

A Randomized Controlled Trial of Screening in the Community to Reduce Fractures in Older Women: The SCOOP Study

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SUMMARY

Background

Despite effective assessment tools and medications targeting osteoporosis and related fractures, screening for fracture risk is not currently advocated in the UK. We tested whether a community-based screening intervention could reduce fractures in older women.

Methods

We conducted a two-arm randomised controlled trial in women aged 70 to 85 years comparing a screening programme using the FRAX risk assessment tool versus usual management. The primary outcome was the proportion of individuals experiencing one or more osteoporosis-related fractures over a five-year period. In the screening arm, treatment was recommended in women identified to be at high risk of hip fracture, according to the FRAX 10-year hip fracture probability. This study was registered on the ISRCTN registry (ISRCTN 55814835).

Findings

12 483 eligible women, identified from primary care, participated in the trial. Of 6 233 randomised to screening, treatment was recommended in 898 (14.4%). Osteoporosis medication use was higher at the end of year one in the screening group compared to controls (15.3% vs 4.5%, respectively), with uptake particularly higher (78.3% at 6 months) in the screening high risk subgroup. Screening did not reduce the incidence of all osteoporosis-related fractures (hazard ratio: 0.94, $p=0.178$, 95% C.I. : 0.85 to 1.03), nor the overall incidence of all clinical fractures (hazard ratio: 0.94, $p=0.183$, 95% C.I. : 0.86 to 1.03) but there was strong evidence for a reduction in hip fractures, a pre-specified secondary outcome (hazard ratio : 0.72, $p=0.002$ 95% C.I. : 0.59 to 0.89). There was no evidence of differences in mortality, anxiety levels or quality of life.

Interpretation

A systematic, community-based screening programme of fracture risk in older women in the UK is feasible. Whilst there was no reduction in overall fracture rate the intervention was effective in reducing hip fractures by an estimated 28%.

Funding

The Arthritis Research United Kingdom (ARUK), formerly the Arthritis Research Campaign (ARC), and the Medical Research Council (MRC) of the UK jointly funded this trial.

Introduction

There are approximately 9 million osteoporotic or fragility (low trauma) fractures worldwide per year.¹ In developed nations, around one in three women and one in five men aged 50 years or more will suffer a fragility fracture during their remaining lifetime, most commonly at sites such as the hip, distal forearm, vertebrae and humerus. In the UK, around 536 000 people suffer fragility fractures each year, including 79 000 hip fractures, with a cost in 2010 estimated at £3.5 billion expected to rise to £5.5 billion per year by 2025.² For the individual, a hip fracture can be devastating with loss of independence and less than one third of patients making a full recovery; mortality at one year post-fracture is approximately 20%.³

Advances in osteoporosis management over the last two decades include development of effective low-cost treatments and easily accessible fracture risk assessment tools, such as FRAX[®]. Bone mineral density (BMD) measurement alone has a relatively low sensitivity for fracture risk and is therefore of limited utility for mass screening;^{4,5} the FRAX tool, however, has been shown to increase the sensitivity for fracture risk above that provided by measuring BMD in isolation.⁶ Although underpinning many guidelines internationally, no formal studies have prospectively examined the utility of using FRAX to target intervention and reduce fracture incidence.

The aim of the *SCOOP* ('screening for prevention of fractures in older women') trial was to assess the effectiveness of a FRAX-based, community screening programme for UK women aged 70 to 85 years in reducing the incidence of fractures over a five year period.

Methods

Study Design

The *SCOOP* clinical study was a pragmatic, unblinded, two group, parallel, randomised controlled trial to assess the effectiveness and cost-effectiveness of screening to prevent fractures in older women. Details of the methods have been published.⁷

The primary end-point was the proportion of participants experiencing at least one osteoporosis-related fracture, defined in more detail below, over the five-year follow-up. Follow-up data collection points were at 6, 12, 24, 36, 48 and 60 months post-randomisation.

Participants

Participants in or around seven regions in England: Norwich, Southampton, Bristol, Birmingham, Manchester, York and Sheffield. Women age 70-85 years were identified through primary care lists. Those currently on prescription anti-osteoporotic medications (excluding vitamin D or calcium) were excluded (though anyone who had used such medication at any time in the past could be included); any individuals deemed, by their family doctor, to be unsuitable to enter a research study (e.g. known dementia, terminally ill, recently bereaved, etc.) were also excluded.

Where a large number of potential participants were identified, a number were excluded, at random, to ensure for practical reasons that no practice had more than 500 participants.

Written, informed consent was obtained from all participants. At this point, a self-filled questionnaire captured the FRAX risk factors prior to each woman being randomised to the intervention (screening) or control arm. Baseline data comprised age, sex, height and weight for Body Mass Index (BMI) calculation, and dichotomised risk variables including a prior fragility fracture since the age of 50 years, parental history of hip fracture, current tobacco smoking, any long-term

use of oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis and daily alcohol consumption of ≥ 3 units daily. If the respondent did not know the answer to an individual question a negative response was assumed.

Randomisation

Allocation to study arm was conducted using blocked randomisation (block length 6), stratified by recruiting region and age group (70 to 74 years, 75 to 79 years and 80 to 85 years). Randomisation was carried out, once relevant data were obtained, using an on-line web-based system. This was set up by an independent data-programmer from the Norwich Clinical Trials Unit. A 1:1 allocation ratio was used.

Intervention Arm

In the screening arm, the baseline risk factor questionnaire was used to calculate the 10-year probability of hip and major osteoporotic fracture using the FRAX risk algorithm.⁸ The hip fracture probability was then used to decide whether or not a participant should be invited for a DXA scan to assess BMD. The 10-year probability of hip fracture for each participant was compared to an assessment threshold for each 5-year age-band (column 1, Table 1), as determined previously in an analysis of treatment cost-effectiveness in the UK.⁹ Each participant was classified as low or high risk of fracture, depending on whether their individual 10-year hip fracture probability was below or above the threshold probability for their age. Participants classified as low risk received a letter (also notified to their GP) confirming their low risk status with a recommendation that no further action was necessary. The remaining participants were invited to undergo a local, DXA-based femoral neck BMD measurement and the 10-year hip fracture probability was recalculated with inclusion of BMD. Height and weight were measured at the DXA visit and the BMI information updated. The presence of rheumatoid arthritis was removed from this calculation as it may have been confused with osteoarthritis by participants and reliance on self-report of rheumatoid arthritis is not recommended for the FRAX algorithm.¹⁰ The final risk category, either low or high risk of fracture, (i.e. below or above the age category intervention threshold, column 2, Table 1) was communicated to the participant and GP by letter; participants above the threshold were advised to make an appointment with their family doctor to discuss treatment options.

Control Arm

Apart from a letter to the GP informing them of their patient participating in the study, no additional information was provided and they received standard care as usual. The baseline 10-year fracture probabilities, without the inclusion of BMD, were calculated at the end of the trial for comparative purposes only.

Outcomes

The primary outcome was the proportion of participants experiencing at least one osteoporosis-related fracture during the five-year follow-up period. Pre-specified secondary outcomes were the proportions of participants experiencing at least one hip fracture; any clinical fracture; and mortality. Mortality was ascertained by flagging all randomized subjects via the Office of National Statistics (ONS); deaths notified by family members and GPs were also confirmed by ONS data. The impacts on anxiety (using the short 6-item version of the State-Trait Anxiety Index (STAI)¹¹) and health related quality of life (measured with EQ-5D and SF-12) were also pre-specified secondary endpoints. Family doctors were asked to record any adverse events related to the screening process.

Fracture Ascertainment

Fracture events were captured from a variety of sources. Participants self-reported any fractures occurring since the previous follow-up, including date and anatomical site of fracture, and hospital attended (if any). Routine hospital episode statistics (HES) data¹, comprising information on hospital inpatient stays and emergency department attendance, were interrogated to identify fractures in any of the study participants from the point of randomisation until the end of follow-up. Primary care records were similarly screened for fractures based upon formal Read codes.

Where self-report or emergency department attendance were the sole source of information, or where there was missing information regarding exact dates or anatomical site of fracture, further verification included requests to primary care practices and searches of radiology records at local hospitals. Vertebral fractures documented within 6 months of randomisation were excluded due to uncertainty over the actual date of occurrence.

Only verified fractures, at any anatomical site, within the five-year follow-up period, were included as outcomes. The level of trauma associated with the incident fracture was not recorded. Incident osteoporosis-related fractures were defined as those excluding the hands, feet, nose, skull or cervical vertebrae. Hip fractures were defined as verified fractures with a specific description of 'neck of femur' or 'proximal femur'. Those described as 'sub-trochanteric', 'femoral shaft', 'distal femur' or simply 'femoral' were not categorised as hip fractures.

Statistical Analysis

Cox's proportional hazards model was used to estimate the hazard ratio between the two study arms for fractures (whether osteoporosis-related, clinical or hip fractures), together with a 95% confidence interval. Recruiting region, baseline FRAX risk value (without BMD, to allow use for control participants) and self-reported falls at baseline were included in the model. These variables were included as prognostic factors and agreed prior to data analysis. Death or withdrawal from the study were treated as censoring events. A similar approach was used to compare rates of mortality, with study withdrawal as a censoring event. The analysis of quality of life data and anxiety data used a general linear model with recruiting region, age and baseline value of the outcome included along with treatment arm at each time point. A repeated measures linear model (with repeated outcome being at the 6 follow-up time points) was also carried out.

All analyses were conducted on an intention-to-treat basis with participants analysed according to the group to which they were randomised, irrespective of whether screening was completed.

Sample Size

The sample size was based upon the ratio of hazard for the two groups for any osteoporosis-related fracture over the follow-up period taking into account the expected recruitment time and expected censored observations due to death.¹² Assumptions included a 2.5% annual incidence of fractures and a death rate of approximately 4.2% per annum in UK women aged 70-85 years.^{13,14} Assuming a screening sensitivity of at least 65%, a treatment effect of 35% (i.e. a 35% relative reduction in fractures in individuals on active treatment), and 80% uptake of treatment in the high risk group, a relative reduction in risk of fracture of 18% was estimated, i.e. a hazard ratio of around 0.82. This indicated a sample size of 5790 women per arm would

provide 90% power with 5% significance based upon the stated hazard ratio; a fracture rate of 2.0% in the control group would reduce the power to 82%. The target sample size was thus set at 11580, with 5790 per arm.

Ethical Approval and Funding

Full ethical approval was obtained from the North Western - Haydock Research Ethics Committee of England in September 2007 (REC 07/H1010/70). The trial was registered on the International Standard Randomised Controlled Trial Register in June 2007 (ISRCTN 55814835). The Arthritis Research United Kingdom (ARUK), formerly the Arthritis Research Campaign (ARC), and the Medical Research Council (MRC) of the UK jointly funded this trial.

Role of the funding bodies

The funders of the study played no role in the study design, data collection, data analysis, data interpretation or writing of this report. The corresponding author had full access to all data used in this study and had final responsibility for the decision to submit for publication.

Findings

Participants

Participant progress through the trial is illustrated in Figure 1. A total of 52 033 women aged 70 to 85 years were identified. Following exclusions for concurrent anti-osteoporosis medication use (n=6 927, 13.3%), being deemed unsuitable to enter a research study by their family doctor (n=3 473, 6.7%) or other exclusion reasons (n=3 033, 5.8%; e.g. ensuring no more than 500 participants per practice), letters of invitation were sent to 38 600 women. A further 569 were subsequently excluded when found to be using anti-osteoporosis medication, not originally noted or initiated after the time of initial identification. Of the 38 031 remaining eligible women, 11 068 (29.1%) didn't respond (despite a reminder letter) and 13 870 (36.5%) declined to take part. Thus, 13 029 women consented to participate, and a total of 12 495 (32.9% of those eligible) were randomised. The first randomisation was carried out in April 2008 and the last in July 2009. The last follow-up was in July 2014. The number of women randomised in each of the seven regions ranged from 1632 to 2055.

Twelve participants were excluded post-randomisation: nine were on anti-osteoporotic medication at randomisation, two were mistakenly entered into the trial twice and one withdrew from the trial post-randomisation. Thus, the results pertain to 12 483 appropriately randomised participants.

Baseline Characteristics

The screening group comprised 6 233 women with 6 250 in the control group. As expected for a randomised trial of this size, the two groups were closely comparable at baseline (Table 2). Compared to those declining participation, participants reported a better education, higher social- economic status, and more frequent histories of previous fracture or parental hip fracture.

Screening Details

Approximately half of those in the screening arm (3 064, 49.2%) were categorised as initial high risk and were invited to have a DXA scan. Of these, 247 (8.1%) did not provide a BMD result (157

declined the invitation, 81 unable to have hip BMD measured and nine died before scan) and consequently did not have an updated fracture risk calculated. Of those with BMD measured at the femoral neck, 898 (14.4% of the screening arm) were deemed to be at high risk after recalculation of their FRAX hip fracture probability (Table 2). The mean femoral neck T-score was -2.6 for this group. The average time from randomisation to notification of risk category in those invited for a DXA scan was 78 days.

There were no serious adverse events related to screening recorded.

Use of anti-osteoporosis medication

By the end of the first year, 953 participants in the screening arm (15.3% of those randomised to the screening arm) had had at least one prescription compared with just 264 (4.5%) in the control arm. Exposure to treatment was higher in those categorised as high risk in the screening arm with 703 (78.3%) having received at least one prescription within 6 months of randomisation. Over the remaining years of follow-up, the proportion on treatment remained fairly constant in the screening arm, at around 13% to 14%, whereas there was a steady increase in treatment exposure in the control arm, with 833 (10.1%) receiving some prescription medication in the final 12 months of follow-up. During the course of the study, around 24% of the screening arm participants received at least one prescription for anti-osteoporosis medication compared with 16% of the control arm.

Efficacy Outcomes

The follow-up period provided 59 401 person-years of observation. Table 3 shows details of the fracture events by group. Overall, 1 975 osteoporosis-related fractures were identified in 1 657 individuals, 13.3% of those randomised. The most common site of fracture was the distal forearm (614 individuals experienced 638 fractures, 338 in the control arm and 300 in the screening arm) followed by the hip (382 individuals experienced 392 fractures, 225 in the control arm and 167 in the screening arm). The estimated rate of new clinical fractures per 100 person years were: overall 3.3, wrists 1.1, hips 0.66.

Over 5 years, the proportion of individuals experiencing an osteoporosis-related fracture (the primary outcome) was similar in the screening arm compared to the control arm (12.9% v 13.6%) with an adjusted hazard ratio (HR) of 0.94 (p=0.178, 95% C.I. : 0.85 to 1.03). A similar result was observed for any clinical fracture (15.3% v 16.0%, HR = 0.94, p=0.183, 95% C.I. : 0.86 to 1.03). In contrast, in a pre-specified secondary analysis, screening led to a relative reduction in hip fractures of 28% compared with usual care (2.6% v 3.5%, HR = 0.72, p=0.002, 95% C.I. : 0.59 to 0.89).

Over 5 years, mortality rates were similar in the screening and control arms (8.8% v 8.4% respectively, HR = 1.05, p=0.436, 95% C.I. : 0.93 to 1.19).

There was no evidence of any impact of screening on anxiety levels (Table 4, p=0.515, repeated measures ANOVA). Those in the high risk group had higher levels of anxiety at baseline, prior to screening, but throughout the study period the mean difference between the high risk group and low risk group, or between the screening and control groups, were extremely small. We found no evidence of an impact on quality of life assessed by the EQ-5D or SF-12 (Tables 5 and 6).

Discussion

The *SCOOP* study did not demonstrate an effect of screening for fracture risk on the primary outcome of any osteoporosis-related fracture. It did lead to a statistically and likely clinically significant decrease in hip fractures. As with any clinical trial, conclusions based upon secondary outcomes need to be treated with a degree of caution and not over-emphasised. To the best of our knowledge, though, this is the first time that a community-screening approach, based upon fracture risk, has demonstrated any subsequent fracture reductions. Indeed, in 2013, the National Screening Committee of the UK noted an absence of evidence supporting the introduction of screening for fracture risk in postmenopausal women;¹⁵ the one trial of screening identified,¹⁶ commencing in the 1990s, was deemed not to provide sufficiently current evidence. An alternative recent approach that screened for prevalent vertebral fractures in primary care has shown promise but had treatment uptake as the primary outcome, rather than any decrease in fractures, and has not undergone a formal cost-effectiveness analysis.¹⁷

The *SCOOP* study has demonstrated the feasibility of a community based, screening programme in women aged 70 to 85 years to reduce hip fractures. The overall screening process was relatively straightforward. Completion of the initial FRAX questionnaire was very good and the DXA scan attendance rate was high; few individuals decided not to, or were unable to, attend for a scan. There was no observed increase in average anxiety levels post-screening and an integrated qualitative study, conducted at the time of the trial, suggested screening was acceptable to both participants and primary care physicians.¹⁸

There are a number of limitations that need to be considered. Participants represented around only one third of those eligible. There was evidence of a healthy selection bias; for example, the mortality rate over 5 years was less than half of that expected (8.6% versus an expected 19.0%, based upon the age distribution at entry).¹⁴ Those participating also tended to be better educated and of a higher socio-economic status than those actively declining. Only 14% of those screened were deemed at high risk, lower than the expected 20-40% of post-menopausal women (depending on age) according to the UK NOGG guidelines.¹⁹ Nonetheless, the rates of fracture observed were actually higher than predicted prior to the study commencement. The discrepancy could be due to a genuine increase in fracture rates since 2001, or an under-estimation based upon the primary care Read coding recorded in 2001,¹³ or perhaps a combination of the two factors.

Whilst there was no evidence that screening might reduce overall osteoporosis-related fracture incidence, there was strong evidence for a decrease in hip fractures. A number of reasons need to be considered for these results. Contamination with increased uptake of treatment in the control arm could have lessened the impact of the intervention; however treatment uptake in the first 6 months was very low (20% of that seen in the intervention arm) with a roughly linear increase thereafter. This suggests no significant early influence of contamination on prescribing in the control arm. Treatment in the control arm may have increased over time with changes in standard management of osteoporosis in primary care subsequent to changes in national or local guidelines, hence reducing any between group differences. This could explain the lack of effect regarding all OP-related fractures but would not account for the effect on hip fractures. The discrepancy is more likely explained by the screening method which used the 10-year risk of *hip* fracture, rather than the risk of *any* major osteoporotic fracture. Whilst the FRAX algorithm can calculate both, and the two risk values are related, they are not perfectly correlated nor

interchangeable. Using the hip fracture risk as the screening approach would, of course, be more sensitive to predicting, and therefore better at preventing, hip fractures, rather than fractures at other sites. This is likely to explain the discrepancy seen.

The absolute size of decrease in hip fracture rates was 0.9%, requiring 111 individuals to be screened in order to avert one hip fracture. The relative risk reduction of 28%, though somewhat less than the 40% reduction observed in clinical trials of osteoporosis medication, is substantial given the absence of treatment in the greater majority of the screening group and treatment for a proportion of the controls. While it is possible that the reduction was due to more than just an effect of prescribed medication, for example the process may have influenced behaviour to reduce hip fractures in a selected group more open to the influence of risk information, there is little evidence that provision of simple health-related information can substantially reduce fracture risk; studies addressing strategies to reduce fall risk, for example, have not been associated with significant decreases in fracture risk.²⁰ The effect seen must also be considered in light of the efficacy of current treatment. With more efficacious therapies available in future the rate of hip fracture reduction is likely to increase.

Analyses of the cost of screening are currently underway and will be published in full elsewhere. However, preliminary findings indicate that the cost per prevented osteoporotic-related fracture being less than £4 500, and the cost per prevented hip fracture less than £8 000. Additionally, the cost per QALY gained, estimated under various scenarios, was less than £20 000.

In conclusion, despite no overall reduction in fractures, this trial has demonstrated that community screening, based upon the FRAX probability of hip fracture, leads to a significant reduction in hip fractures in older women. Cost-effectiveness analyses are ongoing but the SCOOP study provides promise of an effective community-based management strategy in the UK, and elsewhere, to reduce hip fractures.

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The 'SCOOP Study Team' consists of the authors and the following researchers who worked directly on the SCOOP study

Birmingham : Nicola Crabtree, Helen Duffy, Jim Parle, Farzana Rashid, Katie Stant
Bristol : Kate Taylor, Clare Thomas (nee Emmett)

Manchester : Emma Knox, Cherry Tenneson, Helen Williams
Norwich: David Adams, Veronica Bion, Jeanette Blacklock, TonyDyer

Sheffield : Selina Bratherton (nee Simpson), Matt Fidler, Katharine Knight, Carol McGurk, Katie Smith, Stacey Young

Southampton : Karen Collins, Janet Cushnaghan

York : Catherine Arundel, Kerry Bell, Laura Clark, Sue Collins, Sarah Gardner, Natasha Mitchell

Contributions

EL was responsible for the organisation and co-ordination of the trial. LS was the Chief Investigator and also responsible for the data-analysis. LS, CC, SC, RF, NG, IH, AH, RH, AHo, JK, TM, TO, TP, DT and EM developed the trial design. All authors contributed to the writing of the final trial manuscript. All members of the *SCOOP Study Team* contributed to the management or administration of the trial.

Declarations of Interest

Professor N Harvey has received consultancy, lecture fees and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, Servier, Shire, UCB, Consilient Healthcare and Internis Pharma

Professor McCloskey has been, or currently is, an advisor or speaker for ActiveSignal, Amgen, AstraZeneca, Consilient Healthcare, GSK, Hologic, Internis, Lilly, Medtronic, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, Servier, Synexus, Tethys, UCB, Warner Chilcott. He has also received research support from these plus I3 Innovus, the IOF and Unilever.

Professor Kanis has held grants from Amgen, Lilly, Unigene and Radius Health; non-financial support from Medimaps, Asahi and AgNovos; Professor Kanis is the architect of FRAX but has no financial interest

Professor Cyrus Cooper has received consultancy fees and honoraria from Amgen, Danone, Eli Lilly, GSK, Medtronic, Merck, Nestle, Novartis, Pfizer, Roche, Servier, Shire, Takeda and UCB.

No other declarations of interest are reported. Acknowledgments

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<i>Age Group</i>	<i>BMD Threshold</i>	<i>Treatment Threshold¹</i>
70-74	5.18%	5.24%
75-79	6.81%	6.87%
80-84	8.46%	8.52%
85	8.39%	8.99%

1: Post-BMD measurement

Table 1: Risk Thresholds for invitation for BMD Measurement and Treatment. Based upon the FRAX 10-year probability of hip fracture.

		<i>Non-participants (N=15097)¹</i>	<i>Control (N=6250)</i>	<i>Screening (N=6233)</i>	<i>Screened High Risk (N= 898)</i>
<i>Has a degree?</i>	<i>Yes</i>	1080 (9.9%)	1266 (20.3%)	1270 (20.4%)	182 (20.3%)
<i>Social Class³</i>	<i>I</i>	570 (5.8%)	641 (10.3%)	615 (9.9%)	86 (9.6%)
	<i>II</i>	2206 (22.4%)	1827 (29.2%)	1871 (30.0%)	266 (29.6%)
	<i>IIIN</i>	1651 (16.8%)	1094 (17.5%)	1015 (16.3%)	211 (23.5%)
	<i>IIIM</i>	3196 (32.5%)	1626 (26.0%)	1622 (26.0%)	163 (18.2%)
	<i>IV</i>	1476 (15.0%)	718 (11.5%)	1471 (12.1%)	112 (12.5%)
	<i>V</i>	739 (7.5%)	244 (3.9%)	250 (4.0%)	38 (4.2%)
<i>Ethnic group</i>	<i>White</i>	10955 (98.4%)	6160 (98.6%)	6157 (98.8%)	893 (99.4%)
	<i>Black</i>	66 (0.6%)	26 (0.4%)	26 (0.4%)	1 (0.1%)
	<i>Asian</i>	65 (0.6%)	18 (0.3%)	25 (0.4%)	3 (0.3%)
	<i>Other</i>	47 (0.4%)	23 (0.4%)	15 (0.2%)	1 (0.1%)
<i>Fallen in past year?</i>	<i>Yes</i>	2186 (19.9%)	1700 (27.2%)	1744 (28.0%)	295 (33.0%)
<i>Broken bone since 50?</i>	<i>Yes</i>	1859 (17.0%)	1463 (23.4%)	1399 (22.4%)	409 (46.0%)
<i>Parents broken hip?</i>	<i>Yes</i>	536 (5.3%)	577 (9.2%)	585 (9.4%)	354 (41.6%)
<i>Smoker?</i>	<i>Yes</i>	826 (7.4%)	290 (4.6%)	290 (4.7%)	86 (9.6%)
<i>Alcohol units ≥3/day?</i>	<i>Yes</i>	383 (3.4%)	225 (3.6%)	219 (3.5%)	60 (6.7%)
<i>Glucocorticoid Use?</i>	<i>Yes</i>	--	312 (5.0%)	316 (5.1%)	113 (13.3%)
<i>Rheumatoid Arthritis?</i>	<i>Yes</i>	--	410 (6.6%)	426 (6.8%)	79 (9.3%)
<i>Secondary Causes of OP?</i>	<i>Yes</i>	--	1408 (22.5%)	1483 (23.8%)	267 (29.7%)
<i>Age (at response)</i>	<i>Mean (SD)</i>	76.8 (5.84)	75.5 (4.14)	75.4 (4.16)	77.2 (4.40)
<i>BMI</i>	<i>Mean (SD)</i>	26.1 (4.90)	26.7 (4.75)	26.7 (4.71)	24.4 (4.06)
<i>FRAX 10 year HIP</i>	<i>Mean (SD)</i>	--	8.5% (7.3%)	8.5% (7.4%)	17.9% (10.9%)
<i>Fracture Probability²</i>					
<i>FRAX 10 year Major OP</i>	<i>Mean (SD)</i>	--	19.3% (8.8%)	19.3% (8.9%)	30.0% (10.7%)
<i>Fracture Probability²</i>					

1: Percentages are of those providing a non-missing answer.

3: Prior to BMD results.

3: Based on the National Readership Survey (NRS) grading : I : higher managerial or professional; II : intermediate managerial or professional; IIIN : Non-manual skilled workers; IIIM : Manual skilled workers; IV : Semi-skilled workers; V: unskilled or casual workers

Table 2 : Baseline Characteristics

	<i>Control</i> (N=6250)	<i>Screening</i> (N=6233)	<i>Hazard Ratio</i> ¹ (95% C.I.)
<i>OP-Related</i>			
No Fracture	5398	5428	
Fracture	852 (13.6%)	805 (12.9%)	0.94 (0.85 , 1.03) p=0.178
<i>Hips</i>			
No Fracture	6032	6069	
Fracture	218 (3.5%)	164 (2.6%)	0.72 (0.59 , 0.89) p=0.002
<i>All Clinical</i>			
No Fracture	5248	5282	
Fracture	1002 (16.0%)	951 (15.3%)	0.94 (0.86 , 1.03) p=0.183
<i>Mortality</i>			
Survive	5725	5683	
Died	525 (8.4%)	550 (8.8%)	1.05 (0.93 , 1.19) p=0.436

1: Adjusted for Recruiting Region, Baseline FRAX Probability and Falls.

Table 3 : Efficacy Outcomes. All clinical fractures included all osteoporosis (OP)-related fractures as well as fractures of the hands, feet, ankle, face and skull.

	<i>Low Risk (N=5088)</i>	<i>High Risk (N= 898)</i>	<i>Control (N=6250)</i>	<i>Estimated Difference¹</i>	<i>p-value²</i>
<i>Baseline</i>	10.1 (3.65)	10.5 (3.73)	10.2 (3.68)	-	-
<i>6 Months</i>	10.2 (3.78)	10.2 (3.74)	10.2 (3.67)	0.045	0.961
<i>12 Months</i>	10.2 (3.71)	10.3 (3.91)	10.2 (3.70)	-0.085	0.809
<i>24 Months</i>	10.2 (3.71)	10.4 (3.76)	10.2 (3.76)	-0.154	0.562
<i>36 Months</i>	10.3 (3.73)	10.5 (3.87)	10.3 (3.73)	-0.081	0.756
<i>48 Months</i>	10.4 (3.78)	10.4 (3.68)	10.4 (3.75)	-0.093	0.647
<i>60 Months</i>	10.5 (3.83)	10.6 (3.70)	10.4 (3.81)	-0.184	0.226
			<i>Repeated Measures Analysis</i>	<i>Group³ Group*Time⁴</i>	0.515 0.942

1: Control – High Risk, adjusted for Recruiting Region, Age and Baseline STAI.

2: Test of any group difference

3: Repeated Measures ANOVA test of between group difference

4: Repeated Measures ANOVA test of group by time interaction

Table 4 : State-Trait Anxiety Inventory (Short Form) over five years follow-up, Mean (SD). This scale ranges from 6 to 24, with lower scores indicating lower levels of anxiety.

	<i>Intervention (N=6233)</i>	<i>Control (N=6251)</i>	<i>Estimated Difference¹</i>	<i>p-value²</i>
<i>Baseline</i>	0.74 (0.24)	0.74 (0.23)	-	-
<i>6 Months</i>	0.74 (0.24)	0.74 (0.24)	-0.003	0.394
<i>12 Months</i>	0.74 (0.25)	0.73 (0.25)	-0.010	0.020
<i>24 Months</i>	0.71 (0.27)	0.72 (0.26)	-0.003	0.537
<i>36 Months</i>	0.68 (0.29)	0.69 (0.28)	-0.006	0.273
<i>48 Months</i>	0.67 (0.31)	0.66 (0.30)	-0.008	0.154
<i>60 Months</i>	0.63 (0.33)	0.63 (0.32)	-0.003	0.642
		<i>Repeated Measures Analysis</i>	<i>Group³ Group*Time⁴</i>	0.154 0.586

1: Control – Intervention, adjusted for Centre, Age and Baseline EQ-5D

2: Test of group difference

3: Repeated Measures ANOVA test of between group difference

4: Repeated Measures ANOVA test of group by time interaction

Table 5 : EQ-5D over five years follow-up (Deaths imputed to zero).

	<i>Intervention (N=6233)</i>	<i>Control (N=6250)</i>	<i>Estimated Difference¹</i>	<i>p-value²</i>
<i>Baseline</i>	45.0 (10.5)	45.3 (10.2)	-	-
<i>6 Months</i>	44.8 (10.8)	44.8 (10.7)	-0.26	0.087
<i>12 Months</i>	44.5 (11.3)	44.6 (11.3)	-0.23	0.182
<i>24 Months</i>	43.0 (12.7)	43.3 (12.4)	-0.06	0.753
<i>36 Months</i>	41.6 (14.1)	41.7 (13.9)	-0.22	0.349
<i>48 Months</i>	40.1 (15.5)	40.1 (15.3)	-0.26	0.317
<i>60 Months</i>	38.3 (16.7)	38.3 (16.6)	-0.20	0.481
		<i>Repeated Measures Analysis</i>	<i>Group³ Group*Time⁴</i>	0.237 0.881

1: Control – Intervention, adjusted for Centre, Age and Baseline SF-12.

2: Test of group difference

3: Repeated Measures ANOVA test of between group difference

4: Repeated Measures ANOVA test of group by time interaction

Table 6(a): SF-12(Physical Health) over five years follow-up (Deaths imputed to zero).

	<i>Intervention (N=6233)</i>	<i>Control (N=6250)</i>	<i>Estimated Difference¹</i>	<i>p-value²</i>
<i>Baseline</i>	53.1 (8.5)	53.1 (8.5)	-	-
<i>6 Months</i>	52.4 (9.5)	52.2 (9.5)	-0.24	0.164
<i>12 Months</i>	51.8 (10.3)	51.6 (10.3)	-0.17	0.382
<i>24 Months</i>	50.8 (12.3)	51.1 (11.9)	0.29	0.210
<i>36 Months</i>	49.4 (14.3)	49.6 (14.3)	0.07	0.805
<i>48 Months</i>	47.9 (16.4)	47.9 (16.3)	0.19	0.535
<i>60 Months</i>	46.0 (18.3)	46.3 (18.2)	0.56	0.103
		<i>Repeated Measures Analysis</i>	<i>Group³ Group*Time⁴</i>	0.554 0.056

1: Control – Intervention, adjusted for Centre, Age and Baseline SF-12.

2: Test of group difference

3: Repeated Measures ANOVA test of between group difference 4:

Repeated Measures ANOVA test of group by time interaction

Table 6(b): SF-12(Mental Health) over five years follow-up (Deaths imputed to zero).