RESEARCH ARTICLE

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The Importance of Recent Prevalent Fracture Site for Imminent Risk of Fracture – A Retrospective, Nationwide Cohort Study of Older Swedish Men and Women

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ABSTRACT

There is limited evidence regarding which fracture types carry the highest risk for subsequent fracture. The aim of this study was to investigate how the risk of imminent fracture depends on index fracture site. This nationwide retrospective cohort study utilized national registers in Sweden to determine the risk of fracture according to recent (≤2 years) index fracture site and according to an old (>2 years) prevalent fracture compared with the risk observed in controls without a fracture. All Swedes 50 years or older between 2007 and 2010 were included in the study. Patients with a recent fracture were designated a specific fracture group depending on the type of previous fracture. Recent fractures were classified as major osteoporotic fracture (MOF), including fractured hip, vertebra, proximal humerus, and wrist, or non-MOF. Patients were followed until December 31, 2017, censored for death and emigration, and the risk of any fracture and hip fracture was assessed. A total of 3,423,320 persons were included in the study, 70,254 with a recent MOF, 75,526 with a recent non-MOF, 293,051 with an old fracture, and 2,984,489 persons with no previous fracture. The median time of follow-up for the four groups was 6.1 (interquartile range [IQR] 3.0–8.8), 7.2 (5.6–9.4), 7.1 (5.8–9.2), and 8.1 years (7.4–9.7), respectively. Patients with a recent MOF, recent non-MOF, and old fracture had a substantially increased risk of any fracture (hazard ratio [HR] adjusted for age and sex 2.11, 95% confidence interval [CI] 2.08–2.14; HR 2.24, 95% CI 2.21–2.27; and HR 1.77, 95% CI 1.76–1.78, respectively) compared with controls. All recent fractures, MOFs, and non-MOFs, as well as older fractures, increase the risk of subsequent fracture, suggesting that all recent fractures should be included in fracture liaison services and that case-finding strategies for those with older fractures may be warranted to prevent subsequent fractures. © 2023 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: FRACTURE RISK ASSESSMENT; FRACTURE PREVENTION; GENERAL POPULATION STUDIES

Introduction

Fractures, particularly at the hip and spine, increase suffering, morbidity, and mortality at high societal and healthcare costs.[1] At 50 years of age, the lifetime risk of sustaining a fragility fracture is 50% for women and 20% for men.[2] Patients sustaining a first fracture have a pronounced and increased risk of recurrent fracture, especially during the first 2 years following the index fracture.[3,4]

Osteoporosis medications, such as bisphosphonates, denosumab, teriparatide, and romosozumab, are effective at increasing bone mineral density (BMD) and reducing fracture risk by approximately 40% for hip fractures and by 45%–70% for vertebral fractures.[5] Despite the availability of these efficient treatments, the probability of receiving osteoporosis medication in the United States within a year after hip fracture declined rapidly, from 40.2% in 2002 to 20.5% in 2011.[6] Structured secondary prevention programs known as Fracture Liaison Services (FLSs),

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which target patients with recent fractures, have been implemented worldwide[7] and are associated with higher rates of BMD testing, treatment initiation, better medication adherence, and a decrease in the risk of recurrent fracture.[8,9] However, there is no clear consensus in available guidelines about which fracture types should be included in the FLSs.

The international Capture the Fracture campaign recommends including fragility fractures excluding fractures of the face, skull, scaphoid, and digits.[10] In Sweden, the official national recommendations use the terms osteoporotic fracture, low-energy fracture, and fragility fracture interchangeably, highlighting fractures of hip, vertebra, wrist, humerus, and pelvis, while excluding fractures in the head, hands, and feet.[11] Some FLSs include wrist, shoulder, and hip fractures,[12] while others also include vertebral fractures.[13,14] In the UK, the National Osteoporosis Guideline Group refers to osteoporotic or fragility fracture but without specifying fracture codes.[15] Osteoporotic fracture, or major osteoporotic fracture (MOF), is a loosely defined term comprising fractured hip, vertebral, wrist, upper arm, and sometimes pelvis. The risk of subsequent fracture depends on the site of recent fracture.[16] However, the fact that MOF fracture sites are common and associated with low BMD and osteoporosis,[17] does not necessarily imply that fractures at other less common skeletal sites lack association with low BMD and osteoporosis. Also, available evidence suggests that high-energy trauma and low-energy trauma fractures show similar relationships with low BMD and future fracture risk.[18,19] Thus, the terms osteoporotic, minimal trauma, fragility, and low-energy fracture leave room for subjective interpretation, and the fracture sites included in the FLS vary. When faced with the challenge of implementing a FLS, there is no clear guidance or evidence as to which fracture sites to include.

The primary aim of this study was to investigate whether the risk of subsequent fracture after a recent fracture depended on fracture site and whether index fractures at skeletal sites other than those considered major osteoporotic sites conferred a similar risk elevation. If risk estimates are similar for fractures at other sites, not considered traditionally osteoporotic, inclusion of these fracture types may be warranted in FLSs.

Methods

Study design

This nationwide retrospective cohort study used national registers in Sweden to compare the risk of fracture between patients with recent fractures (≤2 years), depending on the site, with old fractures (>2 years), and control patients without previous fractures (Fig. 1). All Swedish men and women who were born in 1977 or earlier and were alive in 2005 were given a random baseline date between 2007 and 2010. Those aged 50 years or older and alive at baseline were included in the study. Patients with a recent fracture (≤2 years) were designated a specific fracture group depending on the type of previous fracture using four-character categories of ICD-10 (International Statistical Classification of Diseases and Related Health Problems – Tenth Revision). To allow subgroup analyses, these categories of recent fracture were also classified as either MOF, including fractured hip, vertebrae, proximal humerus, and wrist, or non-MOF. The study was funded by the Swedish Research Council and the Sahlgrenska University Hospital and approved by the Swedish Ethical Review Authority.

Data sources

Information regarding fractures and comorbidities were retrieved from The National Patient Register, including hospital-based diagnoses from both inpatient and outpatient visits. Socioeconomic data were retrieved from Statistics Sweden and date of death from the Swedish Cause of Death Register. Medication data were collected from the Swedish Prescribed Drug Register, starting July 1, 2005. In Sweden, all

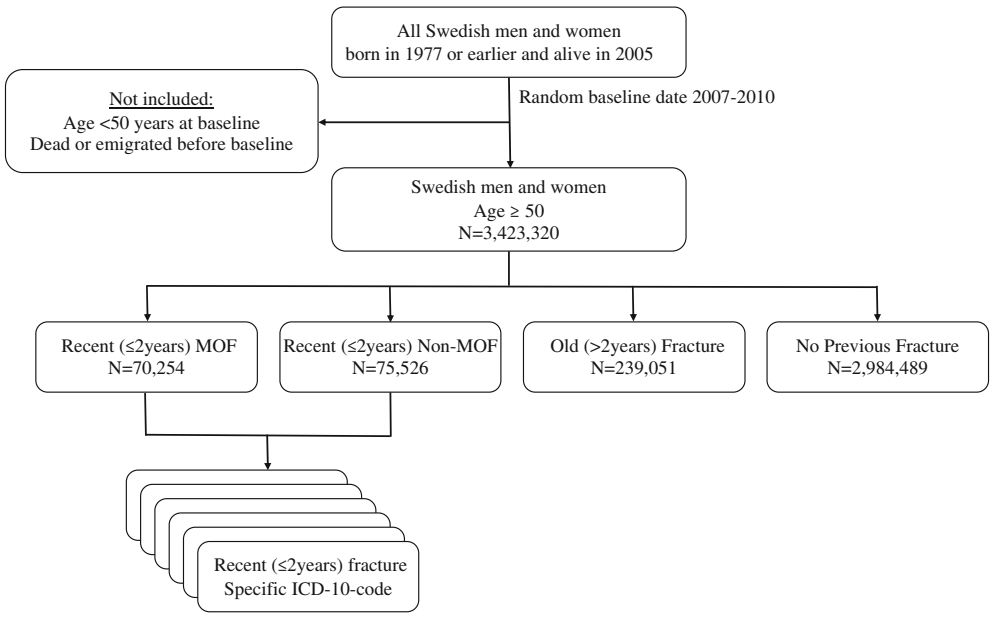

Fig. 1. Study population. The groups with recent fractures were assigned first, so patients in the group with old fractures do not have recent fractures. The historical register window stretches to 1998, that is, the group with no previous fracture had no known fractures during the last 9–13 years. MOF = major osteoporotic fracture, including fractured hip, vertebrae, proximal humerus, and wrist.

Table 1. Baseline Characteristics

	Recent (≤2 years) MOF	Recent (≤2 years) non-MOF	Old (>2 years) fracture	No previous fracture
N	70,254	75,526	293,051	2,984,489
Age, years mean (SD)	75.64 (11.98)	68.90 (12.52)	70.19 (12.30)	65.47 (10.78)
50–64, *n* (%)	15,577 (22.2)	33,234 (44.0)	111,682 (38.1)	1,582,059 (53.0)
65–79, *n* (%)	23,448 (33.4)	23,794 (31.5)	103,417 (35.3)	1,012,925 (33.9)
≥80, *n* (%)	31,229 (44.5)	18,498 (24.5)	77,952 (26.6)	389,505 (13.1)
Female sex, *n* (%)	53,339 (75.9)	44,709 (59.2)	182,880 (62.4)	1,522,107 (51.0)
Inclusion year				
2007, *n* (%)	17,142 (24.4)	17,951 (23.8)	59,857 (20.4)	750,958 (25.2)
2008, *n* (%)	17,111 (24.4)	18,473 (24.5)	69,479 (23.7)	750,795 (25.2)
2009, *n* (%)	17,781 (25.3)	19,142 (25.3)	77,803 (26.5)	743,404 (24.9)
2010, *n* (%)	18,220 (25.9)	19,960 (26.4)	85,912 (29.3)	739,332 (24.8)
Osteoporosis medication the last year, *n* (%)	11,497 (16.4)	7,561 (10.0)	30,610 (10.4)	132,933 (4.5)
Multiple recent fracture sites (≥2), *n* (%)	7,541 (10.7)	8,318 (11.0)	0 (0.0)	0 (0.0)
Multiple recent fracture sites (≥3), *n* (%)	1,013 (1.4)	1,381 (1.8)	0 (0.0)	0 (0.0)
Charlson Comorbidy Index, mean (SD)	1.12 (1.64)	0.87 (1.49)	0.74 (1.36)	0.51 (1.16)
0, *n* (%)	36,445 (51.9)	46,561 (61.6)	193,032 (65.9)	226,4609 (75.9)
1, *n* (%)	12,575 (17.9)	11,027 (14.6)	39,144 (13.4)	280,034 (9.4)
2, *n* (%)	10,521 (15.0)	9,604 (12.7)	34,952 (11.9)	282,976 (9.5)
≥3, *n* (%)	10,713 (15.2)	8,334 (11.0)	25,923 (8.8)	156,870 (5.3)
Charlson Comorbidy Index, components				
Dementia, *n* (%)	5,915 (8.4)	2,975 (3.9)	9,093 (3.1)	27,711 (0.9)
Ischemic heart diseases, *n* (%)	9,753 (13.9)	8,377 (11.1)	27,985 (9.5)	202,946 (6.8)
Congestive heart failure, *n* (%)	7,120 (10.1)	4,953 (6.6)	16,152 (5.5)	83,578 (2.8)
Cerebrovascular diseases, *n* (%)	7,236 (10.3)	5,633 (7.5)	18,101 (6.2)	97,351 (3.3)
Diseases of arterioles and capillaries, *n* (%)	2,729 (3.9)	2,350 (3.1)	8,176 (2.8)	55,951 (1.9)
Chronic pulmonary disease, *n* (%)	5,630 (8.0)	4,844 (6.4)	15,046 (5.1)	86,947 (2.9)
Chronic liver disease, *n* (%)	707 (1.0)	751 (1.0)	2,139 (0.7)	11,910 (0.4)
Tumor without metastasis, *n* (%)	8,329 (11.9)	7,386 (9.8)	27,123 (9.3)	237,084 (7.9)
Lymphoma or leukemia, *n* (%)	824 (1.2)	629 (0.8)	2,198 (0.8)	17,102 (0.6)
Diabetes, *n* (%)	7,101 (10.1)	7,104 (9.4)	23,171 (7.9)	171,679 (5.8)
With end organ damage, *n* (%)	2,518 (3.6)	2,745 (3.6)	9,015 (3.1)	60,523 (2.0)
Renal failure, mild, *n* (%)	1,780 (2.5)	1,460 (1.9)	4,064 (1.4)	25,192 (0.8)
Renal failure, moderate, *n* (%)	76 (0.1)	64 (0.1)	226 (0.1)	1,353 (0.0)
Hemiplegia, *n* (%)	597 (0.8)	448 (0.6)	1,243 (0.4)	4,555 (0.2)
Peptic ulcer disease, *n* (%)	1,795 (2.6)	1,509 (2.0)	4,593 (1.6)	27,687 (0.9)
Solid metastasis, *n* (%)	819 (1.2)	714 (0.9)	2,212 (0.8)	19,063 (0.6)
Oral prednisolone, *n* (%)	5,741 (8.2)	4,900 (6.5)	17,469 (6.0)	117,950 (4.0)
Previous alcohol-related diseases, *n* (%)	2,032 (2.9)	3,821 (5.1)	9,478 (3.2)	33,450 (1.1)
Drugs used in alcohol dependence, *n* (%)	324 (0.5)	824 (1.1)	1,881 (0.6)	9,508 (0.3)
Opiods, *n* (%)	34,361 (48.9)	28,686 (38.0)	52,203 (17.8)	33,2556 (11.1)
Drugs used in opioid dependence, *n* (%)	69 (0.1)	88 (0.1)	260 (0.1)	1,174 (0.0)
Selective seretonin reuptake inhibitors, *n* (%)	13,219 (18.8)	11,581 (15.3)	36,656 (12.5)	222,918 (7.5)
Nonsteroidal anti-inflammatory agents, *n* (%)	12,781 (18.2)	16,820 (22.3)	51,337 (17.5)	525,772 (17.6)

Note: Baseline characteristics per group depending on recency and site of previous fracture. Multiple recent fractures refer to the recent 2-year period. Charlson Comorbidity Index and alcohol-related diseases were calculated using a historical window of 5 years. Medication use was recorded using a historical 1-year window. For detailed definitions of variables, see Table S2.

inhabitants are assigned a personal identification number at birth or at the time of immigration, enabling linkage between the registers.

Variables

Any fracture, MOF, hip fracture, and death were assessed as outcomes. Any fracture included all nonpathological fracture diagnoses regardless of type of trauma. Hip fracture included fractures of the femoral head, neck, trochanter, or subtrochanteric part of the femur accompanied by a code for surgical procedure. Covariates with a potential impact on an individual's risk of fracture were selected; the patient's age, sex, and inclusion year, as well as last year's osteoporosis medication, multiple recent fractures, and the Charlson Comorbidity Index (to summarize and quantify comorbidity).[20] The osteoporosis medication variable included the last 12 months' prescriptions from both hospitals and primary care facilities as well as codes representing nonprescribed medications. Furthermore, variables for prednisolone use, variables linked to alcohol and opioid use, and variables for the use of selective serotonin reuptake inhibitors (SSRIs) and nonsteroidal anti-inflammatory drugs (NSAIDs)

Table 2. Outcomes Per Group of Fracture History

	Recent (≤2 years) MOF	Recent (≤2 years) non-MOF	Old (>2 years) fracture	No previous fracture
N	70,254	75,526	293,051	2,984,489
Time at risk, years median (IQR)	6.1 (3.0–8.8)	7.2 (5.6–9.4)	7.1 (5.8–9.2)	8.1 (7.4–9.7)
Any fracture				
n (%)	23,430 (33.4%)	23,290 (30.8%)	79,555 (27.1%)	459,975 (15.4%)
Rate, per 1000 person-years	68.7 (67.9–69.6)	52.4 (51.8–53.1)	44.7 (44.4–45.0)	20.5 (20.5–20.6)
HR (95% CI) model 1	2.11 (2.08–2.14)	2.24 (2.21–2.27)	1.77 (1.76–1.78)	Ref. (1)
HR (95% CI) model 2	1.97 (1.94–1.99)	2.09 (2.07–2.12)	1.75 (1.73–1.76)	Ref. (1)
HR (95% CI) model 3	2.05 (2.01–2.10)	2.34 (2.29–2.40)	1.79 (1.77–1.82)	Ref. (1)
Major osteoporotic fracture				
n (%)	14,879 (21.2%)	11,804 (15.6%)	44,393 (15.1%)	240,227 (8.0%)
Rate, per 1000 person-years	39.8 (39.2–40.4)	23.7 (23.3–24.1)	23.0 (22.8–23.3)	10.3 (10.3–10.3)
HR (95% CI) model 1	1.98 (1.95–2.01)	1.86 (1.83–1.90)	1.62 (1.61–1.64)	Ref. (1)
HR (95% CI) model 2	1.89 (1.86–1.93)	1.78 (1.74–1.81)	1.62 (1.60–1.63)	Ref. (1)
HR (95% CI) model 3	1.78 (1.75–1.81)	1.67 (1.63–1.70)	1.57 (1.55–1.59)	Ref. (1)
Hip fracture				
n (%)	7,437 (10.6%)	5,255 (6.96%)	20,516 (7.00%)	99,671 (3.34%)
Rate, per 1000 person-years	18.3 (17.9–18.7)	9.99 (9.72–10.3)	10.1 (9.99–10.3)	4.17 (4.14–4.19)
HR (95% CI) model 1	1.73 (1.69–1.78)	1.71 (1.66–1.76)	1.51 (1.48–1.53)	Ref. (1)
HR (95% CI) model 2	1.65 (1.61–1.69)	1.62 (1.58–1.67)	1.50 (1.47–1.52)	Ref. (1)
HR (95% CI) model 3	1.67 (1.60–1.74)	1.71 (1.63–1.80)	1.47 (1.43–1.51)	Ref. (1)
Death				
n (%)	37,915 (54.0%)	26,465 (35.0%)	101,759 (34.7%)	593,369 (19.9%)
Rate, per 1000 person-years	88.9 (88.1–89.8)	49.0 (48.4–49.6)	48.9 (48.6–49.2)	24.5 (24.5–24.6)
HR (95% CI) model 1	1.71 (1.70–1.73)	1.55 (1.53–1.57)	1.39 (1.38–1.40)	Ref. (1)
HR (95% CI) model 2	1.53 (1.51–1.54)	1.38 (1.36–1.40)	1.34 (1.33–1.35)	Ref. (1)
HR (95% CI) model 3	1.35 (1.33–1.38)	1.29 (1.26–1.32)	1.35 (1.33–1.36	Ref. (1)

Note: Outcomes per groups of fracture history. Event rates were calculated as the number of events per 1000 person-years and are presented with exact Poisson 95% confidence intervals. The multivariable Cox model was adjusted in three steps: model 1 for age and sex; model 2 with added adjustment for inclusion year, osteoporosis medication, multiple recent fractures, and Charlson Comorbidity Index; model 3 with added adjustment for oral prednisolone, alcohol-related disease, drugs used in alcohol dependence, opoids, drugs used in opoid dependence, SSRI, and NSAID. All *p*-values <0.001.

were defined. All variables are described in detail with codes in Tables S1 and S2.

Statistical analyses

Descriptive baseline statistics for the four groups (recent MOF, recent non-MOF, old fracture, and no previous fracture) are presented in terms of counts with percentage for categorical variables and averages with standard deviations (SDs) for continuous variables. Event rates were calculated as the number of events per 1000 person-years and are presented with exact Poisson 95% CIs. Cox regression models were used to calculate hazard ratios (HRs), adjusted for age and sex (model 1), and with gradually increased multivariable adjustment (model 2 and model 3). The follow-up time was censored for end of study (December 31, 2017), emigration, and death. The Cox assumption of proportional hazards was tested using graphical methods. To assess the risk of fracture among patients with recent fracture per specific diagnosis (ICD-10 four characters), all groups with $n > 410$ were included, rendering 80% power to detect a 50% risk difference compared with the no-fracture group. Forest plots were used to present the HRs per ICD-10 four-character categories. Interactions were tested using multivariable-adjusted Cox models, with interaction terms for the categorical group variable (recent MOF, recent non-MOF, old fracture versus no fracture), sex and age, respectively. For analysis of interaction, *p* values less than .10 were considered significant. We performed subgroup analyses per sex and age group and sensitivity analyses with censoring after 2 years and 1 year, respectively, as well as excluding patients with multiple recent fractures. To assess the potential impact of death as a competing risk, for a subset of 30,000 randomly selected persons in each case group and 90,000 in the control group, the subdistribution HRs for fracture was analyzed using a Fine and Gray model with death as the competing risk.[21] Statistical analyses were performed using R version 4.02 and R-Studio version 1.4.1106.

Results

Study population

A total of 3,423,320 persons were included in the study. At baseline, 70,254 had had a recent MOF and 75,526 a recent non-MOF, and 293,051 had experienced a fracture more than 2 years ago, while 2,984,489 persons had no previous fractures. The mean (SD) age for the groups were 75.6 (12.0), 68.9 (12.5), 70.2 (12.3), and 65.5 (10.8) years, respectively. Osteoporosis medication use the last year was more common among patients with recent MOF (16.4%) than in patients with recent non-MOF (10.0%) and in patients with fractures more than 2 years ago (10.4%). The proportion of osteoporosis medication use was the smallest in persons without previous fractures (4.5%). Charlson Comorbidity Index was higher among patients with a recent MOF, followed by patients with a recent non-MOF and those with older fractures (Table 1). The median follow-up time ranged from 8.1 (IQR 7.4–9.7) years for persons without fracture to 6.1 (IQR 3.0–8.8) years for patients with a recent MOF (Table 1).

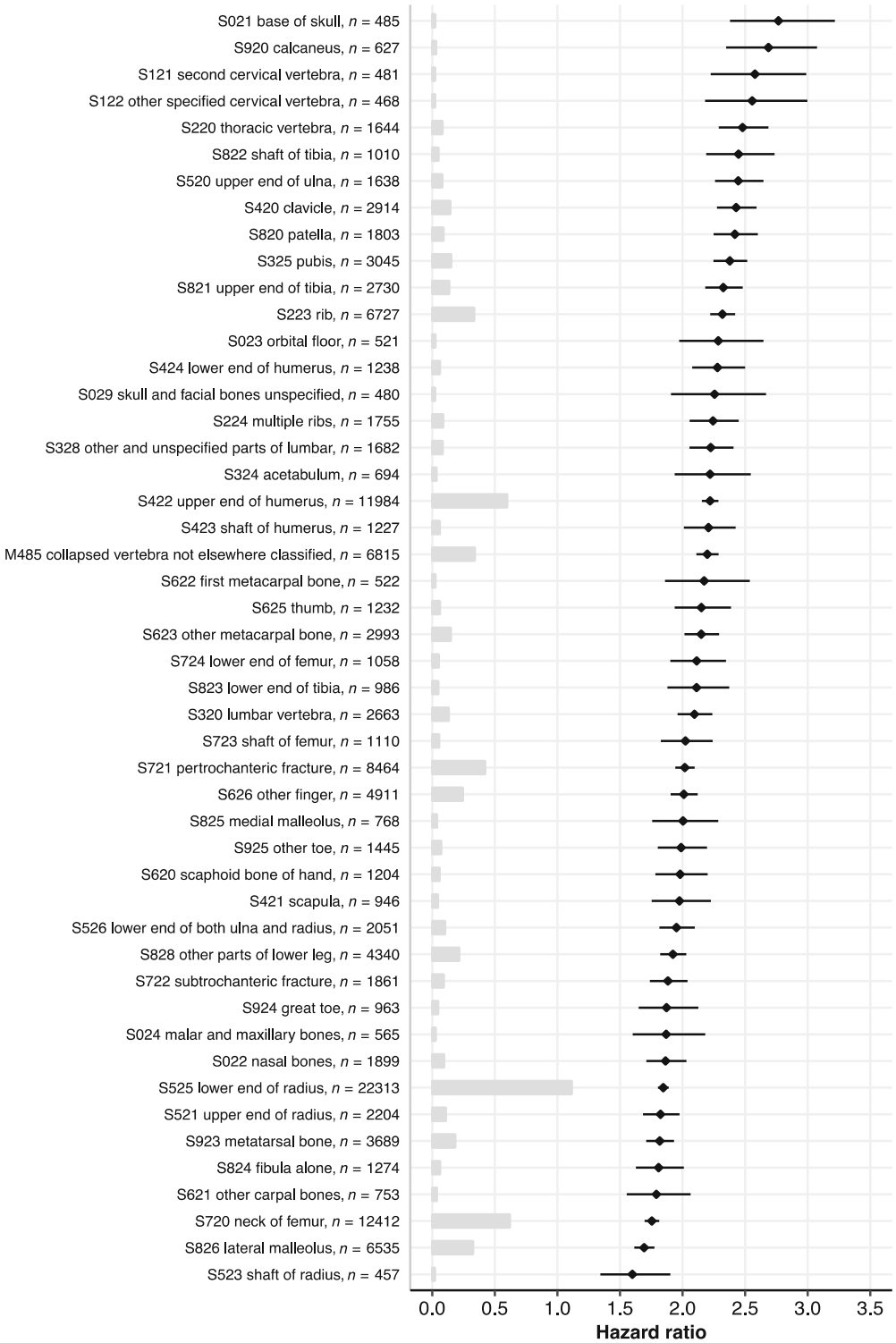

Fig. 2. Risk of any fracture per site of recent fracture. Adjusted hazard ratios and number of patients at risk per site of recent fracture (≤2 years) using ICD-10 four-character categories compared with patients with no previous fracture. Only categories with sufficient power (≥0.80) to detect a 50% increased risk are presented ($n > 410$). The Cox model is adjusted for age, sex, inclusion year, osteoporosis medication, multiple recent fractures, and Charlson Comorbidity Index (= model 2). All p values < .001.

Risk of fracture

During follow-up, 23,430 (33.4%) patients with recent MOF, 23,290 (30.8%) with recent non-MOF, 79,555 (27.1%) with old fractures, and 459,975 (15.4%) with no previous fracture sustained a new fracture of any kind, translating to incidence rates of 68.7 (67.9–69.6), 52.4 (51.8–53.1), 44.7 (44.4–45.0), and 20.5

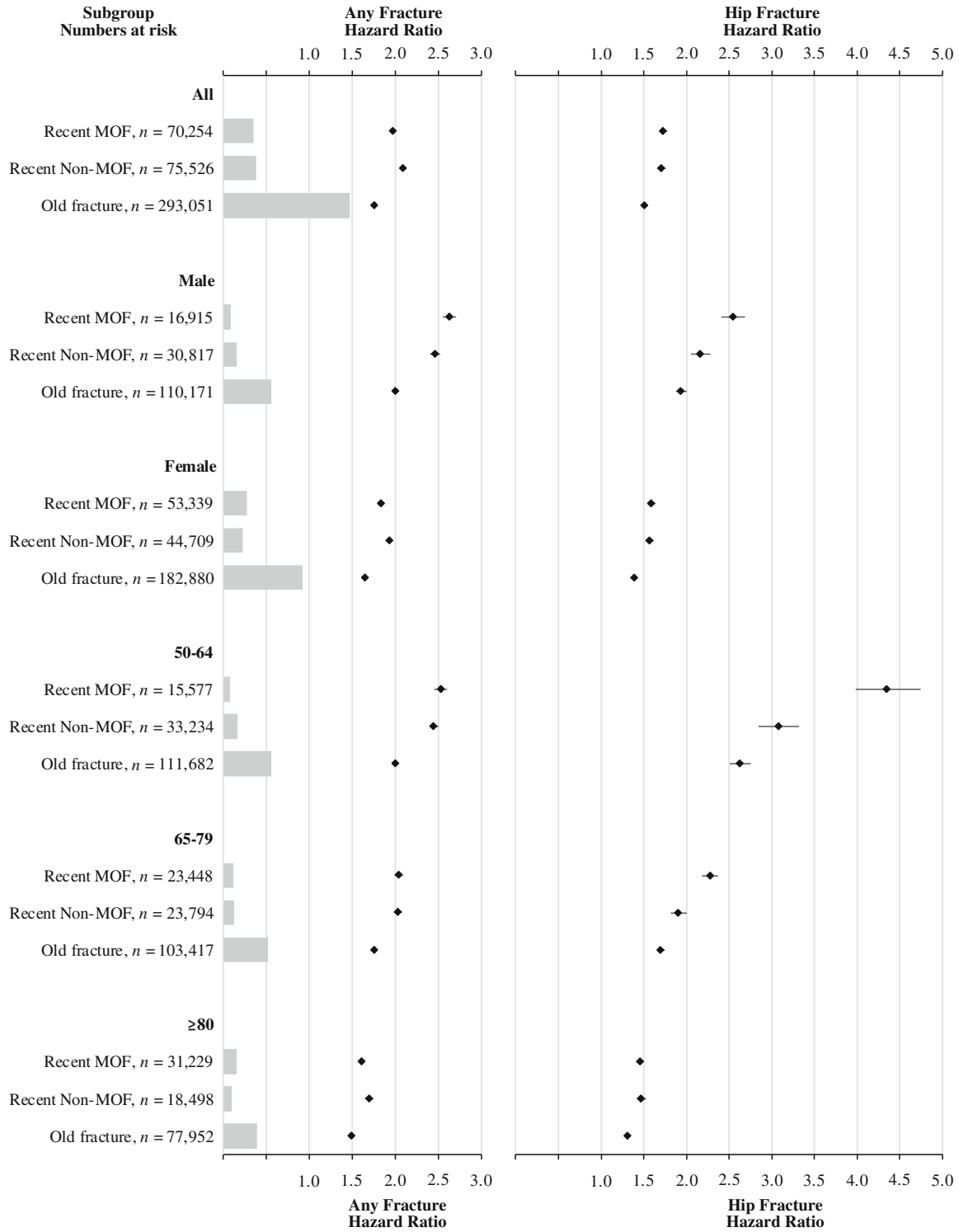

Fig. 3. Risk of any and hip fracture per age, sex, and group of fracture history. Subgroup analyses per sex and age group with adjusted HRs with 95% CIs for any fracture, hip fracture, and number of patients at risk per group of fracture history with no previous fracture as reference. The Cox model is adjusted for age, sex, inclusion year, osteoporosis medication, multiple recent fractures, and Charlson Comorbidity Index (= model 2). All p values < .001 including those for the interaction terms. Incidence, rates, and HRs are presented in Tables S3 and S4.

(20.5–20.6) fractures per 1000 person-years, respectively. Patients with a recent MOF, recent non-MOF, and an older fracture had a substantially increased risk of any fracture (HR adjusted for age and sex 2.11 [95% CI 2.08–2.14], HR 2.24 [2.21–2.27], and HR 1.77 [1.76–1.78], respectively) compared with controls without a previous fracture, associations that were only

marginally affected by multivariable adjustment (Table 2, Fig. S1*A*). Similar but less pronounced associations were found between previous fracture group and incident MOF and hip fracture (Table 2, Fig. S1*B*). For all specific fracture diagnoses (ICD-10 four characters), the risk was consistently increased by between 50% and 170% (Fig. 2).

Risk of fractures per sex

Compared with controls with no previous fracture, the risk of any and hip fractures was consistently higher in patients with recent fracture, both recent MOF and non-MOF, regardless of sex, while the risk increase among patients with older fractures was less pronounced (Fig. 3, Table S3). The relative risk increase was most pronounced among men, regardless of fracture site (Fig. S2*A*, *B*).

Risk of fractures per age group

Compared with controls with no previous fracture, the risk of any fracture and hip fracture was consistently higher in patients with recent fracture, both recent MOF and non-MOF, regardless of age group, while the risk increase among patients with older fractures was less pronounced (Fig. 3, Table S4). The relative risk increase was most pronounced among the youngest age group, regardless of fracture site (Fig. S2*C*-*E*). For the youngest age group, 50–64 years, the different femoral fractures provided the highest risk estimates. For both the age group 50–64 and 65–79 years, most index fracture sites were associated with a higher risk of subsequent fracture than what was observed for the most common index fracture site, that is, the distal radius (S525).

Risk of fractures with follow-up censored after 1 or 2 years

Compared with controls with no previous fracture, the risk of any and hip fractures was consistently higher in patients with recent fracture, both recent MOF and non-MOF, slightly lower among patients with older fractures, but more pronounced with shortened follow-up time (Tables S5 and S6). Generally, the relative risks were higher with 1 or 2 years of follow-up compared with complete follow-up, regardless of fracture site with HRs ranging between 2 and 6 (Fig. S2*F*, *G*).

Risk of fractures with patients with multiple recent fractures excluded

Because multiple recent fractures were allowed in the main analyses and only the most recent fracture site allowed to contribute, a sensitivity analysis was performed excluding patients with multiple recent fractures. Exclusion of these patients did not materially change the observed associations (Table S7, Fig. S2*H*).

Mortality and competing risk

During follow-up, there were 37,915 (54.0%) deaths among the patients with recent MOF, 26,465 (35.0%) among the patients with recent non-MOF, 101,759 (34.7%) among the patients with old fractures, and 593,369 (19.9%) among the patients with no previous fracture, translating to incidence rates of 88.9 (88.1–89.8), 49.0 (48.4–49.6), 48.9 (48.6–49.2), and 24.5 (24.5–24.6) per 1000 person-years, respectively. Mortality rates in all groups increased with increasing age span (Table S4). Patients with recent MOF, non-MOF, and old fracture had a significantly increased risk of death (HR adjusted for age and sex 1.71 [1.70–1.73]), HR 1.55 [1.53–1.57], and HR 1.39 [1.38–1.40], respectively), compared with controls with no previous fracture, associations slightly attenuated by multivariable adjustment (Table 2). Adjusted subhazard ratios for the association between patients with recent MOF, recent non-MOF versus patients with no previous fracture calculated using Fine and Gray and any fracture with death as a competing risk were similar to the HRs obtained using the corresponding Cox regression but yielded lower risk estimates, particularly for recent MOF (Table S8).

Discussion

This nationwide cohort study included all persons 50 years or older, followed them from baselines ranging between the years 2007 and 2010 until the end of 2017, death, or emigration. Patients with recent fractures at baseline had a substantially higher risk of any recurrent fracture, regardless of index fracture site and regardless of fracture type definition, according to the MOF or non-MOF classification. These risk increments were even more pronounced when the follow-up was limited to 1 and 2 years. As expected, patients with a recent MOF (including hip fracture patients) had a higher mortality than was observed in the other investigated groups, and adjusting for competing risk yielded a less pronounced increase in fracture risk in this group, a tendency not clearly observed in the recent non-MOF group. These findings demonstrate that the risk of recurrent fracture is consistently high regardless of index fracture site, indicating that current efforts by secondary fracture prevention programs should target all patients with recent fractures, not only those with MOFs, even though this approach will require more resources.

Interestingly, the risk of subsequent fracture was even slightly higher in patients with a recent index fracture of a nonmajor osteoporotic type than in those with a traditional MOF type. Although this might be explained by the higher proportion of osteoporosis medication use in patients with recent MOFs (16.4%) than in patients with recent non-MOFs (10.0%), indicating that secondary prevention efforts indeed are more successful in patients with MOFs, the risk difference tendency remained after adjusting for osteoporosis medication and was even more pronounced with shorter follow-up time. Given that the risk difference remained also in the analysis using the 1-year truncated follow-up, it is unlikely that the difference in osteoporosis medication use could be the only underlying reason. Thus, future studies are needed to confirm these findings. In the Kaplan–Meier curves, the incidence in the recent MOF group appears to dominate and the recent non-MOF appears equivalent to the group with old fractures. However, this graph should be interpreted with caution since it is unadjusted and there are considerable age differences between the groups.

Here, we adjusted the analyses for a minimal number of potential confounders since the aim was to investigate how fracture risk was determined by site of index fracture and not to attempt to explain any underlying mechanisms. Increased understanding regarding which index fractures that confer an increased risk for subsequent fracture is important for designing secondary prevention strategies to reduce fracture incidences.

Notably, the risk of subsequent fracture was considerably increased even for fractures older than 2 years, indicating that in addition to FLSs for recent fractures, case-finding strategies

to identify those with old fractures may be warranted to enable the prevention of subsequent fractures.

The risk of subsequent fracture was higher in younger patients than in older and higher in men than in women, for those with recent MOF and non-MOF, indicating that imminent fracture risk is complex and to some extent age and sex dependent. We find it noteworthy that most fracture sites were associated with a higher risk of subsequent fracture than that observed for wrist fracture, which is the most common fracture type.

Despite the widely accepted notion that fractures of the skull, fingers, and toes are not associated with an increased fracture risk, to our knowledge, no confirming large studies providing robust data to support this assumption are available. Stone et al. attempted to estimate the proportion of various fracture types that were attributable to low bone mass.[17] They studied the central BMD in 9704 community-dwelling women aged 65 years and older and compared women sustaining various fractures with women not sustaining fractures. Almost all fracture types were associated with lower bone mass. However, because the groups created were based upon incident events, the results might have been biased, which limited the interpretation of the findings. In the present study, we did not have access to BMD and could not investigate the association between BMD and index fracture site. Thus, the increased risk of fracture seen after all types of index fracture could, to a large extent, be BMD independent and be due to other risk factors, such as increased risk of fall, heredity, or general frailty not captured using the Charlson Comorbidity Index. However, the available evidence demonstrates that patients with a high fracture risk, regardless of whether they have osteoporosis or osteopenia, benefit from osteoporosis medication.[22-25]

In this analysis, the mortality rate was considerable in the groups with a previous fracture, and more so in the group with recent MOFs. Considering that the competing risk of death still yielded associations between recent and subsequent fractures, the risk estimates for recent MOFs was less pronounced. However, the increased risk of fracture regardless of MOF classification was consistent across age groups, being present also in the youngest age group with a substantially lower mortality, supporting a mortality-independent increase in fracture risk regardless of MOF classification.

This study is the by far largest cohort study examining the risk of subsequent fracture in patients with a recent fracture depending on fracture site, allowing for an investigation with adequate statistical power of rare fracture sites. The adjustment of key anthropometrics, repeated fractures, osteoporosis medications, and Charlson Comorbidity Index indicates associations regardless of these factors with minimal bias.

The analysis presented here has limitations. First, causality cannot be determined due to the observational design. Second, there were considerable differences between the groups in terms of age, sex, and comorbidity. However, the associations were consistent regardless of subgroup analyses and adjustment. Third, BMD data were not available, but because fracture risk is the key component in determining treatment indication, it may be argued that this is of subordinate importance. Fourth, generally, register studies have limitations in accurately capturing fracture events. However, the positive predictive value for diagnosis in the inpatient register is high, ranging from 85% to 95%.[26] For humeral fractures in particular, the National Patient Register has a high level of completeness (97%) but lower accuracy (70%), which is at least partly remedied by the wash-out period that was used of 5 months for fracture events at the same skeletal site.[27]

In conclusion, patients with a recent fracture had an increased risk of subsequent fracture, regardless of index fracture site and MOF classification. In contrast to previous belief and many current clinical guidelines, the present results indicate that all patients with recent fracture, regardless of fracture site, should be included in secondary prevention programs such as FLSs.

Disclosures

Dr. Axelsson has received lecture fees from Lilly, Meda/Mylan, and Amgen, all outside the submitted work. Mr. Litsne has no conflicts of interest. Prof. Lorentzon has received lecture fees from Astellas, Amgen, Lilly, UCB Pharma, Radius Health, Meda/Mylan, GE-Lunar. and Santax Medico/Hologic, all outside the submitted work.

Author Contributions

Kristian F. Axelsson: Conceptualization; investigation; funding acquisition; writing – original draft; methodology; validation; visualization; writing – review and editing; software; formal analysis; project administration; data curation; resources. **Henrik Litsne:** Investigation; data curation; formal analysis; software; methodology; writing – review and editing; validation. **Mattias Lorentzon:** Conceptualization; investigation; funding acquisition; writing – review and editing; visualization; validation; methodology; supervision; resources; formal analysis; project administration; software.

Data Availability 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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