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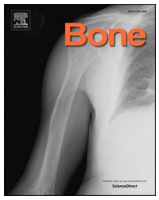

Full Length Article

Real-world effectiveness of osteoporosis screening in older Swedish women (SUPERB)

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ABSTRACT

Summary: Older women diagnosed with osteoporosis and referred to their general practitioners (GPs) exhibited significantly higher osteoporosis treatment rates and a reduced fracture risk compared to non-osteoporotic women who were not referred to their GPs.

Objective: The objective of this study was to investigate treatment rates and fracture outcomes in older women, from a population-based study, 1) diagnosed with osteoporosis, with subsequent referral to their general practitioner (GP), 2) women without osteoporosis, without referral to their GP.

Methods: In total, 3028 women, 75–80 years old were included in the SUPERB cohort. At inclusion, 443 women were diagnosed with osteoporosis (bone mineral density (BMD) T-score ≤ -2.5) at the lumbar spine or hip, did not have current or recent osteoporosis treatment, and were referred to their GP for evaluation (referral group). The remaining 2585 women without osteoporosis composed the control group. Sensitivity analysis was performed on subsets of the original groups. Adjusted Cox regression (hazard ratios (HR) and 95 % confidence intervals (CI)) analyses were performed to investigate the risk of incident fractures and the incidence of osteoporosis treatment.

Results: Cox regression models, adjusted for age, sex, body mass index (BMI), smoking, alcohol, glucocorticoid use, previous fracture, parent hip fracture, secondary osteoporosis, rheumatoid arthritis, and BMD at the femoral neck, revealed that the risk of major osteoporotic fracture was significantly lower (HR = 0.81, 95 % CI [0.67–0.99]) in the referral group than in the controls. Similarly, the risk of hip fracture (HR = 0.69, [0.48–0.98]) and any fracture (HR = 0.84, [0.70–1.00]) were lower in the referral group. During follow-up, there was a 5-fold increase (HR = 5.00, [4.39–5.74]) in the prescription of osteoporosis medication in the referral group compared to the control group.

Conclusion: Screening older women for osteoporosis and referring those with osteoporosis diagnosis was associated with substantially increased treatment rates and reduced risk of any fracture, MOF, and hip fracture, compared to non-osteoporotic women.

1. Introduction

Osteoporosis and fragility fractures represent significant public health challenges on a global scale. Annually >8.9 million fractures are attributed to osteoporosis worldwide [1]. Sweden has among the highest incidences of osteoporotic fractures per year worldwide, and in 2019 approximately 124.000 fragility fractures were estimated, with an expected 30 % increase by 2034 [2].

Every fracture could cause devastating consequences for the individual resulting in disability, impaired quality of life, chronic pain, and an elevated risk of mortality especially following hip and vertebral fractures [3–5]. Moreover, osteoporosis places a substantial burden on

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healthcare systems depleting important economic and human resources. The annual cost of osteoporosis is estimated at 57 billion € in EU27 + 2 countries [2]. Despite that effective treatments have been available for several decades, only a fraction of this cost is allocated to disease prevention [6]. For instance, previous studies have demonstrated that zoledronic acid can reduce the risk of vertebral fractures by approximately 70 % after just 2 years of treatment [7]. Another potent antiresorptive agent, denosumab, not only mitigates fracture risk but also induces significant increases in bone mineral density (BMD) over time [8–10]. Furthermore, with modern osteoanabolic agents, the effect on bone density and fracture risk reduction is even greater [11] yet the majority of the treatment arsenal is left unused [11–15].

Alarmingly, data from the STORM study cohort, representing a quarter of the Swedish population, revealed that only 10 % of patients received antiresorptive treatment within 1 year after a fragility fracture [16]. Similar results from the SUPERB cohort indicate that only 22 % of women 75–80 years with treatment indication received osteoporosis medication [17]. Similar findings that revealed considerable treatment gaps in other settings have been published previously [18–20]. The diagnosis of osteoporosis has proven effective in narrowing the treatment gap, emphasizing its critical role in mitigating this issue [20].

The available diagnostic methods and tools for predicting fractures, such as bone densitometry by dual-energy x-ray absorptiometry (DXA) and the fracture risk assessment tool FRAX, have demonstrated their effectiveness in identifying individuals at risk for osteoporotic fractures [21–23]. However, despite their proven utility, these approaches remain vastly underutilized [24,25]. To bridge the treatment gap, various strategies aimed at enhancing both primary and secondary prevention have been suggested and put into practice. The implementation of health care pathways or Fracture Liaison Services (FLS) has significantly enhanced secondary prevention, especially in identifying individuals at high fracture risk who urgently require osteoporosis treatment [26,27].

Strategies aiming at primary prevention, such as screening older adults for high fracture risk using the FRAX tool, have been shown to reduce the risk of hip fracture as demonstrated in a recent meta-analysis [28]. However, this approach has faced scrutiny from various publications, national and international committees, and guidelines. The debate on screening effectiveness has oscillated between those questioning its utility [29–31] and those advocating for its adoption [32–34]. A comprehensive review of recent randomized studies concludes that screening indeed offers benefits in reducing hip fracture incidence [35].

The present study aimed to investigate whether osteoporosis screening is associated with increased treatment rates and reduced fracture incidence in selected women from the SUPERB cohort.

2. Methods

2.1. Study subjects

Recruitment for the (SUPERB) **S**ahlgrenska **U**niversity Hospital **P**rospective **E**valuation of **R**isk of **B**one Fractures was performed between 2013 and 2016 in Gothenburg, Sweden. The main aim of the SUPERB study was to identify risk factors for fragility fractures. Using data from the Swedish national population register, 6832 women aged 75–80 from the greater Gothenburg area were randomly identified and asked to participate in the study. To be able to participate, women needed to be ambulant, understand Swedish, and have at least one hip that could be evaluated by DXA. Out of 6832 women, 3368 either declined or did not respond and 436 met any exclusion criteria, resulting in a total of 3028 individuals included in the SUPERB study.

The study protocol was approved by the Regional Ethics Review Board (ERB) in Gothenburg and all participants signed an informed consent before participating in the study.

2.2. Intervention

In accordance with the ERB, participants with potentially serious incident findings such as DXA verified osteoporosis ($n = 443$) at the lumbar spine or the total hip (T-score ≤ -2.5) were referred to their general practitioner (GP) for further assessments, general medical advice, and potential medical treatment. The referral process included the DXA report with BMD and T-score values as well as FRAX probabilities for MOF and hip fracture, with a recommendation for further evaluation and potentially initiating osteoporosis treatment, if deemed appropriate. However, the final decision regarding treatment initiation was at the discretion of GP and the patient, enabling individualized medical care. The referrals were sent out to 88 different primary care clinics in the greater Gothenburg area, covering most primary care clinics in the catchment area.

Participants who were referred to their GPs for further assessments were considered as the referral group. The remaining 2585 women without osteoporosis (T-score > -2.5), not referred to a GP composed the main control group (Fig. 1).

2.3. Sensitivity analysis

Due to the substantial differences in BMD, FRAX 10-year probabilities, and current treatment rates between groups in the main analysis, sensitivity analyses were also performed investigating 1) untreated osteoporotic women who were referred to the GP (having a T-score ≤ -2.5 at the lumbar spine or the total hip ($n = 411$)) and 2) women without osteoporosis treatment who were not referred to a GP (having BMD-values at the lumbar spine or total hip, indicating low BMD (T-score of greater than -2.5 and lower than -2.3; $n = 217$) (Fig. 1)).

2.4. Eligibility for treatment

Using the recently issued Swedish Osteoporosis Society (SvOS) clinical osteoporosis guidelines (2021 edition, [36]) treatment eligible women at baseline were identified. The SvOS guidelines recommends osteoporosis treatment in individuals with.

(1) previous hip or spine fracture related to osteoporosis, (2) osteoporosis T-score ≤ -2.5 and a FRAX-score ≥ 20 % without a prevalent osteoporotic fracture, (3) low BMD (T-score ≤ -1.0), other (than spine or hip) prevalent fracture and a FRAX-score ≥ 20 % for a MOF, or (4) 5 mg of daily oral glucocorticoid treatment >3 months, in combination with another risk factor (age > 65 years, previous fracture or osteopenia).

2.5. Anthropometrics

Body height was measured twice with a standardized wall-mounted stadiometer. A third measurement was obtained if the two height measurements differed by ≥ 5 mm, the mean was used in the analysis. Body weight was measured to the nearest 0.1 kg using the same standardized scale in all women.

2.6. Questionnaires on medical history and physical activity

Information regarding medical history, clinical risk factors, fracture, smoking, parental history of hip fracture, oral glucocorticoid use, diabetes, rheumatoid arthritis, and high alcohol consumption were assessed using a validated questionnaire [37]. Self-reported fractures sustained after the age of 50 years and at any location, except the skull and face, were included in the FRAX-score calculations. Medical history including prior or current treatment was also assessed by questionnaires. The Physical Activity Scale for the Elderly (PASE) was used to estimate physical activity in the last 7 days before inclusion [38].

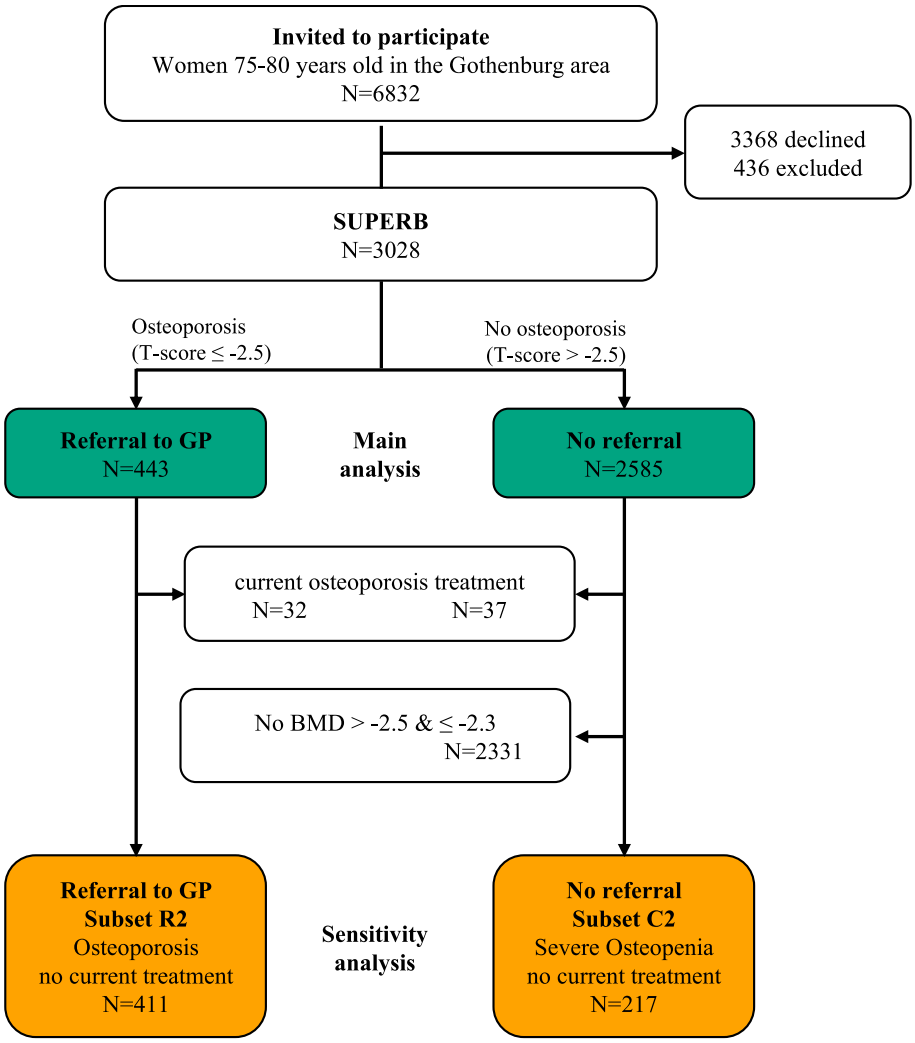

Fig. 1. Study population flow-chart.

2.7. Bone densitometry and vertebral fracture assessment

The same DXA device (Hologic discovery, Hologic, Waltham, MA, USA) was used on most subjects (n = 2995) to acquire information regarding areal BMD (aBMD) (femoral neck, total hip, lumbar spine L1-L4). Another 33 women were examined with a Hologic QDR 4500/A Delphi DXA (Waltham, MA, USA). Cross-calibration between the two machines was performed and has been described previously [17]. Trabecular bone score (TBS) was calculated using the mean of L1 to L4, excluding fractured vertebrae.

Vertebral fractures were identified with the use of lateral scans by DXA and graded using the semi-quantitative classification of Genant [39]. Vertebral fracture assessment (VFA) was performed by two experienced physicians as described in previous publications [40–42]. VFA reproducibility had an intra-observer agreement of 98.9 % for all vertebral fractures and 100 % for moderate to severe vertebral fractures.

2.8. Incident fractures, injurious falls, mortality, and osteoporosis medication

The regional x-ray archives for the Västra Götaland region were assessed from baseline (March 2013 to April 2016) until November 2022 to March 2023 to retrieve data on incident fractures. All radiology reports were reviewed and in cases with a missing report, an experienced orthopedic (LJ) surgeon was consulted to determine the existence of a fracture. Incident fractures were categorized as 1) major osteoporotic fracture (MOF; including hip, lumbar spine, wrist, or proximal humerus), 2) any type of fracture (excluding those of the skull, fingers, and toes), and 3) hip fracture. Incident injurious falls were identified using the national Patient register using ICD-10 codes for a non-skeletal fall injury resulting in a hospital visit or admission (W00-W19 code and a S00-T14 diagnosis, but not a simultaneous fracture code). Mortality data were obtained from the regional population registry (Västfolket). Data on osteoporosis medication were retrieved from the National Prescribed Drug Register. The follow-up time for injurious falls and osteoporosis medication ended on December 31st 2021.

2.9. Statistical analysis

Independent samples t-test was used to investigate differences between groups regarding continuous variables. For dichotomous variables, $\chi 2$ and Fisher exact tests were used. Values are presented as mean ± SD for continuous variables and number together with the percentage of participants for dichotomous variables unless stated otherwise.

Cox proportional hazards models were used to investigate the association between groups (referral to GP and control group) and incidence of fractures, injurious falls, death, and the prescription of osteoporosis medication. Multivariable Cox models were adjusted for age, body mass index (BMI), clinical risk factors (CRFs) included in FRAX (previous fracture, parental hip fracture, smoking, alcohol consumption,

glucocorticoids, rheumatoid arthritis, secondary osteoporosis, and femoral neck BMD). Stepwise backward logistic regression was performed to assess variables that were associated with incident osteoporosis medication.

Fine and Gray analysis considering the competing risk of death was used to investigate associations between the group variable (referral and control group) and incident fractures. Out of the whole cohort (n = 3028), 212 (7.0 %) women had 259 missing data points in clinical risk factors variables: premature menopause (n = 151), hyperthyroidism (n = 6), chronic liver disease (n = 9), diabetes mellitus (n = 3) inflammatory bowel disease (n = 11), previous fractures (n = 9), parental hip fractures (n = 49), smoking (n = 4), glucocorticoids (n = 7), rheumatoid arthritis (n = 7) and alcohol use (> 21 units/week; n = 3). Statistical imputation using the MICE package in R-studio (Multivariate imputation by Chained Equations) was utilized for missing clinical risk factors in FRAX using a single imputation with 10 iterations. In addition to the fracture outcomes, all the other CRFs were included in the imputation. For all statistical analyses, a P value <0.05 was considered significant. Statistical analyses were performed with SPSS Statistics Version 25 and RStudio (RStudio, Inc., Boston, MA).

3. Results

3.1. Baseline characteristics

In the referral group, women were slightly older (0.2 %, p = 0.05), had a lower body weight (11 %, p < 0.01) and height (1.1 %, p < 0.01), and had a higher frequency of prior osteoporosis medication use (9.5 % vs 6.7 %, p = 0.04) compared to controls. Additionally, prevalent fractures were more common among women with osteoporosis (43.8 % vs. 35.7, p = 0.04), but no difference between groups were seen for prevalence of VFA identified vertebral fracture or severity of vertebral fracture (Table 1). The FRAX 10-year probabilities with or without FN-BMD adjustments were also higher in the referred women compared to the controls (Table 1).

3.2. T-scores, TBS and VFA-identified vertebral fractures at baseline

The referral group had significantly lower BMD T-scores at the lumbar spine (−126.3 %, p < 0.01), total hip (−71 %, p < 0.01), and femoral neck (−46.5 %, p < 0.01), as well as lower TBS (−7.7 %%, p < 0.01) than the control group (Table 1). There was no significant difference in the prevalence of a VFA-verified vertebral fracture between the groups (25.6 % vs. 23.9 %, p = 0.46).

3.3. Incident osteoporosis medication

During a median, 6.6-year follow-up period (with an interquartile range IQR of 5.7–7.3 years), 330 (74.5 %) women in the referral group were prescribed medication for osteoporosis, compared to 694 (26.8 %) in the control group. The incidence of prescription was 5 times higher in the intervention group than in the controls (Hazard Ratio (HR) 5.00, 95 % confidence interval (CI) 4.39–5.74). Multivariate adjustments for age, BMI, CRFs, and FN-BMD did not materially change this association (HR 3.45, 95 % CI 2.97–4.02) as shown in Table 2. The most common prescription for both groups was oral bisphosphonates, in particular alendronate accounted for 94.2 % of all prescriptions in the referral group and 77.1 % in the non-referral group as shown in Supplemental Table S1. In those starting alendronate treatment, medication adherence in the short term was high, with 85.5 % collecting a further prescription of alendronate or switching directly to another treatment option in the referral group. The corresponding proportion in the non-referral group was 86.2 %. Those receiving incident osteoporosis medications in the non-referral group had a higher prevalence of oral glucocorticoid use, previous fracture, a high FRAX MOF score, a low BMI, and rheumatoid arthritis. Furthermore, women with any incident fracture were more likely to receive osteoporosis medication during follow-up (HR 3.18, 95 % CI 2.66–3.81; Supplemental Table S2).

3.4. Association between referred and incident fractures

During a median, [IQR] follow-up period of 7.3 [4.4–8.4] years, 179 (40.4 %) women had a fracture in the referral group and 904 (35 %) in the control group (Table 2). A higher percentage of MOF was observed in the referral group (30.9 %, 137 fractures) than in the control group (26 %, 671 fractures). Likewise, more hip fractures (43, 9.5 %) were observed in the referral group than in the control group (195, 7.5 %). In unadjusted Cox regression models, referral was associated with a statistically significant increased risk of any fracture (HR 1.18, 95 % CI 1.01–1.39) and MOF (HR 1.21, 95 % CI 1.01–1.45). For hip fracture, this association was non-significant (HR 1.29, 95 % CI 0.93–1.80). Using fully adjusted Cox regression models including adjustments for FN-BMD the associations changed significantly and a reduction in relative fracture risk was observed instead: any fracture (HR 0.84, 95 % CI 0.70–1.00), MOF (HR 0.81, 95 % CI 0.67–0.99), hip fracture (HR 0.69, 95 % CI 0.48–0.98) as shown in Table 2 and Fig. 2. Similar associations were found when considering the competing risk of death using Fine and Gray models (Supplement Table S3).

An additional Cox model, with adjustment only for clinical risk factors differing between groups (in Table 1), found similar results as in the main analyses (Supplemental Table S4).

3.5. Mortality

During the follow-up period, there was no significant difference in mortality between the referral and control groups. Specifically, 87 (19.6 %) occurred in the referral group, compared to 480 (18.6 %) deaths in the control group, unadjusted (HR 1.05, 95 % CI 0.84–1.32). These associations were also non-significant in a fully adjusted Cox regression model (HR 0.94, 95 % CI 0.74–1.21; Table 2).

3.6. Incident injurious falls

Referral was not significantly associated with incident injurious falls without fracture (HR 0.99, 95 % CI 0.78–1.27), regardless of statistical adjustment (Table 2).

3.7. Sensitivity analysis

3.7.1. Study subsets

Sensitivity analysis was conducted on women without current osteoporosis treatment at baseline, divided into 2 groups: 1) The referral group (R2) with 411 women who were referred due to presence of osteoporosis (T-score ≤ −2.5) at the lumbar spine or the total hip, and 2) the control group (C2), consisting of *217* women (C2) who were not referred to a GP. The latter group was selected based on low BMD (T-score of greater than −2.5 and lower than −2.3 at the total hip or lumbar spine).

3.7.2. Baseline characteristics

In the R2 group, women had a 3.6 % lower body weight (p = 0.01) and reported more prevalent fractures 43.1 % vs. 34.6, respectively (p = 0.04) than women in the C2 group. Previous treatment with osteoporosis medication was more common in the C2 group (14.7 % vs. 10.2 %, p = 0.04) compared with the R2 group (Supplement Table S5).

3.7.3. Incident fractures

In the osteoporotic and referred to GP subset (R2), there was a lower incidence of MOF compared to the control group (C2) (29.9 % vs. 38.7 %, p = 0.03). Similarly, incident any and hip fractures were less common in the R2 group than in the C2 group (39.2 %) vs. (46.5 %) and (10.5 %) vs. (13. 8 %), respectively, but these differences were, not statistically

Table 1
Baseline characteristics.

	No referral N = 2585	Referral to GP n = 443	p-value
Age (years)	77.76 ± 1.62	77.92 ± 1.66	0.05
Weight (kg)	69.8 ± 12.2	62.5. ± 9.6	<0.01
Height (cm)	162.1 ± 58.5	160.3 ± 77.0	<0.01
BMI (kg/m^2)	26.6 ± 4.9	24.3 ± 3.5	<0.01
Previous fracture	923(35.7)	194(43.8)	0.04
Parental hip fracture	448(17.3)	85(19.2)	0.34
Prevalent vertebral fracture*	596(23.9)[a]	110(25.6)[b]	0.46
Vertebral fracture grade 1	302(13.7)	54 (14.4)	0.71
Vertebral fracture, grade 2–3	282 (12.9)	58(15.3)	0.20
Smoking	131(5.1)	27(6.1)	0.36
Oral glucocorticoids	91(3.5)	12(2.7)	0.48
Rheumatoid arthritis	106(4.1)	14(3.2)	0.43
Secondary osteoporosis**	698(27.0)	89(20.1)	0.02
Excessive alcohol intake	16(0.6)	1(0.2)	0.49
PASE-score	103.6 + 50.9[c]	105.9 ± 50.1[d]	0.37
T-score femoral neck	−1.5 ± 0.8[c]	−2.41 ± 0.6	<0.01
T-score total hip	−1.0 ± 0.9[c]	−2.1 ± 0.7	<0.01
T-score lumbar spine	−0.63 ± 1.4[e]	−2.79 ± 0.9[f]	<0.01
FRAX® MOF w/o BMD	33.0 ± 13.1	36.2 ± 13.2	<0.01
FRAX® MOF w BMD	21.6 ± 10.9	31.4 ± 13.7	<0.01
FRAX® Hip w/o BMD	20.0 ± 13.4	23.1 ± 14.3	<0.01
FRAX® Hip w BMD	9.9 ± 10.1	18.2 ± 14.0	<0.01
TBS	1.22 ± 0.1[g]	1.13 ± 0.1[h]	<0.01
Previous osteoporosis treatment	174(6.7)	42(9.5)	0.04
Current osteoporosis treatment	288(11.2)	32(7.2)	<0.01
Osteoporosis diagnosis***	514(19.9)	102(23)	0.13

Cohort characteristics for continuous variables are presented either as means and standard deviations (SD) or n and (%) for dichotomous variables. Significant *p*-values are shown in bold. BMI = body mass index; PASE = physical activity scale for the elderly; MOF = major osteoporotic fracture. Oral glucocorticoid use for 3 months or more with daily 5 mg of prednisolone or equivalent = yes. Information on previous and current osteoporosis treatment was obtained from a questionnaire at baseline. BL = baseline. GP = General practitioner. TBS = Trabecular bone score. FRAX MOF and hip scores are shown calculated with and without femoral neck BMD.

* Secondary osteoporosis includes insulin-dependent diabetes mellitus, hyperparathyroidism, hyperthyroidism, chronic liver disease, malnutrition, premature menopause.

** Verified by vertebral fracture assessment (VFA).

*** Self-reported osteoporosis diagnosis.

[a] $N = 2493$,
[b] $N = 430$,
[c] $N = 2572$,
[d] $N = 442$,
[e] $N = 2570$,
[f] $N = 440$,
[g] $N = 2560$,
[h] $N = 441$.

significant ($p = 0.07$ and $p = 0.21$, respectively).

In unadjusted Cox regression models, referral of untreated osteoporotic women was associated with a statistically significant reduced risk of any fracture (HR 0.76, 95 % CI 0.59–0.98), and MOF (HR 0.69, 95 % CI 0.52–0.91); Table 3). The Hazard Ratio for hip fracture became significant only in fully adjusted models (HR 0.49, 95 % CI 0.30–0.82).

The observed associations between referral, any fracture, and MOF were not materially changed using fully adjusted models (Table 3).

When considering death as a competing risk using Fine and Gray models, highly similar associations between referral and fracture risk were observed (Supplement Table S3).

3.7.4. *Incidence of osteoporosis medication prescriptions*

The incidence of osteoporosis medication prescriptions was over 4 times higher in the referral group (R2) than in the control group (C2), HR 4.24, 95 % CI (3.27–5.51), as indicated in Table 3 and Supplement Fig. 1. Also, after multivariate adjustments for CRFs, and BMD of the femoral neck this association remained consistent (HR 4.21, 95 % CI 3.23–5.49). Notably, the incidence of prescription of osteoporosis medication during the first year of the follow-up period was considerably higher in the referral group (R2) compared to the control group (C2), HR 17.10, 95 % CI (9.70–29.90).

3.7.5. *Injurious falls*

Referral did not show a statistically significant association with the incidence of injurious falls without fracture (HR 0.92, 95 % CI 0.61–1.37), also after accounting for statistical adjustments (Table 3).

3.8. *Treatment eligibility*

Out of the whole cohort of 3028 women, 1397 individuals (46.1 %) were identified having treatment indication according to the most recent SvOS guidelines (2021 edition, [36]). Treatment eligibility was most commonly due to presence of osteopenia in combination with prevalent fracture and a FRAX MOF probability above 20 % ($n = 815$), or due to a VFA-identified vertebral fracture ($n = 706$) or having osteoporosis with a FRAX MOF score above 20 % without previous fragility fractures ($n = 179$).

Treatment eligible women had considerably lower BMD and higher 10-year FRAX probabilities for fracture than ineligible women (Supplemental Table S6). Eligible women were older, taller and weighed less than the controls, and had a higher prevalence of most CRFs included in FRAX. However, no significant group-to-group differences were found for smoking, alcohol use, or rheumatoid arthritis prevalence. Similarly, a lower PASE score was observed in those eligible for treatment. Only 400 (28.7 %) had current or previous osteoporosis treatment.

Adjusted Cox regression models demonstrated that those eligible for treatment had a higher risk of any fracture (HR 1.38 95 % CI, (1.14–1.57)) and MOF (HR 1.35 95 % CI, (1.12–1.62) than ineligible (Supplemental Table S7).

4. Discussion

We observed that older women diagnosed with osteoporosis based on DXA (WHO criteria BMD T-score of −2.5 or less) when entering the SUPERB study and subsequently referred to their GP for evaluation and consideration of osteoporosis treatment, were significantly more likely to receive osteoporosis medications and less likely to experience fractures than controls who were not referred.

Cox regression models adjusted for multiple variables including femoral neck BMD revealed a reduced hazard ratio for any fracture and MOF in the referral group when compared to non-osteoporotic women. To account for the substantial BMD differences between osteoporotic women and controls in the main analysis, we conducted a sensitivity analysis comparing women with osteoporosis to women with low BMD with T-score values close to osteoporosis. As expected and similar to the main analysis, the prescription of osteoporosis medication in the sensitivity analysis was markedly higher, and the risk of any fracture, MOF, and hip fracture was significantly lower in the referral group than in the control group with low BMD. These findings strongly support the usefulness of population screening using DXA to increase treatment rates and reduce fractures in older women.

Despite its significant impact and serious consequences [4], osteoporosis remains largely underdiagnosed and undertreated [2,17]. Within this cohort, only 16.7 % percent of women with BMD criteria of osteoporosis had current or previous osteoporosis treatment.

Although, universal acceptance of screening as a necessity for fracture risk reduction has not been achieved [30,31,43], expert groups in the United States and Canada such as the US Preventive Services Task Force (USPSTF) [25,44] and the Canadian Osteoporosis Society [45] recommend DXA assessment in postmenopausal women 65 years and

Table 2
Association between referral, fracture risk, osteoporosis medication and mortality.

	No referral (no osteoporosis) n = 2585	Referral to GP (osteoporosis) n = 443	*p-value*
Time at risk, years (IQR)	7.3 (4.4–8.4)	7.3 (4.4–8.4)	
Any fracture			
No. (%)	904 (35 %)	179 (40.4 %)	
HR, unadjusted	1 (Reference)	1.18 (1.01–1.39)	0.04
HR, adjustment model 1	1 (Reference)	0.83 (0.70–0.99)	0.04
HR, adjustment model 2	1 (Reference)	0.84 (0.70–1.00)	0.05
Major osteoporotic fracture			
No. (%)	671 (26.5 %)	137 (30.9 %)	
HR, unadjusted	1 (Reference)	1.21 (1.01–1.45)	0.05
HR, adjustment model 1	1 (Reference)	0.81 (0.66–0.99)	0.04
HR, adjustment model 2	1 (Reference)	0.81 (0.67–0.99)	0.04
Hip fracture			
No. (%)	195 (7.5 %)	43 (9.5 %)	
HR, unadjusted	1 (Reference)	1.29 (0.93–1.80)	0.12
HR, adjustment model 1	1 (Reference)	0.69 (0.48–0.98)	0.04
HR, adjustment model 2	1 (Reference)	0.69 (0.48–0.98)	0.04
Death			
No. (%)	480 (18.6 %)	87 (19.6 %)	
HR, unadjusted	1 (Reference)	1.05 (0.84–1.32)	0.67
HR, adjustment model 1	1 (Reference)	0.94 (0.74–1.21)	0.64
Injurious falls			
Time at risk (years)	6.6 (5.7–7.3)	6.6 (5.8–7.3)	
No. (%)	438 (16.9)	75 (16.9 %)	
HR, unadjusted	1 (Reference)	0.99 (0.78–1-27)	0.96
HR, adjustment model 1	1 (Reference)	0.93 (0.71–1.21)	0.58
Prescription of incident osteoporosis medication			
No. (%)	694 (26.8 %)	330 (74.5 %)	
HR, unadjusted	1 (Reference)	5.00 (4.39–5.74	<0.001
HR, adjustment model 1	1 (Reference)	3.45 (2.97–4.02)	<0.001

Hazard Ratios (HR) and 95 % Confidence Intervals are presented.
Model 1 = Multivariable adjustment for age, sex, BMI, smoking, alcohol, glucocorticoid use, previous fracture, parent hip fracture, secondary osteoporosis, rheumatoid arthritis, and BMD at the femoral neck.
Model 2 = Model 1 + Adjustment for previous treatment with osteoporosis medications.

older.

The current strategies aiming to minimize the diagnostic and treatment gap, such as secondary prevention programs (FLS) have been previously proven effective [26]. Nevertheless, they also bear some limitations. FLSs primarily focus on secondary fracture prevention services but they do not address primary fracture prevention. In contrast, screening could serve as a valuable method to identify individuals who have not experienced previous fractures but still require fracture preventive strategies, monitoring, or treatment. Recent studies indicate that even when patients are referred to a GP within the context of an FLS, the necessary treatment is not always initiated, especially in cases of low provision (type D FLSs), which solely informs the patients on the DXA results, resulting in a meager 8 % treatment rate after a fracture [46]. This underscores the importance of adopting a comprehensive approach where screening or FLS encompasses risk assessment, DXA examination for evaluation, and finally targeted interventions using osteoporosis medications.

In various domains, preventive medicine remains in its infancy, but new diagnostic and preventive modalities in modern medicine are constantly emerging. These innovations, including cutting-edge technologies like artificial intelligence with deep learning diagnostic models [47,48], and genetic risk scores have demonstrated promising results [49,50]. Looking ahead to a future focused on primary prevention, the integration of DXA screening with such innovative techniques could potentially enhance our ability to identify at-risk individuals and implement targeted interventions.

This study possesses important strengths but also limitations. While the SUPERB-cohort is population-based, it is worth noting that the included women may have opted to participate due to existing risk factors and heightened concern about bone health and fracture risk. This may have introduced a selection bias and even impacted the adherence to osteoporosis treatment at a later stage. In this study, the inclusion rate was 47.4 %, comparable to the 45 % in the Swedish MrOs cohort [37], higher than what was observed in the SCOOP screening study but lower than in the ROSE study [32–34]. The extensive testing program, involving multiple methods to measure skeletal characteristics, blood drawing, and time-consuming questionnaires and physical function tests, may have contributed to a lower participation rate than in the ROSE screening study, which included younger individuals and considerably less extensive testing procedures [32–34].

Although referral resulted in a significant increase in the use of osteoporosis medication, our study does not offer a conclusive causal explanation for the observed reduction in fracture risk. Nevertheless, it appears highly plausible that greater utilization of osteoporosis medication would indeed lead to fewer fractures. We cannot rule out that the osteoporosis diagnosis also led to behavioural changes that consecutively precipitated a reduction of fracture risk. However, the lack of association between referral and injurious falls without fracture, argues against an effect of referral on behaviour changes, as well as against selection bias in the group selection. The lack of association between referral, death and injurious falls without fracture, further supports the notion that the lower fracture risk observed in those referred is not influenced by reduced frailty.

Although the statistical power (based on a post hoc analysis) was only moderate, the observed association aligning with our hypothesized direction, across all fracture categories (MOF, any fractures, and hip fractures) further supports our findings.

The referred proportion would have been substantially different if the inclusion criteria had included FRAX scores or CRFs, such as patients with osteoporotic fractures, clinical vertebral fractures, and other important CRFs. However, the SUPERB study was designed as an observational study rather than an intervention study, only women who met the osteoporosis criteria according to the BMD were referred as per recommendation by the regional ERB. It is likely that different results would have been observed if the much larger proportion of participants who met the current osteoporosis treatment criteria, as recommended by the SvOS [36], were referred to primary care. Acknowledging the limitations of the osteoporosis T-score as a sole screening parameter, we present data from the cohort according to the SvOS treatment eligibility criteria to discern individuals that would require treatment according to these recommendations. The results showed that 46.1 % of women within the SUPERB cohort satisfied the clinical guidelines for osteoporosis treatment, and that this criterion was associated with increased fracture risk, yet only 28.7 % had current or recent osteoporosis treatment, further emphasizing the importance of screening to identify individuals at risk.

Modern and more potent treatment options such as sequential treatments, involving osteoanabolics followed by antiresorptives, for osteoporosis could potentially further magnify the effect of screening on fracture risk reduction [15]. Our study did not include a socioeconomic analysis. While the cost of DXA measurements varies across different regions and healthcare systems, they are generally considered low and cost-effective. On the other hand, the cost and burden of fragility fractures are substantial and constantly increasing [2]. Since the population of this study was elderly women in Sweden above 75 years, study findings may not be representative or applicable to other populations in

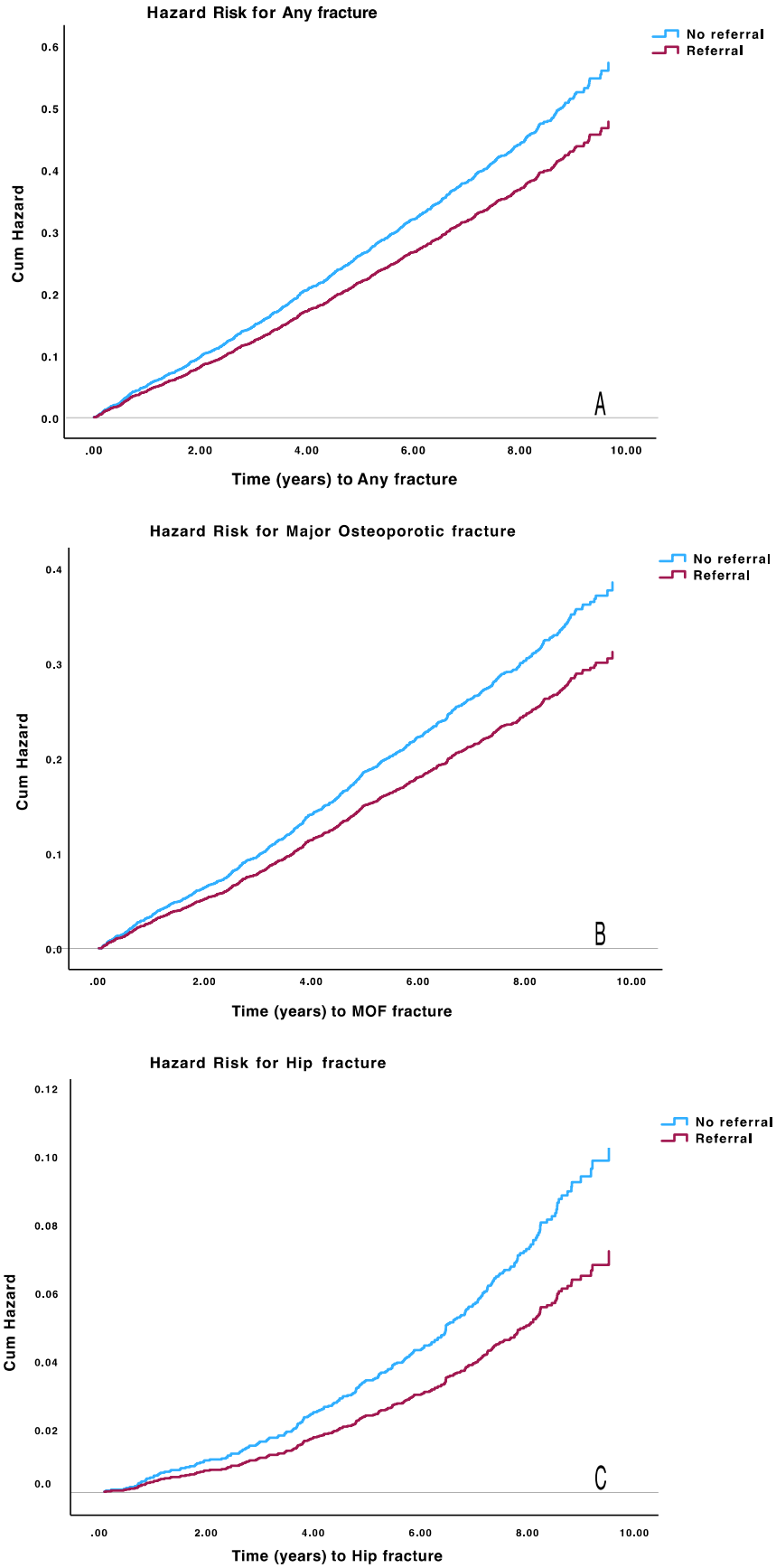

Fig. 2. Cumulative hazard of fracture risk is presented for the referral and control group. The hazard functions are adjusted for age, BMI, and clinical risk factors included in FRAX and femoral neck BMD. A) Any fracture, B) Major osteoporotic fracture, C) Hip fracture.

Table 3
Sensitivity analysis: Fracture risk, osteoporosis medication, and mortality.

	No referral (C2)	Referral to GP (R2)	*p-value*
	(n = 217)	(n = 411)	
Time at risk,years/(IQR)	7.3 (4.4–8.4)	7.3 (4.4–8.4)	
Any fracture			
No. (%)	101 (46.5)	161 (39.2)	
Rate (/1000 person years)	81.5	62.4	
HR, unadjusted	1 (Reference)	0.76 (0.59–0.98)	0.03
HR, adjustment model 1	1 (Reference)	0.73 (0.57–0.94)	0.02
HR, adjustment model 2	1 (Reference)	0.75 (0.58–0.96)	0.02
Major osteoporotic fracture			
No. (%)	84 (38.7)	123 (29.9)	
Rate (/1000 person years)	64.7	44.7	
HR, unadjusted	1 (Reference)	0.69 (0.52–0.91)	0.009
HR, multivariable adjusted 1	1 (Reference)	0.65 (0.49–0.87)	0.003
HR, multivariable adjusted 2	1 (Reference)	0.66 (0.50–0.88)	0.004
Hip fracture			
No. (%)	30 (13.8)	43 (10.5)	
Rate (/1000 person years)	19.4	14.0	
HR, unadjusted	1 (Reference)	0.71 (0.45–1.13)	0.16
HR, adjustment model 1	1 (Reference)	0.48 (0.29–0.79)	0.004
HR, adjustment model 2	1 (Reference)	0.49 (0.30–0.82)	0.006
Death			
n (%)	47 (21.7)	83 (20.1)	
Rate (/1000 person years)	28.5	25.9	
HR, unadjusted	1 (Reference)	0.91 (0.63–1.30)	0.59
HR, adjustment model 1	1 (Reference)	0.94 (0.65–1.36)	0.76
Injurious falls			
Time at risk (years)	6.6 (5.7–7.3)	6.6 (5.8–7.3)	
No. (%)	37 (17.1 %)	66 (16.1 %)	
Rate (/1000 person years)	27.4 (19.3–37.8)	25.3 (19.6–32.2)	
HR, unadjusted	1 (Reference)	0.92 (0.61–1.37)	0.68
HR, adjustment model 1	1 (Reference)	0.89 (0.59–1.34)	0.57
Prescription of incident osteoporosis medication			
No. (%)	71 (32.7 %)	307 (74.7 %)	
Rate (/1000 person years)	62	366	
HR, unadjusted	1 (Reference)	4.24 (3.27–5.51)	<0.001
HR, adjustment model 1	1 (Reference)	4.21(3.23–5.49)	<0.001

Hazard Ratios (HR) and 95 % Confidence Intervals are presented.
Model 1 = Multivariable adjustment for age, sex, BMI, smoking, alcohol, glucocorticoid use, previous fracture, parent hip fracture, secondary osteoporosis, rheumatoid arthritis, and BMD at the femoral neck.
Model 2 = Model 1 + Adjustment for previous treatment with osteoporosis medications.

other different regions. The key strengths of this study lie in its extended duration of follow-up and the inclusion of a substantial number of incident fractures, all of which were verified through X-ray archives.

In conclusion, older women participating in a population-based study and identified having osteoporosis using DXA and referred to their GP, had considerably higher osteoporosis treatment rates, and lower fracture risk after BMD adjustments, compared to women without osteoporosis. These findings support the usefulness of population-based screening using DXA to prevent fractures in older women.

CRediT authorship contribution statement

Michail Zoulakis: Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Kristian F. Axelsson:** Writing – review & editing, Visualization, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation. **Henrik Litsne:** Writing – review & editing, Software, Methodology, Investigation, Data curation. **Lisa Johansson:** Writing – review & editing, Methodology, Data curation. **Mattias Lorentzon:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

Dr. Axelsson has received lecture fees from Lilly, Meda/Mylan, and Amgen, all outside the submitted work. Dr. Johansson has received lecture fees from UCB Pharma, all outside the submitted work. Professor Lorentzon has received lecture fees from Astellas, Amgen, UCB Pharma, Medison Pharma, Jansen-Cilag, Viatris, and Parexel International, all outside the submitted work. All other authors have no conflicts of interest.

Data sharing statement

Data cannot be made publicly available for ethical and legal reasons. Such information is subject to legal restrictions according to national legislation. Specifically, in Sweden confidentiality regarding personal information in studies is regulated in the Public Access to Information and Secrecy Act (SFS 2009:400). The data underlying the results of this study might be made available upon request, after an assessment of confidentiality. There is thus a possibility to apply to get access to certain public documents that an authority holds. In this case, the University of Gothenburg is the specific authority that is responsible for the integrity of the documents with research data. Questions regarding such issues can be directed to the head of the Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. Contact information can be obtained from medicin@gu.se.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2024.117204.

References

[1] O. Johnell, J.A. Kanis, An estimate of the worldwide prevalence and disability associated with osteoporotic fractures, Osteoporos. Int. 17 (12) (2006) 1726–1733.
[2] J.A. Kanis, et al., SCOPE 2021: a new scorecard for osteoporosis in Europe, Arch. Osteoporos. 16 (1) (2021) 82.

[3] D. Bliuc, et al., The impact of nonhip nonvertebral fractures in elderly women and men, J. Clin. Endocrinol. Metabol. 99 (2) (2014) 415–423.
[4] M. Lorentzon, et al., Osteoporosis and fractures in women: the burden of disease, Climacteric 25 (1) (2022) 4–10.
[5] O. Johnell, et al., Mortality after osteoporotic fractures, Osteoporos. Int. 15 (1) (2004) 38–42.
[6] J.H. Byun, et al., The efficacy of bisphosphonates for prevention of osteoporotic fracture: an update Meta-analysis, J Bone Metab 24 (1) (2017) 37–49.
[7] K.W. Lyles, et al., Zoledronic acid and clinical fractures and mortality after hip fracture, N. Engl. J. Med. 357 (18) (2007) 1799–1809.
[8] P.D. Miller, et al., Denosumab or Zoledronic acid in postmenopausal women with osteoporosis previously treated with Oral bisphosphonates, J. Clin. Endocrinol. Metab. 101 (8) (2016) 3163–3170.
[9] B. Jönsson, et al., Cost-effectiveness of Denosumab for the treatment of postmenopausal osteoporosis, Osteoporos. Int. 22 (3) (2011) 967–982.
[10] S.R. Cummings, et al., Denosumab for prevention of fractures in postmenopausal women with osteoporosis, N. Engl. J. Med. 361 (8) (2009) 756–765.
[11] M. Lorentzon, Treating osteoporosis to prevent fractures: current concepts and future developments, J. Intern. Med. 285 (4) (2019) 381–394.
[12] F. Borgström, et al., Fragility fractures in Europe: burden, management and opportunities, Arch Osteoporos 15 (1) (2020) 59.
[13] D.L. Kendler, et al., Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial, Lancet 391 (10117) (2018) 230–240.
[14] J.P. Brown, et al., Romosozumab improves lumbar spine bone mass and bone strength parameters relative to alendronate in postmenopausal women: results from the active-controlled fracture study in postmenopausal women with osteoporosis at high risk (ARCH) trial, J. Bone Miner. Res. 36 (11) (2021) 2139–2152.
[15] K.G. Saag, et al., Romosozumab or alendronate for fracture prevention in women with osteoporosis, N. Engl. J. Med. 377 (15) (2017) 1417–1427.
[16] B. Freyschuss, et al., Real-world effectiveness of anti-Resorptive treatment in patients with incident fragility fractures—the STORM cohort—a Swedish retrospective observational study, J. Bone Miner. Res. 37 (4) (2022) 649–659.
[17] M. Lorentzon, et al., Extensive undertreatment of osteoporosis in older Swedish women, Osteoporos. Int. 30 (6) (2019) 1297–1305.
[18] D.W. Barton, C.J. Behrend, J.J. Carmouche, Rates of osteoporosis screening and treatment following vertebral fracture, Spine J. 19 (3) (2019) 411–417.
[19] D.H. Solomon, et al., Osteoporosis medication use after hip fracture in U.S. patients between 2002 and 2011, J. Bone Miner. Res. 29 (9) (2014) 1929–1937.
[20] E. McCloskey, et al., The osteoporosis treatment gap in patients at risk of fracture in European primary care: a multi-country cross-sectional observational study, Osteoporos. Int. 32 (2) (2021) 251–259.
[21] D. Marshall, O. Johnell, H. Wedel, Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures, Bmj 312 (7041) (1996) 1254–1259.
[22] S.R. Cummings, et al., Bone density at various sites for prediction of hip fractures. The study of osteoporotic fractures research group, Lancet 341 (8837) (1993) 72–75.
[23] J.A. Kanis, et al., A decade of FRAX: how has it changed the management of osteoporosis? Aging Clin. Exp. Res. 32 (2) (2020) 187–196.
[24] C. Beaudoin, et al., Performance of predictive tools to identify individuals at risk of non-traumatic fracture: a systematic review, meta-analysis, and meta-regression, Osteoporos. Int. 30 (4) (2019) 721–740.
[25] M. Viswanathan, et al., Screening to prevent osteoporotic fractures: updated evidence report and systematic review for the US preventive services task ForceUSPSTF evidence report: screening to prevent osteoporotic FracturesUSPSTF evidence report: screening to prevent osteoporotic fractures, JAMA 319 (24) (2018) 2532–2551.
[26] K.F. Axelsson, et al., Effectiveness of a minimal resource fracture liaison service, Osteoporos. Int. 27 (11) (2016) 3165–3175.
[27] K.F. Axelsson, et al., Association between recurrent fracture risk and implementation of fracture liaison Services in Four Swedish Hospitals: a cohort study, J. Bone Miner. Res. 35 (7) (2020) 1216–1223.
[28] T. Merlijn, et al., Fracture prevention by screening for high fracture risk: a systematic review and meta-analysis, Osteoporos. Int. 31 (2) (2020) 251–257.
[29] Solutions for Public Health, Screening for Osteoporosis in Postmenopausal Women. (External review against programme appraisal criteria for the UK National Screening Committee), 2019.
[30] UK National Screening Committee, Screening for Osteo- porosis in Postmenopausal Women 08 November 2019, 2019.
[31] EUnetHTA OTCA19 Assessment Team, Screening for osteoporosis in the general population. Collaborative Assessment. Diemen (The Netherlands): EUnetHTA; 2019. Report No.: OTCA19, 2019.
[32] K.H. Rubin, et al., Effectiveness of a two-step population-based osteoporosis screening program using FRAX: the randomized risk-stratified osteoporosis strategy evaluation (ROSE) study, Osteoporos. Int. 29 (3) (2018) 567–578.
[33] E.V. McCloskey, et al., A Meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX, J. Bone Miner. Res. 31 (5) (2016) 940–948.
[34] L. Shepstone, et al., Screening in the community to reduce fractures in older women (SCOOP): a randomised controlled trial, Lancet 391 (10122) (2018) 741–747.
[35] E.V. McCloskey, et al., Population screening for fracture risk in postmenopausal women — a logical step in reducing the osteoporotic fracture burden? Osteoporos. Int. 33 (8) (2022) 1631–1637.
[36] S.O Swedish Osteoporosis Society, Clinical guidelines, 2021. https://svos.se/vardprogram_osteoporos_svos.pdf.
[37] H Johansson, et al., Low bone mineral density is associated with increased mortality in elderly men: MrOS Sweden, Osteoporos. Int. 22 (5) (2011) 1411–1418.
[38] R.A. Washburn, et al., The physical activity scale for the elderly (PASE): evidence for validity, J. Clin. Epidemiol. 52 (7) (1999) 643–651.
[39] H.K. Genant, et al., Vertebral fracture assessment using a semiquantitative technique, J. Bone Miner. Res. 8 (9) (1993) 1137–1148.
[40] L. Johansson, et al., Vertebral fractures and their association with health-related quality of life, back pain and physical function in older women, Osteoporos. Int. 29 (1) (2018) 89–99.
[41] L. Johansson, et al., The prevalence of vertebral fractures is associated with reduced hip bone density and inferior peripheral appendicular volumetric bone density and structure in older women, J. Bone Miner. Res. 33 (2) (2018) 250–260.
[42] L. Johansson, et al., Improved fracture risk prediction by adding VFA-identified vertebral fracture data to BMD by DXA and clinical risk factors used in FRAX, Osteoporos. Int. 33 (8) (2022) 1725–1738.
[43] J.A. Kanis, et al., European guidance for the diagnosis and management of osteoporosis in postmenopausal women, Osteoporos. Int. 19 (4) (2008) 399–428.
[44] S.J. Curry, et al., Screening for osteoporosis to prevent fractures: US preventive services task force recommendation statement, Jama 319 (24) (2018) 2521–2531.
[45] A. Papaioannou, et al., 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary, Cmaj 182 (17) (2010) 1864–1873.
[46] K. Axelsson, Aspects of fracure prevention (The role of fracture liaison services and alendronate), in: Doctoral Thesis Sahlgrenska Academy, 2020, p. 55.
[47] P.H.S. Kalmet, et al., Deep learning in fracture detection: a narrative review, Acta Orthop. 91 (2) (2020) 215–220.
[48] J. Nicolaes, et al., Detection of vertebral fractures in CT using 3D convolutional neural networks, in: Y. Cai, L. Wang, M. Audette, G. Zheng, S. Li (Eds.), CSI 2019. LNCS 11963, Springer, Cham, 2020, pp. 3–14, https://doi.org/10.1007/978-3-030-39752-4_1.
[49] J.A. Mitchell, et al., Genetic risk scores implicated in adult bone fragility associate with pediatric bone density, J. Bone Miner. Res. 31 (4) (2016) 789–795.
[50] M. Nethander, et al., BMD-related genetic risk scores predict site-specific fractures as well as trabecular and cortical bone microstructure, J. Clin. Endocrinol. Metabol. 105 (4) (2020) e1344–e1357.