**Impact of population-based or targeted BMD interventions on fracture incidence**

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**Abstract**

*Purpose/introduction*

To investigate the impact of population level or targeted alterations to BMD on the incidence of fractures.

*Methods*

We used a simulated cohort of 49,242 women with age and BMI distribution from the UK, and prevalence of other clinical risk factors based on European FRAX® cohorts. Using FRAX probabilities of major osteoporotic fracture (MOF: hip, clinical vertebral, wrist, proximal humerus) and hip fracture, calculated with femoral neck BMD, we determined the expected number of fractures over 10 years, stratified by 10 year age band from 50 years. We then investigated the effect of i: uplifting all individuals with T score below -2.5 to be exactly -2.5 (high-risk strategy); and ii: shifting the entire BMD distribution upwards (population strategy).

*Results*

Overall, the high-risk strategy prevented 573 MOF including 465 hip fractures. Moving the BMD T-score distribution upward by 0.27SD gave an equivalent reduction in numbers of MOF; for hip fractures prevented this was 0.35SD. A global upward 0.25SD BMD shift prevented 524 MOF including 354 hip fractures, with corresponding figures for an increase of 0.5SD being 973 MOF prevented and 640 hip fractures prevented. The ratio of hip fracture to MOF prevented differed by the two approaches, such that for the high-risk strategy the ratio was 0.81, and for the population strategy was 0.68 (0.25SD BMD uplift) and 0.66 (0.5SD BMD uplift). The numbers of fractures prevented by the high-risk strategy increased with age. In contrast the age-related increase in numbers of fractures prevented with the population strategy rose with age, but peaked in the 70-79 year age band and declined thereafter.

*Conclusions*

Both strategies reduced the numbers of expected incident fractures, with contrasting relative impacts by age and fracture site. Whilst the current analysis used UK/European anthropometric/risk factor distributions, further analyses calibrated to the distributions in other settings globally may be readily undertaken. Overall, these findings support the investigation of both population level interventions and those targeted at high fracture risk groups.

*Summary*

In a simulated population of older women, we demonstrate that an upward shift in the population distribution of BMD by approximately 0.3SD may decrease the risk of incident fractures to the same extent as an intervention targeted to those with T-score less than -2.5.

**Introduction**

Although current strategies for fracture risk assessment identify those who are at high risk of fracture, this group represents only a small proportion of the total number of individuals who experience a fragility fracture [1]. Importantly, the majority of fractures arise from the population at low-moderate risk, simply because there are many more such individuals than those defined as being at high fracture risk [1-3]. This leads to the question of whether an intervention which affects a risk factor across the whole population might serve as an effective strategy in reducing the population burden consequent to osteoporotic fractures [4]. Bone mineral density (BMD) is normally distributed in the population and amenable to pharmacological interventions [5]. There is also evidence that factors such as diet, lifestyle, and physical activity influence BMD throughout life, and that environmental factors, and thus potentially interventions, very early in life may influence bone development[4]. Such considerations raise the possibility that public health approaches aimed at improving bone mineral density across the population might usefully reduce the fracture burden in subsequent years [4, 6]. To date, however, the number of fractures prevented by such an intervention compared with the impact of targeting those individuals judged to be at high risk of fracture (as is the basis of fracture risk assessment currently across the world) has not been well characterised [7-10]. In the present analysis, we used a simulated cohort of older women to describe the theoretical impact of a population-wide alteration to the BMD distribution, compared with a targeted approach focused on those with densitometrically defined osteoporosis, on incident fracture rates over a 10-year period.

**Methods**

The study cohort was a simulated population of women age 50–89 years based on the UK age and BMI distribution and European age-specific prevalence of risk factors. The distribution of the clinical risk factors by age was estimated by determination of a set of conditional distributions using cohorts of European women used in the development of FRAX® as previously described [11-13]. Except for BMD and BMI, the variables were zero-one (at a given age). The probability that a zero-one variable, representing the dichotomous present/absent clinical risk factors in FRAX, assumed the value one, was estimated by multivariable logistic regression analysis including other variables that were significantly correlated to the current zero-one variable. Osteoporosis was defined from femoral neck BMD of U.S. white non-Hispanic women (age 20–29 years) of the NHANES III study as a reference value [14]. A T-score of -2.5 SD represented a BMD of 0.577 g/cm2 at the femoral neck[15]. A simulated population of 49,242 women aged 50–89 years in the UK was thus generated. Simulations of greater numbers of women (up to 100,000) indicated that this number provided stability of the estimates of the risk factor distribution [16].

We used this simulated cohort to investigate the expected number of fractures over a 10-year period. Thus, we calculated FRAX probability of major osteoporotic fracture (MOF: hip, clinical vertebral, distal forearm, proximal humerus) and hip fracture (with femoral neck BMD) to estimate the expected number of fractures over 10 years, stratified by 10-year age band from 50 years. Two scenarios were examined (Figure 1): A “high-risk strategy” determined how many hip or MOF would be prevented if all women aged 50 years or more from the index population with a BMD T-score below -2.5 were to have a BMD T-score of exactly -2.5. The “population strategy” determined how many fractures would be prevented if all women aged 50 years or more were to increase femoral neck BMD by a finite amount (entire T-score distribution shifted upward by 0.1, 0.2, 0.25, 0.5 or 0.75 SD). We have previously used a similar approach to demonstrate the value of the high-risk strategy for hip fracture prevention at the global level [17], but importantly in that analysis, the alteration in BMD also incorporated associations between BMD and clinical risk factors in the model. Here we focus purely on the effect of an alteration in BMD itself for both the high-risk and population strategies. We additionally investigated the population BMD shift which would be required to prevent a number of fractures equivalent to that prevented by the high-risk strategy. For the sake of brevity, the decrease in the number of fractures as a result of a high-risk or population strategy was termed prevented fractures or preventable fractures. The analyses are purely descriptive, and we did not undertake statistical testing of any differences observed. Since this analysis was based on a simulated cohort, there was no requirement for ethics or IRB approval.

**Results**

*Characteristics of the simulated cohort*

The mean (SD) age of the simulated cohort was 65.8 (10.5) years and the baseline characteristics of the simulated participants are presented in Table 1. Table 2 documents the number of MOF and hip fractures expected over the next 10 years by age-band.

*Numbers of fractures prevented*

In total, 6203 MOF and 1959 hip fractures were expected over 10 years’ follow-up. Overall, the high-risk strategy prevented 573 MOF including 465 hip fractures. Figure 2 demonstrates the comparative effect of the population strategy, such that moving the BMD T-score distribution upward by 0.27 SD gave an equivalent reduction in numbers of MOF; the corresponding figure for the equivalent number of hip fracture prevented was 0.35 SD.

We used 0.25 SD and 0.5 SD population shifts as illustrative examples of the effect of the population strategy. Thus, a global upward shift of BMD by 0.25 SD prevented 524 MOF including 354 hip fractures. The figures for a population increase of 0.5 SD were 973 MOF prevented including 640 hip fractures. These findings are summarised in Table 2 and Figure 3. Supplementary Table 1 documents the comparative findings for all population T-score adjustments. The ratio of hip fracture to MOF prevented differed by the two approaches. Thus, for the high-risk strategy the ratio was 0.81. The ratios were lower for the population strategy: for example, 0.68 with an uplift of 0.25 SD BMD and 0.66 with the population increase of 0.5 SD.

*Patterns of fracture prevention by age*

The numbers of fractures prevented by the high-risk strategy, both MOF and hip fracture, increased with age. In contrast the age-related increase in numbers of MOF or hip fractures prevented with the population strategy rose with age, but peaked in the 70-79 year age band and declined thereafter. Table 2 documents the ratio of number of hip to MOF prevented by 10-year age band.

**Discussion**

The present study quantifies the gains in fractures saved when applying global or high risk strategies. We have thus demonstrated, in a simulated cohort of older women, that both population-based and targeted strategies are expected to reduce the numbers of incident fractures in a population. The effects differed somewhat by fracture site (likely a consequence of the different gradient of risk with BMD by fracture site) and by age band. Thus, the T-score intervention (high-risk strategy), which might be regarded as corresponding to our current approach of targeting those at highest fracture risk, prevented a greater number of hip fractures relative to MOF, compared with the population strategy (which might be viewed as representing the results of a successful public health intervention). Consistent with this observation, the high-risk strategy prevented most fractures in the oldest age band; in contrast the population strategy appeared to prevent most fractures in a younger age (70-79-year age band). It was notable however that even a very modest 0.1 SD increase in BMD population-wide would be expected to result in a tangible reduction in the fracture burden (4% decrease in MOF and 8% for hip fracture).

We used a large simulated cohort of women, with the UK age and BMI distribution, and prevalence of risk factors based on the European FRAX cohorts. This permitted alteration of BMD in the models in a uniform way across the cohort without changing the other risk factors for fracture. This specific model may not be generalisable to men or other populations, and differs from the approach used previously to model the high-risk intervention, in which correlations between BMD and clinical risk factors were incorporated in a global simulation [17]. However, such a model calibrated to the age and BMI distribution of a different country within Europe could be readily constructed; models based on populations in other continents would also be possible given sufficient information on the age and BMI distribution, and availability of suitable cohorts from which to draw the distribution of other risk factors. Thus the concept and methodology is readily transferable to other country settings internationally.

Importantly, we do not have empirical evidence from a real-life study, but the reliability of the FRAX methodology for fracture prediction has been amply demonstrated [18, 19]. Ideally, population-wide intervention studies would be required to test any proposed interventions which might result in such a generalised shift in BMD distribution. However, in the same way that a randomised trial encompassing everyone in a population categorised to be at high fracture risk is clearly impractical, undertaking a truly population-wide intervention is also highly unlikely to be feasible. Thus, studies investigating public health level interventions may be tested to establish proof of concept in a more circumscribed randomised clinical trial if the intervention lends itself to this approach, for example micronutrient supplementation; other interventions such as changes in national guidance or service provision may require other approaches such as controlled before and after analyses and interrupted time series analyses. If an intervention shows potential benefit in a trial setting (efficacy) then it needs to be tested for real-world benefit (effectiveness) in the setting in which it will be delivered. The general approach to these, often complex, interventions has been described in detail by the UK Medical Research Council [20], and potential examples of early life interventions are described below. With any such study, the estimates are likely to be overestimates of benefit, since in any population intervention not all the population are reached, and some only partially reached; in any targeted intervention likewise not everyone at high risk receives, or complies with, a therapeutic intervention [8]. In the present study, our aim was not to document the exact impact, but to demonstrate the general principle that a population-wide changing BMD could lead to substantial reductions in the fracture burden.

The quantitative benefits of population versus targeted approaches to improve skeletal health have received scant attention in the literature to date. The underlying principles of population interventions were meticulously articulated by Geoffrey Rose in his seminal 1985 paper “Sick individuals and sick populations”. Rose clearly sets out the pros and cons of the two types of intervention. The approach was applied to osteoporosis by Cooper and Melton in 1992 [9], and the potential for the use of calcium supplementation in the population or high-risk scenario investigated by Kanis in 1999 [8]. However, current international guidelines on the assessment and treatment of osteoporosis focus on those individuals found to be at high fracture risk, usually on the basis of case finding (in practice if not also in principle) [5, 21], either on the basis of a fracture risk assessment with a tool such as FRAX, or on the basis of a prior fracture [22]. The advantage of the targeted approach is that it offers substantial benefit for the individuals identified. Conversely there are potential disadvantages in the associated message of ill-health, the necessity to take medicines, and indeed the difficulty of identifying cases in the first place. This approach identifies only a small proportion of the population, meaning that the vast majority receive no benefit. Indeed, it is absolutely clear globally that there is a substantial treatment gap in both primary and secondary fracture prevention with the minority of individuals at high fracture risk internationally receiving appropriate assessment and treatment.

In contrast, the population approach, in our manuscript the example being that of achieving a rise in the overall BMD distribution, achieves only a very small benefit at the individual level but yields an impact on fractures at the population level comparable to that from the targeted approach, albeit in a partly different set of individuals. This approach thus pre-empts any inadequacies in case finding focused on patients at high risk of osteoporotic fractures, but of course may not achieve sufficient increase in BMD at the individual level to provide adequate protection. The different pattern of fracture reduction between MOF and hip by age band between the two approaches will likely influence the health economic impact of either approach. The greater reduction in hip fracture relative to MOF with the high-risk intervention is consistent with the higher gradient of risk per SD reduction in BMD than is observed for the other MOF fracture types [23]. The population approach can potentially be linked with a much more positive message and a more behaviourally appropriate intervention, for example removing a risk factor, adding an intervention perceived as being more acceptable. The only study we were able to identify, prior to our own, to address this issue in terms of fracture prevention demonstrated that a programme of intervention directed to those with a T score of -1 or below might reduce the overall burden of hip fracture by 18.4%. A similar reduction could be obtained by shifting the entire population bone density distribution upwards by 0.3 SD [10]. Our findings demonstrate similar effect sizes and suggest that both approaches may have the potential for substantial contributions in reducing the fracture burden.

Although approaches to primary and secondary prevention of fragility fractures in older age are well established [5, 24], there is scant evidence pertaining to the use of specific measures in the context of population-wide interventions. Indeed, the quality of evidential support for such interventions should ideally be consistent with that already established for approaches targeted to individuals at high fracture risk. A key initial question relates to the practicalities of what interventions might be undertaken at the population level. Although novel nutritional interventions show potential benefits [25], there is still scant evidence that optimising adult or childhood health behaviour (e.g. smoking cessation) and optimising nutrition and physical activity will result in sufficient stabilisation of BMD, let alone achieve an increase across the population [4, 8]. However there is increasing evidence that the environment in early life, for example in utero and early infancy, may influence the trajectory of skeletal accrual to peak bone mass in early adulthood, and that the magnitude of this peak protects from the onset of osteoporosis [4, 26]. Indeed poor early growth is associated with increased risk of adult hip fracture [27], and adverse femoral geometry [28]. Maternal vitamin D supplementation has now been shown in two randomised, placebo-controlled trials to lead to improved offspring bone mass [29, 30], and process of, and barriers to, implementation of this intervention explored [31]. Convincing long-term benefits into old age of course remain to be established, but the available evidence has established the principle that early interventions may have the potential to improve bone mass and thus are likely to reduce fracture risk in older age [4].

In conclusion, we have demonstrated that both population-wide and targeted interventions to improve BMD result in substantial reduction in the future fracture burden in the population. Although the approaches gave a similar magnitude of overall fracture prevention, they differed in impact by age and fracture site. Whilst this exemplar analysis used and age and BMI distribution from the UK and a clinical risk factor distribution from European FRAX cohorts, the methodology is generic and, as long as the background epidemiological data are adequate, could easily be applied to distributions from other countries worldwide amongst women or indeed amongst men. Overall, our findings support the investigation of population-based public health approaches to fracture prevention in addition to the targeting of treatment to high-risk groups.

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**Disclosures**

Nicholas C Harvey,John A Kanis, Enwu Liu, Liesbeth Vandenput, Mattias Lorentzon, Cyrus Cooper, Eugene McCloskey, Helena Johansson declare that they have no conflicts of interest in relation to this work.

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**Table 1:** Baseline characteristics and 10-year FRAX probabilities (%) in the simulated population.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **50-59 years; n=17,183** | **60-69 years; n=15,223** | **70-79 years; n=10,576** | **80-89 years; n=6260** |
|  |  | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** |
| Age, years |  | 54.9 | 2.9 | 64.6 | 2.9 | 74.6 | 2.9 | 84.2 | 2.7 |
| T-score |  | -1.00 | 1.03 | -1.44 | 0.99 | -1.91 | 0.96 | -2.38 | 0.90 |
| BMI, kg/m2 |  | 28.0 | 5.3 | 28.3 | 5.3 | 28.7 | 5.5 | 28.0 | 5.3 |
| FRAX MOF wo |  | 6.57 | 3.48 | 11.67 | 5.89 | 18.35 | 8.07 | 26.56 | 9.51 |
| FRAX hip wo |  | 0.91 | 0.96 | 2.55 | 2.33 | 7.12 | 5.83 | 14.71 | 8.91 |
| FRAX MOF w |  | 6.85 | 4.39 | 11.68 | 7.06 | 17.18 | 9.66 | 22.86 | 10.53 |
| FRAX hip w |  | 1.13 | 2.48 | 2.58 | 4.16 | 6.29 | 7.50 | 11.29 | 9.22 |

wo = FRAX calculated without BMD; w = FRAX calculated with BMD; MOF = major osteoporotic fracture

**Table 2:** Expected and predicted number of fractures prevented over 10 years follow-up, by 10-year age band.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **MOF prevented (n)** |  |  |  |
| **Expected (n)** | **Age (years)** | **BMD +0.5SD** | **BMD +0.25SD** | **T>-2.5** |  |  |  |
| 1177 | 50-59 | 156 | 86 | 50 |  |  |  |
| 1778 | 60-69 | 271 | 148 | 119 |  |  |  |
| 1817 | 70-79 | 315 | 169 | 199 |  |  |  |
| 1431 | 80-89 | 231 | 121 | 205 |  |  |  |
| 6203 | Total | 973 | 524 | 573 |  |  |  |
|  |  |  |  |  |  |  |  |
|  |  | **Hip fractures prevented (n)** | **Ratio Hip:MOF prevented** |
| **Expected (n)** | **Age (years)** | **BMD +0.5SD** | **BMD +0.25SD** | **T>-2.5** | **BMD +0.5SD** | **BMD +0.25SD** | **T>-2.5** |
| 194 | 50-59 | 87 | 50 | 41 | 0.56 | 0.58 | 0.82 |
| 393 | 60-69 | 157 | 89 | 96 | 0.58 | 0.60 | 0.81 |
| 665 | 70-79 | 219 | 120 | 163 | 0.70 | 0.71 | 0.82 |
| 707 | 80-89 | 177 | 95 | 165 | 0.77 | 0.79 | 0.80 |
| 1959 | Total | 640 | 354 | 465 | 0.66 | 0.68 | 0.81 |
|  |  |  |  |  |  |  |  |

**Figure 1: Targeted high risk or population based approach. Adapted from[10],[32]**

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**Figure 2:** Number of fractures per 100 persons over 10 years follow-up: The dotted black (MOF) and grey (hip) lines are the number of fractures per 100 persons expected with no intervention. The solid black (MOF) and grey (hip) lines are the number of fractures per 100 persons when all individual with BMD FN T-score <-2.5 has their T-score shifted upwards to exactly -2.5. The black line with solid rings in black (MOF) and grey line with solid rings in grey (hip) lines are the number of fractures per 100 persons when BMD T-score distribution is shifted upward by 0.1, 0.2, 0.25, 0.5 or 0.75 SD.

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**Figure 3a:** Number of major osteoporotic fractures prevented over 10 years follow-up.

**Figure 3b:** Number of hip fractures prevented over 10 years follow-up.

**Supplementary Table 1:** Expected and predicted number of fractures prevented over 10 years follow-up, by 10-year age band, together with percent reduction in fractures.

|  |  |  |
| --- | --- | --- |
|  |  | **MOF prevented, n (%reduction)** |
| **Expected (n)** | **Age (years)** | **BMD +0.1SD** | **BMD +0.2SD** | **BMD +0.25SD** | **BMD +0.5SD** | **BMD+0.75SD** | **T>-2.5** |
| 1177 | 50-59 | 36 (3.1) | 70 (5.9) | 86 (7.3) | 156 (13.3) | 213 (18.1) | 50 (4.2) |
| 1778 | 60-69 | 62 (3.5) | 120 (6.7) | 148 (8.3) | 271 (15.2) | 374 (21.0) | 119 (6.7) |
| 1817 | 70-79 | 71 (3.9) | 138 (7.6) | 169 (9.3) | 315 (17.3) | 442 (24.3) | 199 (11.0) |
| 1431 | 80-89 | 50 (3.5) | 98 (6.8) | 121 (8.5) | 231 (16.1) | 329 (23.0) | 205 (14.3) |
| 6203 | Total | 219 (3.5) | 426 (6.9) | 524 (8.4) | 973 (15.7) | 1358 (21.9) | 573 (9.2) |
|  |  |  |  |  |  |  |  |
|  |  | **Hip fractures prevented, n (%reduction)** |
| **Expected (n)** | **Age (years)** | **BMD +0.1SD** | **BMD +0.2SD** | **BMD +0.25SD** | **BMD +0.5SD** | **BMD +0.75SD** | **T>-2.5** |
| 194 | 50-59 | 20 (10.3) | 41 (21.1) | 50 (25.8) | 87 (44.8) | 115 (59.3) | 41 (21.1) |
| 393 | 60-69 | 38 (9.7) | 72 (18.3) | 89 (22.6) | 157 (39.9) | 210 (53.4) | 96 (24.4) |
| 665 | 70-79 | 51 (7.7) | 98 (14.7) | 120 (18.0) | 219 (32.9) | 300 (45.1) | 163 (24.5) |
| 707 | 80-89 | 40 (5.7) | 77 (10.9) | 95 (13.4) | 177 (25.0) | 192 (27.2) | 165 (23.3) |
| 1959 | Total | 149 (7.6) | 288 (14.7) | 354 (18.1) | 640 (32.7) | 817 (41.7) | 465 (23.7) |