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ORIGINAL ARTICLE

Differing impact of clinical factors on the risk of fracture in younger and older women in the general population and an osteoporosis clinic population

Rosa Lauppe[1] · Kristina E. Åkesson[2] · Östen Ljunggren[3] · Anna Spångéus[4] · Gustaf Ortsäter[1] · Maurille Feudjo-Tepie[5] · Oskar Ström[1,6]

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Abstract

Summary This study assesses the impact of risk factors for fracture in women aged 80+ and 60–79. The results suggest that risk assessment which fits younger women may not be suited for the 80+ strata as many common risk factors are less predictive in the older compared to the younger cohort.

Purpose This study assesses whether the impact of classical risk factors for fracture due to osteoporosis is different in women aged 80+ and women aged 60–79. Since most prior research on the contribution of risk factors is based on patients below 80 years of age, this study aims to fill this knowledge gap to increase the accuracy of risk assessment in the oldest old.

Methods Retrospective, observational cohort study using Swedish national health register data and BMD data from osteoporosis clinics. Women aged at least 60 were identified from a random sample of the general population and from the BMD databases and allocated to two populations representing patients at different stages of risk assessment. The relative impact of risk factors on fracture risk was assessed using multivariate competing risk regression with fracture as outcome and death as competing event.

Results A total of 163,329 women were included from the general population (52,499 aged 80+) and 22,378 from the BMD databases (4563 aged 80+). The clinical risk factors with relatively highest effect on fracture risk in the older patients were prior fracture and hip T-score below − 2.5 SD. Other included risk factors showed lower impact in the older compared to the younger strata.

Conclusions This study confirms our understanding of the key risk factors for fracture: age, prior fracture, and a low T-score. Regarding remaining risk factors, risk assessment which fits younger women may not be suited for the 80+ strata as many common risk factors are less predictive in the older compared to the younger cohort.

Keywords Clinical risk factors · Elderly · Fractures · Population based · Retrospective · Risk assessment

Introduction

Fracture incidence among women aged 80 and older (80+), sometimes referred to as the oldest old, is considerably higher than among relatively younger women [1, 2]. Fractures in older individuals also entail more serious consequences for the patient and higher costs for society compared to fractures in younger individuals [3]. With increasing life expectancy and aging populations, the incidence of fractures will increase over the coming decades. For instance, the number of hip fractures, generally associated with high impact on morbidity and mortality [4], is estimated to double in the first half of this century [5–7]. Even though evidence from clinical trials is limited, osteoporosis treatment is likely effective in the oldest old [8–13] and could mitigate the expected future increase in

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✉ Rosa Lauppe
rosa.lauppe@quantifyresearch.com

1 Quantify Research, Stockholm, Sweden
2 Department of Clinical Sciences and Skåne University Hospital, Lund University, Malmö, Sweden
3 Uppsala University, Uppsala, Sweden
4 Linköping University, Linköping, Sweden
5 Amgen Ltd, Uxbridge, UK
6 Karolinska Institutet, Stockholm, Sweden

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fractures. Today, patients in the 80+ age group are still undertreated [14].

Clinical risk factors, such as age, prior fracture, or use of systemic glucocorticoids, play an important part in estimating an individual's risk of fracture in clinical practice. However, much of the data on the contribution of risk factors to fracture risk are based on patients below 80 years of age and it is unclear if these clinical risk factors have the same impact and usefulness in risk assessment in patients aged 80 or older. Increasing the accuracy of risk assessment in the oldest old can potentially lead to improved treatment targeting and a reduction in fracture incidence in this age group.

Clinical risk factors are used by physicians for treatment decision or decisions on referral to an osteoporosis clinic for further diagnostic assessment. As these decisions are made in different stages of risk assessment, this study analyzed the contribution of risk factors for two different populations. The "general population" is a randomly drawn sample of the Sweden population and represents individuals at an early stage of risk assessment, when presenting to GPs and secondary care specialists in various fields, who take decisions on referral to osteoporosis clinics for further assessment in case they suspect osteoporosis. The second population ("DXA population") consists of patients who have undergone a DXA scan and thus have come to a later stage of risk assessment. These patients have come to the attention of the health care system for osteoporosis, likely because they presented with one or more clinical risk factors for fracture, and the BMD measurement may further improve risk assessment and treatment decisions. The DXA population likely represents a higher-risk population compared to the general population.

The objective of this study was to investigate and compare the impact of a range of classical risk factors, which can be constructed from administrative data, in women aged 80+ and women aged 60–79 in two populations, the general population, and a potentially higher-risk population of patients with at least one DXA scan. The study aims to assess whether the impact of classical risk factors is different in the oldest old compared to younger women in the two populations and which risk factors are most important in this age group. The findings can serve as an initial guide on which risk factors should be awarded most attention in patients aged 80+, and at different stages of a patient's risk assessment.

Materials and methods

Patient selection and study design

This was a retrospective, observational cohort study with two populations, the general population and DXA population, both drawn from the Nordic Osteoporosis Research Dataset (NORD). NORD is a large compilation of national health register data on fractures, diseases, treatments, and mortality, as well as BMD data from three Swedish osteoporosis clinics (Malmö, Uppsala, and Linköping). Moreover, the data includes a reference population, randomly drawn from the general population. For each individual, data from the National Patient Register, the Swedish Prescribed Drug Register, and the Cause of Death Register were linked via the personal identity number unique to each Swedish citizen. NORD contains over 2 million patients: one million patients with fractures, 400,000 patients treated with osteoporosis drugs, and BMD data for 55,000 individuals.

The general population in this study was selected from the reference population and included women aged 60 years and older during the period between 1 July 2007 and 31 December 2012. The DXA population was selected from the three osteoporosis clinic databases and included women with at least one BMD measurement between the dates 1 July 2007 to 31 December 2015 while at age of 60+. Women with a primary diagnosis of bone metastasis at any time point during the individual look-back period or follow-up were excluded from the study. The general population and the DXA population included 163,329 and 22,378 individuals, respectively.

In each population, individuals were allocated to two cohorts: women aged 60–79 and women aged 80+ at index. Patients who could be allocated to both cohorts were allocated to the 80+ cohort and earlier data was disregarded. Index in the general population was set to July 01 of the year in which a patient first reaches age 60+ during the years 2007–2012. For the DXA population, the first DXA scan at age 60–79 or at age 80+ between the years 2007–2015 served as the index time point.

Included individuals were required to have complete data for a 24-month baseline period before index. After the index time point, patients were followed for a maximum of 5 years or less in case the event of interest (i.e., fracture) or death occurred or the end of data (31 Dec 2015 for the DXA population and 31 Dec 2012 for the general population) was reached before the completion of the 5-year follow-up. Death was treated as a competing risk in the fracture risk analyses.

Clinical risk factors

Patient characteristics and baseline clinical risk factors were observed during the 24-month period leading to the index date. Considered risk factors, extracted from administrative data, were:

– age (used indirectly by dividing patients in age groups 60–79 and 80+)

- previous fracture (hip, vertebra, non-hip non-vertebra; see supplementary material for definition)
- diagnoses related to secondary osteoporosis as specified in Landfeldt et al. [15]
- use of systemic glucocorticoids (as per FRAX definition [16], i.e., exposure to oral glucocorticoids at doses equivalent to at least 5 mg prednisolone daily under more than 3 months)
- comorbidity index, measured with the Charlson-Quan comorbidity index as defined in Quan et al. [17]
- treatment with proton pump inhibitors, a previously suggested risk factor which may contribute to fracture risk [18]
- pre-packaged drug dispensing (ApoDos) (a system where medication is pre-packaged by the pharmacy in small bags for morning, lunch, dinner, and evening) [19]
- exposure to drugs that increase the risk of fall as specified by the Swedish National Board of Health and Welfare (Socialstyrelsen) [20] and Woolcott et al. [21] (above 1500 defined daily doses (DDDs) during the look-back period)

For the DXA population, additional information was available: Body mass index (BMI) and T-score, total hip, and lumbar spine.

The risk factor comorbidities and pre-packaged drug dispensing were added to the analyses as proxies for frailty and biological age. A high comorbidity index is related to increased frailty of patients [22]. The fact that a patient is in need of pre-packaged drugs indicates that the patient is not mentally or physically able to organize medication intake which provides some indication on the patient's biological age.

Fracture identification

Fractures were identified from diagnoses registered in the National Patient Register. For vertebral fractures, only clinically diagnosed and coded fractures were included. The ICD-10 codes used to identify fractures are shown in Table 3 in the supplementary material. An algorithm was used to avoid double counting of fractures in the case of repeated diagnoses at consecutive consultations. The most important rules for identifying new fractures were that a primary fracture diagnosis was required for all fractures to be defined as a new event and hip fractures must further be diagnosed in an inpatient setting. Moreover, a fracture diagnosis reoccurring for the same body site as a previous fracture was only counted as new fracture if at least 6 months had passed since the last fracture diagnosis for the same site and the fracture diagnosis was made during an inpatient episode.

Statistical analysis

Cumulative fracture incidence was calculated for each age strata in each population taking the competing risk of death into account. Similarly, the relative impact of risk factors on fracture risk, measured as sub-distribution hazard ratio (HR), was assessed and compared between age groups using multivariate Fine-Gray competing risk regression [23] with fracture as outcome and death as competing event. When mortality is not treated as competing risk, as in Kaplan-Meier estimates and Cox regressions, the risk of fracture is overestimated as patients are censored at death [24, 25]. This may affect results especially when cohorts under comparison, here younger and older patients, show differences in mortality.

Regressions were run for each age group separately. Age groups were then combined within each population and a multivariate competing risk regression model was estimated with age group as interaction term for each risk factor. The significance of the interaction coefficient was used to determine if the difference in impact of each risk factor between the age groups was significant at the 1%, 5%, and 10% significance level.

The proportion of explained variation in survival time, i.e., time until fracture, was assessed for each risk factor alone and for all risk factors together (referred to as "full model") using an R^2-type measure for proportional-hazards models [26] on a Cox regression model.

To capture only relevant amounts of exposure to drugs which increase the risk of falls, a minimum exposure level was defined, measured as the sum of DDDs for all fall-risk increasing drugs prescribed during the 24-month baseline period. A suitable cutoff was assessed with an R^2-type measure for proportional-hazards models [26] measuring the proportion of explained variance of different exposure levels. For this analysis, 1500 DDD was set as the minimum exposure level for patients to be counted as exhibiting this risk factor.

Results

The general population cohort comprised 163,329 individuals, contributing a total of 603,596 person-years of observation time and 18,330 failure events, i.e., fractures; 52,499 (32%) of the individuals were 80 years or older. The DXA population consisted of 22,378 individuals with a total of 66,695 person-years and 2454 fractures counted as failure event; 4563 (20%) patients were allocated to the 80+ age group. Table 1 summarizes the baseline characteristics of patients aged 60–79 and 80+ in the general and the DXA population. A larger share of patients in the DXA population had records of prior fractures, prior osteoporosis treatment, and use of calcium and vitamin D which indicates the preselection in this population compared to the general population. In both

Table 1 Patient characteristics measured during 24-months baseline period

	General population age group		DXA population age group	
	60–79 % (*n*)	80+, %(*n*)	60–79 % (*n*)	80+, %(*n*)
n	110,830	52,499	17,815	4563
Age, mean	64.3	83.8	68.7	83.4
Fracture in previous 24 months	3.2 (3511)	9.1 (4757)	23.9 (4253)	33.7 (1536)
Hip	0.3 (316)	3.3 (1723)	4.3 (773)	12.8 (583)
Vertebral	0.2 (174)	1.0 (497)	2.4 (418)	5.3 (243)
Non-hip, non-vertebra	2.8 (3064)	5.4 (2837)	17.8 (3174)	17.6 (802)
OP treatment previous 24 months	11.8 (13,051)	11.3 (5911)	23.9 (4248)	33.1 (1509)
Alendronate	2.8 (3076)	7.8 (4071)	15.3 (2714)	23.7 (1079)
Denosumab	0.0 (2)	0.0 (12)	0.3 (46)	0.9 (41)
Zoledronate	0.0 (23)	0.1 (52)	0.4 (62)	1.5 (68)
Oral ibandronate	0.0 (6)	0.0 (6)	0.0 (8)	0.0 (2)
Risedronate	1.0 (1125)	2.0 (1063)	3.6 (638)	5.5 (252)
Raloxifene	0.3 (325)	0.3 (169)	0.7 (124)	0.9 (42)
Hormone replacement therapy	8.0 (8806)	0.8 (443)	4.7 (842)	0.9 (43)
Charlson-Quan comorbidity index = 0	86.4 (95,761)	71.3 (37,416)	66.4 (11,823)	60.8 (2776)
Charlson-Quan comorbidity index = 1–2	11.4 (12,636)	22.8 (12,009)	26.1 (4642)	28.6 (1307)
Charlson-Quan comorbidity index > 2	2.2 (2433)	5.9 (3074)	7.6 (1350)	10.5 (480)
Diagnoses related to secondary osteoporosis	4.1 (4507)	6.8 (3559)	14.8 (2629)	16.6 (755)
Systemic glucocorticoid use	4.6 (5129)	8.0 (4176)	18.6 (3313)	15.8 (722)
≥ 6 months calcium/vitamin D during last 24 months	9.3 (10,317)	15.1 (7919)	29.3 (5226)	45.3 (2068)
Treatment with proton pump inhibitors	18.4 (20,398)	24.3 (12,755)	35.1 (6257)	37.3 (1700)
Pre-packaged drug dispensing (ApoDos)	1.4 (1526)	17.9 (9393)	2.5 (437)	10.8 (494)
Exposure to drugs that increase the risk of fall (> 1500 DDDs)	14.7 (16,249)	35.7 (18,731)	23.8 (4246)	38.3 (1748)
BMI, mean (n)	N/A	N/A	26.1 (17,812)	25.6 (4562)
Baseline lumbar spine BMD, mean g/cm^2 (n)	N/A	N/A	0.96 (17,489)	0.94 (4480)
Baseline total hip BMD, mean g/cm^2 (*n*)	N/A	N/A	0.80 (17,375)	0.72 (4289)
Baseline lumbar spine T-score, SD (*n*)	N/A	N/A	− 1.40 (17,489)	− 1.54 (4480)
Baseline total hip T-score, SD (*n*)	N/A	N/A	− 1.47 (17,375)	− 2.20 (4289)

populations, the older strata were more likely to have fractured during the 24-month baseline period, compared to younger individuals.

The 5-year probability of fracture, shown in Fig. 1, was higher for the older strata in both the general population (22% versus 9%) and the DXA population (26% versus 13%). Although the DXA population showed slightly higher probability of fracture compared to the general population, both populations showed fracture probabilities of the same magnitude.

Generally, the clinical risk factors which had relatively highest effect on fracture risk in the younger women also did so in the older women in both populations; previous fracture showed the highest impact in both the younger and the older strata in the general population and the same could be observed for T-scores in the DXA population.

In the general population, all included clinical risk factors had lower impact on probability of fracture in the older relative to the younger strata, apart from prior non-hip non-vertebral fracture which showed similar presence in both age groups (Table 2). The strongest risk factors among the oldest old in the general population were previous fractures; previous hip fracture and vertebral fracture were estimated to increase the probability of fracture by 1.3 (CI 1.1–1.4) and 1.8 (CI 1.5–2.1), respectively, compared with no previous hip/vertebral fracture.

In the DXA population, where T-scores could be added to the model, the impact of many risk factors, such as previous fracture (all types) and secondary osteoporosis, was lower compared to their impact in the general population. In both age groups in the DXA population, the most influential risk

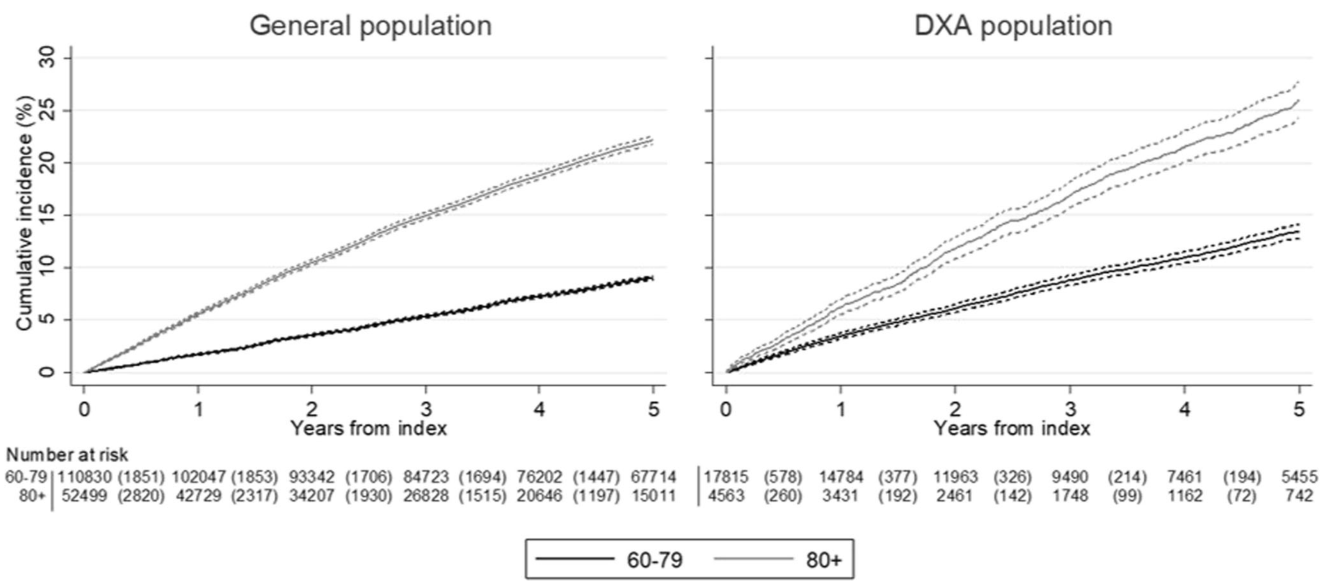

Fig. 1 Cumulative incidence of fracture (with 95% CI) for the general population and the DXA population

Table 2 Impact of clinical risk factors on risk of fracture

Sub-distribution hazard ratios estimated using multivariate Fine-Gray competing risk regression (95% confidence interval)

Risk factor	General population			DXA population		
	Age group		Δ[$]	Age group		Δ[$]
	60–79	80+		60–79	80+	
Previous fracture						
Hip	2.1 (1.6–2.7)	1.3 (1.1–1.4)	***	1.3 (1.1–1.6)	1.0 (0.8–1.2)	**
Vertebra	2.5 (1.8–3.5)	1.8 (1.5–2.1)	*	1.1 (0.8–1.5)	1.4 (1.0–1.8)	
Non-hip, non-vertebra	1.4 (1.3–1.6)	1.5 (1.4–1.6)		1.0 (0.9–1.2)	1.2 (1.0–1.4)	
Charlson-Quan comorbidity[a]						
Comorbidity index = 1–2	1.2 (1.2–1.3)	1.1 (1.0–1.2)	***	1.2 (1.1–1.3)	1.0 (0.8–1.1)	**
Comorbidity index > 2	1.5 (1.3–1.7)	0.9 (0.8–1.0)	***	1.2 (1.0–1.4)	1.2 (0.9–1.5)	
Diagnoses related to secondary osteoporosis	1.3 (1.2–1.4)	1.1 (1.0–1.2)	***	1.0 (0.9–1.2)	0.8 (0.7–1.0)	
Systemic glucocorticoid use	1.3 (1.2–1.4)	1.1 (1.1–1.2)	*	1.0 (0.9–1.5)	1.3 (0.8–1.6)	*
Treatment with proton pump inhibitors	1.1 (1.0–1.1)	1.0 (1.0–1.1)		1.2 (1.1–1.3)	0.9 (0.8–1.1)	**
Pre-packaged drug dispensing (ApoDos)	1.7 (1.5–2.0)	0.9 (0.9–1.0)	***	1.3 (1.0–1.7)	1.4 (1.1–1.7)	
Exposure to drugs that increase falls risk	1.2 (1.2–1.3)	1.0 (1.0–1.1)	***	1.3 (1.2–1.5)	1.0 (0.9–1.2)	**
BMI categories relative normal[b]						
BMI < 18.5	–	–		1.2 (0.9–1.5)	1.2 (0.8–1.6)	
BMI > 25	–	–		1.0 (0.9–1.1)	0.9 (0.7–1.0)	*
Total hip T-score relative to normal[c]						
T-score hip < − 1.0	–	–		1.5 (1.3–1.7)	1.2 (0.9–1.5)	*
T-score hip < − 2.5	–	–		2.5 (2.2–3.0)	1.7 (1.4–2.2)	***

[a] Charlson-Quan comorbidity relative to an index of 0

[b] BMI categories relative to BMI between 18.5–25

[c] Total hip T-score relative to T-score >= − 1.0

[$] Risk factors which showed significantly different impact (*$p \leq 0.1$, **$p \leq 0.05$, ***$p \leq 0.01$) between age groups within each population (assessed with the significance of risk factor-age group interaction terms in a separate model not reported here) factor was a total hip T-score below − 2.5, which conferred a relative risk of fracture of 2.5 (CI 2.2–3.0) in patients aged 60–79 and 1.7 (CI 1.4–2.2) in the oldest old compared to a hip T-score above − 1.

When total hip T-score was replaced with lumbar spine T-score in the multivariate model, the impact on fracture risk was reduced. A spine T-score below − 2.5 increased the probability of fracture with 1.6 (CI 1.4–1.8) and 1.4 (CI 1.2–1.7) for the younger and older strata, respectively, compared to a spine T-score above − 1. The replacement of total hip with lumbar spine T-score did not significantly affect the HRs of the remaining risk factors in the model (Table 4 in supplementary material).

Risk factor-age group interactions were used to identify risk factors differing between age groups. In Table 2, risk factors with interaction terms significantly different from zero were marked with one to three asterisks (*), reflecting different p values, as indicated in the table. In the general population, the majority of included risk factors had a significantly smaller impact in the older strata compared to the younger strata, apart from previous non-hip non-vertebral fracture and PPI treatment. In the DXA population, around half of the included risk factors (previous hip fracture, a comorbidity index between 1 and 2, PPI treatment, fall-risk increasing drugs, and total hip T-score below 1 and below − 2.5) had significantly lower impact in the oldest age group. Of the remaining risk factors which showed slightly higher impact in the 80+ strata, only systemic glucocorticoid use differed significantly between the age groups (10% level). Results suggested that a BMI above 25 decreases fracture risk in the older strata but not in the younger strata.

Since osteoporosis treatment can potentially affect results, a sensitivity analysis was run excluding patients who received treatment during follow-up (Table 5 in supplementary material). In the general population, the share of patients on treatment was 6.5% in the younger strata and 11.1% in 80+ strata. In the DXA population, this was much higher (44.7% in the younger and 59.7% in the older strata) as a DXA scan, index in this population, often precedes treatment decisions. The impact of risk factors on risk of fracture in the general population changed only marginally when patients treated with osteoporosis medication were excluded. Changes in results for the DXA population were more prominent. The impact of prior hip and prior vertebra fracture as well as the impact of a total hip T-score below 1 and below − 2.5 increased in both age groups. The effect of a T-score below − 2.5 increased by more than half in the younger strata. Due to lower sample size, the 95% confidence intervals increased.

Figure 2 shows how much of the variation in time to fracture among individuals could be explained by the included risk factors, both when all risk factors were included in the regression ("full model") and when each risk factor was included on its own. In the entire general population (Fig. 2 a), all included risk factors could together explain roughly 24% of the variation in fracture risk, with age on its own explaining 21%. When the general population cohort was divided into age groups 60–79 and 80+, age in each age group explained less than 4% (data not shown). In the DXA population (Fig. 2 b), roughly 18% could be explained by the full model even though T-scores were available. Total hip T-score was the risk factor which explained the largest share of variation in the DXA population, 13%, five times as much as lumbar spine T-score.

Discussion

The principal findings of this retrospective, observational cohort study, comprising more than 180,000 individuals, are that the key risk factors prior fracture and a T-score below − 2.5 SD are most important in patient aged 60–79 and patients aged 80+. Remaining risk factors commonly used for risk assessment showed lower impact and are thus likely less useful in the oldest old compared to younger patients. This was apparent in the general population but could also be observed in the preselected DXA population of patients suspected to be at risk for fracture.

As sensitivity analysis, patients on osteoporosis treatment during follow-up were excluded from the sample. Although the impact of some risk factors on risk of fracture changed in magnitude compared to the analysis on the full samples, the overall conclusions on relative relations and importance remain unchanged.

In addition to the analysis of risk factors in terms of hazard ratios, this study also investigated the share of the variance in "time to fracture" that could be explained by the risk factors. This analysis adds an important aspect to the study; while hazard ratios represent the increase in base risk due to a factor, the analysis of "share of variance explained" sets this into perspective and shows how much of the differences in absolute risk between individuals can be explained by a risk factor. In this way, it shows the importance of risk factors on group level. The analysis of "share of variance explained" can thus be useful for shaping treatment policy and guiding investment, rather than assessing risk for an individual patient.

This analysis of "share of variance explained" showed that age itself is clearly one of the most important factors to take into account. For the full general population, age could explain by far the highest share of variation in fracture risk between individuals compared to all other risk factors. That this

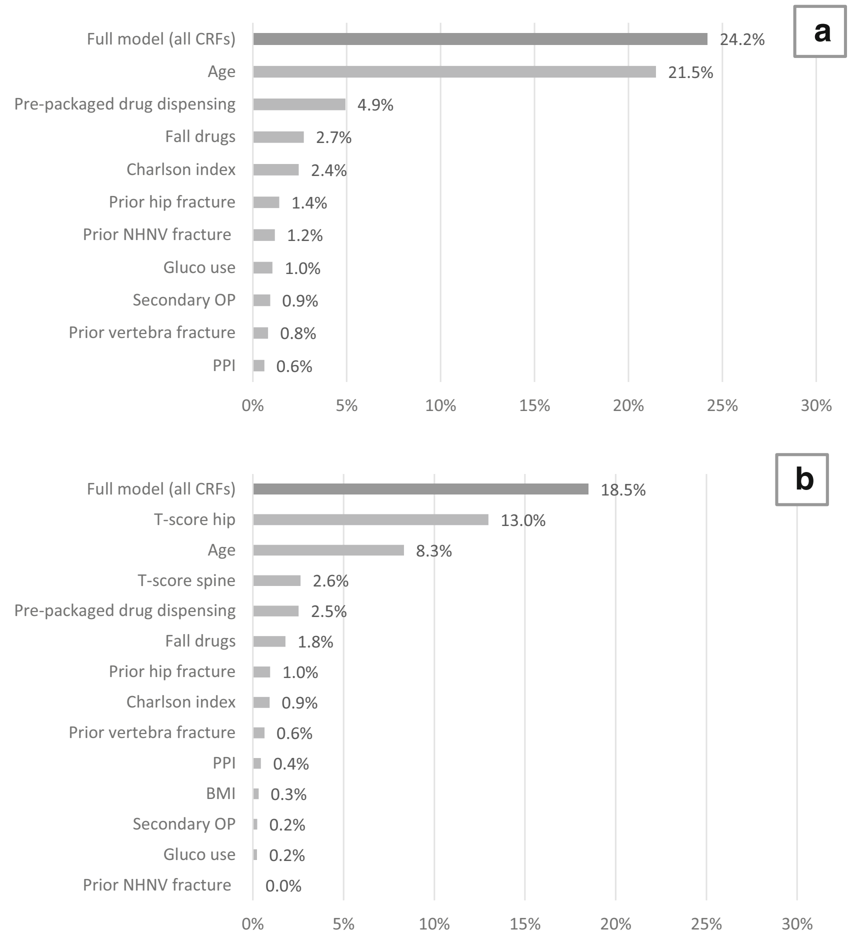

Fig. 2 Variation in time to fracture (in %) explained by clinical risk factors for **a** the general population and **b** the DXA population (full model and each risk factor assessed separately)

share decreased from above 20 to less than 4% when analyzed for the 60–79 and 80+ age groups separately shows that the simple division into "under 80" and "over 80" absorbed much of the importance of age and can be interpreted as sign for the applicability of the cutoff at age 80. However, the suitability of other age cutoffs should be explored further.

In the DXA population, the importance of age was reduced due to the preselection of patients. Differences in T-score at the hip explained the largest share of variance in "time to fracture" between individuals. T-score at the spine explained only a significantly smaller share which confirms that, especially for elderly women, osteoporosis at the total hip may be a more reliable predictor of fracture than a spine measurement [27].

A main strength of this study is that it contributes to filling an important evidence gap in the literature by studying the impact of risk factors in the oldest old in a large patient population. The fact that risk factors were studied in two different populations provides further insight into the importance of risk factors for individuals in the general population and for individuals suspected to be at risk for fracture and referred to osteoporosis clinics for risk assessment. The quality and the high representativeness of the data used in the analysis strengthen the validity of the findings. Swedish registers are well-known for their high degree of validity and completeness that allow for generating real-world evidence of high quality.

A limitation of this analysis is that it is limited to risk factors which can be constructed from administrative data and thus does not include a range of other, potentially important factors used in risk assessment in clinical practice. Risk factors used in the FRAX® Fracture Risk Assessment Tool but not included in this analysis are smoking, alcohol consumption, and parental hip fracture. Furthermore, no natural index time point, for starting the observation, was available for the general population and had to be constructed. Since the date of the DXA scan could be used as index in the DXA population, index definitions differ between populations. Moreover, the algorithm used for the identification of new fractures was designed to minimize double counting of fractures while capturing all new fractures, but in some cases, fractures may have been missed or double counted.

Overall, this study confirms our understanding of the key risk factors for fracture: age, prior fracture, and a low T-score. Regarding the remaining risk factors, results suggest that risk assessment which fits younger patients may not be suited for the oldest old as many of the risk factors included in the analysis appeared less useful in the oldest old compared to younger patients. Prior fracture and, if available, hip T-score below 2.5 SD should receive most attention in the 80+ strata. The results also suggest that age should be given even higher priority as a risk factor on group level than may already be the case and that treatment of patients aged 80 or older may often be warranted, also when limited information on other risk factors is available. Future research is needed to confirm these results and investigate the impact of risk factors which were not included in this analysis, such as some of the risk factors used in the FRAX® Fracture Risk Assessment Tool.

Compliance with ethical standards

Conflict of interest Rosa Lauppe, Gustaf Ortsäter, and Oskar Ström are employed by Quantify Research and were funded by Amgen to conduct this study. Kristina Åkesson received lecture and consultancy fees from Amgen, UCB, Merck, Sandoz, and Eli Lilly. Östen Ljunggren has no current conflict of interest. Anna Spångéus received lecture fees from Amgen and Eli Lilly. Maurille Feudjo-Tepie is employed by Amgen.

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