8.4%) | 550 (8.8%) | 1.05 (0.93–1.19) | 0.436 |

NA, not applicable; SCOOP, screening of older women for prevention of fracture.

**Table 1:** **Efficacy outcomes for the Screening of older women for prevention of fracture study**

Data from table 1 were first published in Ref. [130](#_ENREF_130)

**Glossary [Au: I’ve suggested a number of key glossary terms to improve the accessibility of the text. If you agree, please include a concise, 1–2 sentence definition for each.]**

**Major Osteoporotic Fracture:** a fracture attributable to osteoporosis including the hip, forearm, humerus or a clinically presenting vertebral fracture

**Denosumab:** a fully humanized monoclonal antibody which binds to the receptor activator of RANK ligand, thus blocking the action of RANK ligand. It is delivered via subcutaneous injection as an anti-resorptive agent for the treatment of osteoporosis.

Thoracic kyphosis: an S-shaped deformity of the spine which can be precipitated by osteoporotic vertebral fractures.

Periosteal envelope: the membrane of connective tissue which surrounds bone. It has two layers, an outer fibrous layer and an inner layer which plays a crucial role in osteogenesis.

Bone mineral apparent density (BMAD): is an estimated volumetric bone density. Volume is calculated from the DXA-assessed bone area by assuming the vertebrae are either a cube or a cylinder.  It is a method of reducing the size-dependence of DXA measurements, and is particularly useful in children.

Experimental variograms: Variograms are a mathematical technique which is used to assess the spatial dependence of a spatial random field. Experimental variograms are those acquired through experimental data.