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ORIGINAL RESEARCH

Excess mortality following a first and subsequent osteoporotic fracture: a Danish nationwide register-based cohort study on the mediating effects of comorbidities

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ABSTRACT

Objectives This study aimed to examine the risk of mortality following incident and subsequent osteoporotic fractures, the effect of different fracture type combinations, and the mediating role of postfracture morbidity in a Danish population.

Methods We used the National Patient Registry to identify patients ≥60 years with incident major osteoporotic fracture of the hip, vertebrae, wrist or humerus between 2013 and 2018, and controls matched 1:10 on age and sex. Possible mediators were identified using International Classification of Diseases, 10th Revision codes registered in the 6 months following index fracture. HRs were estimated using Cox regression analyses with 95% CIs. The effect of possible mediators was estimated using mediation analyses.

Results The study included 106 303 patients and 1 062 988 controls. Mortality following index fracture was highest in the month following hip fractures (HR 10.98 (95% CI 10.23 to 11.79) in women and HR 16.40 (95% CI 15.00 to 17.93) in men). Subsequent hip fractures resulted in the highest HRs for all fracture type combinations. In women, the highest HR was observed in patients with index wrist/subsequent hip fractures (HR 2.43 (95% CI 2.12 to 2.78)). In men, the highest HR was observed in patients with index humerus/subsequent hip fractures (HR 2.69 (95% CI 2.04 to 3.54)). Pneumonia mediated the largest proportion of mortality, but dehydration, urinary tract infection and sepsis were also important factors.

Conclusions The highest mortality risk was found in the month immediately following both index and subsequent fracture. The combination of index and subsequent fractures at different skeletal sites had a substantial impact on the risk of mortality. Postfracture morbidities were found mediate the association.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Excess mortality following osteoporotic fracture is well examined, but the impact of index and subsequent fracture type combinations and mediating postfracture comorbidities is unclear.

WHAT THIS STUDY ADDS

⇒ This study shows that the combination of index and subsequent fractures at various skeletal sites impact excess mortality, and that mortality is mediated by comorbidities occurring in the 6 months immediately following fracture.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this study may be of value for clinical guidelines for osteoporotic fracture patients.

INTRODUCTION

The association between osteoporotic fractures and excess mortality is well established, and while the link has been most thoroughly investigated in hip fractures,[1] it has also been observed in other fracture types.[2–4] Patients with a previous fracture have a higher risk of subsequent fracture,[5 6] with studies also observing close to a twofold increase in mortality risk among these patients.[3 5–7] The impact on mortality of different fracture type combinations have been examined to a much lesser extent[8] but may be an important component in understanding this association.

Additionally, comorbidities further complicate mortality following fracture. More than 40% of fracture patients exhibit two or more comorbidities around the time of fracture.[9 10] It has been demonstrated that fracture patients with comorbidities such as chronic obstructive pulmonary disease, cardiovascular or respiratory disease have a higher risk of mortality than those without.[11–15] Further, previous

studies have concluded that comorbidities contributed substantially to excess mortality in hip fracture patients[16] and vertebral fracture patients,[17] respectively. However, studies examining perifracture or postfracture comorbidities have largely been limited to hip fractures.[12 14 18] As such, it is less clear how much of the observed increase in mortality risk is attributable to fracture complications and how much to the fracture itself, especially for fracture sites other than hip. To our knowledge, no studies have examined the mediating role of postfracture comorbidities and complications in a larger population.

The aim of this study was to examine the risk of mortality following incident and subsequent osteoporotic fracture, as well as the association of different fracture type combinations and the ensuing mortality in the Danish population, while also considering the mediating role of postfracture morbidities.

METHODS

Study design and data sources

The study was designed as a matched nationwide register-based cohort study, based on the Danish national registers covering all citizens living in Denmark on 1 January 2013.

In Denmark, administrative data on all individuals are stored in registries and all permanent residents of Denmark have unique identification numbers; thus individual-level linkage of data across registries is possible.[19] We obtained data from the Civil Registration System (CRS) and the National Patient Registry (NPR), provided by The Danish Health Data Authority.

The CRS was established in 1968 and maintains complete records of births, deaths and emigration status of all residents in Denmark.[20] The CRS was used to identify individuals for inclusion in the study, to obtain data on demographic characteristics, deaths and emigration.

The NPR contains data on all inpatient contacts from public hospitals in Denmark since 1977, with outpatient and emergency department contacts included from 1995 and private hospitals from 2003.[21] The NPR was used to retrieve diagnostic codes (International Classification of Diseases, 10th Revision (ICD-10)) for hospital contacts from 2003 to 2018, specifically identifying those representing osteoporotic fractures and selected comorbidity variables (both Charlson Comorbidity Index (CCI) and mediators) during the lookback and study periods (figure 1). In addition to ICD-10 codes, the NPR was used to retrieve the corresponding admission dates to define the date of occurrence for all fractures included in the study as well as admission dates for the aforementioned comorbidities.

The study period started on 1 January 2013 with inclusion of data on fracture patients from the NPR until 31 December 2018. The risk of mortality was followed up until 31 December 2018 (figure 1).

Osteoporotic fractures population

The osteoporotic fracture patients included all Danish citizens sustaining a major osteoporotic fracture (MOF) between 2013 and 2018, aged ≥60 years on the date of their first fracture in the inclusion period (defined as index fracture and index date). For results to be informative on the scenario of an incident osteoporotic fracture, patients were excluded from the study population if they had sustained an MOF within 3 years prior to the index fracture. While this exclusion period is largely arbitrary, it was chosen because it matched the period used by Chen *et al*.[8] Other scenarios were explored as sensitivity analyses.

Fracture events

MOF was defined as a hip, clinical vertebral, humerus or wrist fracture, identified as a primary or secondary

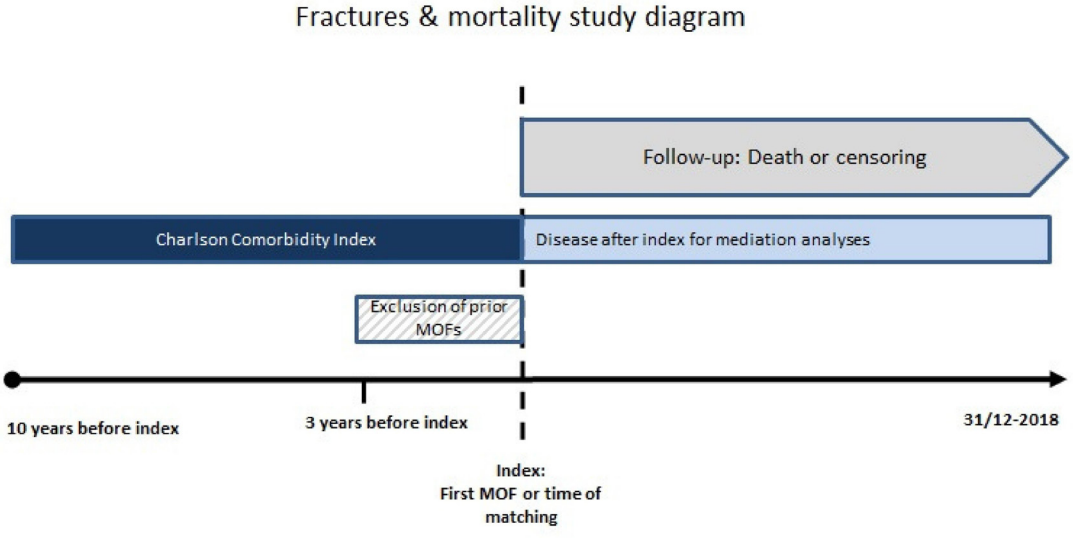

Figure 1 Diagram of study period, study phases and data sources. MOF, major osteoporotic fracture.

diagnosis code in the NPR. ICD-10 coding for MOFs followed the ICD-10 coding applied in the Fracture Risk Evaluation Model.[22 23] Included ICD-10 codes were: S720, S721, S722 (hip), S320, T08, S220, S221, S120, S121, S122 (clinical vertebral), S525, S526 (wrist), S422 and S423 (humerus). For a hip fracture to be included in the study, both an ICD-10 code for a hip fracture and a relevant surgical code (KNFB* or KNFJ4-9) must have been registered a maximum of 7 days apart. Surgical codes for defining hip fractures were chosen as suggested by Hjelholt *et al*.[24]

Subsequent fracture

Subsequent fractures followed the same definition as MOFs and were recorded as the first fracture after index fracture. For subsequent fractures at the same skeletal site as the index fracture, a grace period of 6 months was inserted between the admission date of the index fracture and of the admission date of the subsequent fracture, for the fracture to count as subsequent. This was done to ensure that the two fractures were separate incidents, as a fracture registration in the NPR<6 months of another fracture is likely associated with the first fracture, for example, as a check-up consultation. The same interval has been applied previously by Driessen *et al*.[25]

For subsequent fractures at a different skeletal site than the index fracture, it was restricted that the registered admission date had to occur after the index date.

Controls

Fracture patients were matched 1:10 by sex and year of birth with controls extracted from the CRS on the index date. Controls were assigned the index date of their matched fracture patient. Controls had to be alive at the index date of their respective matched fracture patient. Controls were sampled with replacement and changed status to cases if they sustained a fracture during the study period.

Outcome and definition of study parameters

The main outcome was mortality after the index date identified during the period 1 January 2013 to 31 December 2018 in the CRS. As a secondary outcome, we assessed mortality after cases experienced any subsequent fractures during the period 1 January 2013 to 31 December 2018.

Covariates

Age was calculated on index date and categorised into 5 year age groups (60–64, 65–69, 70–74, 75–79 and ≥80 years). The CCI was used to classify comorbid conditions in the study population recorded within the 10-year period prior to the index date (figure 1). The 17 comorbidities in the CCI were ICD-10-coded as suggested by Quan *et al*.[26] Further, each CCI comorbidity was defined as a separate dichotomous variable as suggested by Möller *et al*.[27]

Mediators (postfracture comorbidity)

Possible mediators were identified among all comorbidities registered in the 6 months following the index date using primary or secondary ICD-10 codes from the NPR (figure 1). ICD-10 codes detailing comorbidities which were unlikely to occur as a result of fracture (eg, H295 Unspecified age-related cataracts) were excluded and similar ICD-10 codes were combined into categories (eg, I500, I501 and I509 categorised as 'Heart failure') following discussion among the authors. Comorbidities which occurred in <0.4% of the fracture population (either as single ICD-codes or categories) were excluded, and the remaining comorbidities were rated by 10 clinicians on a 5-point scale according to how likely the condition was to occur as a result of fracture. Comorbidities which were scored as either 'somewhat likely' or 'very likely' by at least 70% of respondents were included in the mediation analyses.

Statistical analyses

Baseline characteristics of the study population were presented as frequencies for categorical variables. Continuous variables were summarised as medians with quartiles.

The HRs for death were estimated by performing crude and adjusted Cox regression analyses with 95% CIs. We adjusted analyses for age and separate dichotomous CCI comorbidities.[27] All analyses were stratified by sex. Survival time was calculated from index date to time of censoring or death. Controls who during follow-up met the MOF criteria were included as a case on the date of their index fracture. The study population was censored on emigration or at the end of the study period, 31 December 2018. Survival time was split into appropriate intervals to accommodate the non-proportional hazards. In the analyses of subsequent fracture and mortality, we included subsequent fracture and age as time-dependent variables, changing the values of the variables at the date of the subsequent fracture.

According to a counterfactual approach, mediation analyses were performed as suggested by VanderWeele.[28] The HRs adjusted for potential confounders correspond to the total effect of fracture on the risk of death, which can be decomposed into a controlled direct effect (CDE) and the mediated effect. The CDE captures the influence of fracture on the risk of death, if removing the effect of the possible mediator. The CDE was obtained by adjustment for both potential confounders and the mediating factors—the latter were treated as time-dependent variables. Additionally, the proportion eliminated (PE) was estimated.[28] PE describes the proportion of effect which might be removed by eliminating the mediator from the pathway. The 95% CIs for CDE and PE were estimated by bootstrapping using 100 replicates. Mediators resulting in a PE≥15% were reported in the main results. Full mediation analysis was reported in online supplemental materials. Individuals with pre-existing conditions of the mediator in question were excluded.

Four sensitivity analyses were performed. The first sensitivity analysis excluded patients from the fracture population if they sustained an MOF in a 10-year period prior to the date of index fracture, compared with the 3-year exclusion period applied in the main analysis. The second sensitivity analysis applied a 3-month grace period for subsequent fractures within the same skeletal site as the index fracture, compared with the 6 months applied in the main analysis. The third sensitivity analysis applied a fracture hierarchy for patients who sustained multiple fractures on the index date. The hierarchy ranked fractures according to severity as follows: hip>clinical vertebral>humerus>wrist. The most severe fracture (according to the hierarchy) among the multiple fractures sustained on the index date accounted for index and subsequent fractures in analyses. The fourth sensitivity analysis stratified the population based on CCI score=0 or ≥1.

Data management and data analyses were conducted using Stata V.17[29] through a remote VPN access to The Danish Health Data Authority with analysts blinded to the personal identities of the study subjects.

RESULTS

MOFs occurred in 1 77 639 women and 58 692 men aged ≥60 years at time of fracture between 1 January 2013 and 31 December 2018. Of these, 99 502 women and 30 526 men had been diagnosed with an MOF within 3 years prior to the index date and were excluded, resulting in 78 137 women and 28 166 men included in the fracture population. Following 1:10 matching, 781 359 women and 281 629 men were included as controls for a total study population of 1 169 291 persons (figure 2). For a few cases, it was not possible to identify 10 controls. These were matched with the maximum available number of controls.

The fracture population included 106 303 individuals sustaining an MOF between 2013 and 2018, of which 73.5% were women and the median age at time of index fracture was 76.3 years (68.9; 84.5) (table 1). The most common fracture types were wrist and hip at 39 218 and 35 092 individuals, respectively, followed by 21 714 individuals sustaining a humerus fracture and 11 974 individuals sustaining a clinical vertebral fracture (table 1).

Table 2 shows the baseline characteristics of the study population stratified by sex and fracture status. The fracture control populations were overall comparable on age group distributions in both sexes. Distributions varied to a greater extent in terms of CCI comorbidities, with the fracture population displaying a higher occurrence of all comorbidities (table 2).

Table 3 shows risk of death following index fracture with time split into intervals from 1 month to ≥5 years after fracture. Overall, mortality was highest in the first month immediately following fracture before steadily declining over time. Men displayed higher HRs across fracture types compared with women. In both sexes, the highest mortality was observed in the first month following a hip fracture (HR 10.98 (95% CI 10.23 to 11.79) in women and HR 16.40 (95% CI 15.00 to 17.93) in men) (table 3).

Increased HRs were observed among individuals sustaining a subsequent fracture, compared with those only sustaining an index fracture (figure 3). Among

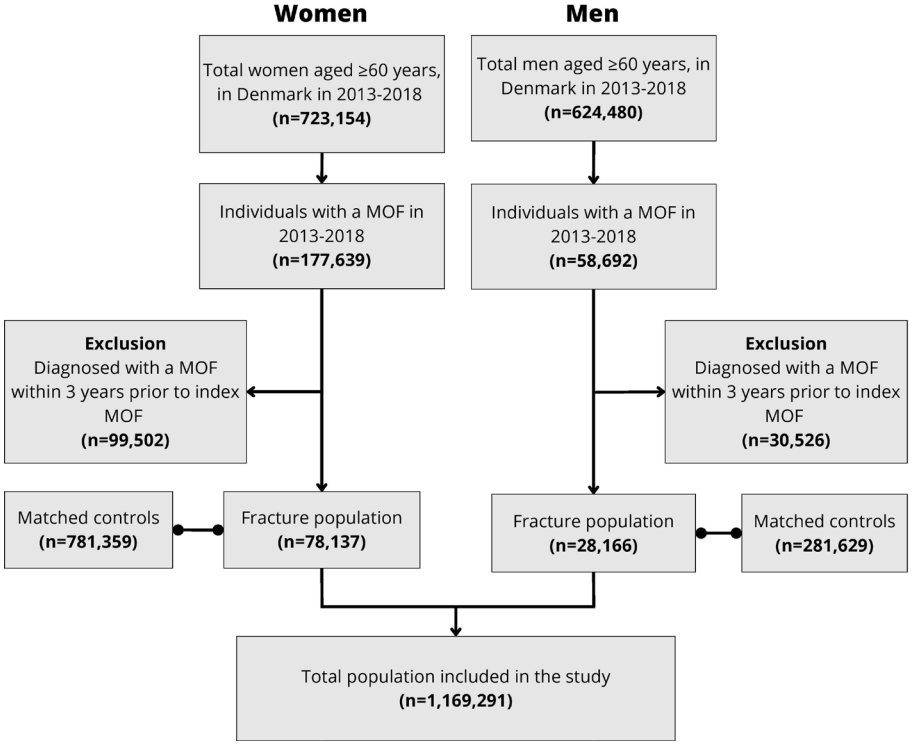

Figure 2 Flow chart of inclusion and exclusion of study population. MOF, major osteoporotic fracture.

Table 1 Index fractures, number and age of fracture population studied according to fracture sites (N=106 303)

Fracture site*	Individuals, N	Women, N (%)	Age (median (Q1; Q3))
MOF	106 303	78 137 (73.5)	76.3 (68.9; 84.5)
Clinical vertebral	11 974	6726 (56.2)	75.9 (69.0; 83.2)
Hip	35 092	23 362 (66.6)	82.3 (74.7; 88.5)
Humerus	21 714	16 393 (75.5)	74.0 (67.7; 81.9)
Wrist	39 218	33 007 (84.2)	72.6 (66.7; 80.4)

*A single case may be included in multiple fracture site categories if more than one fracture was sustained on the index date.
MOF, major osteoporotic fracture.

individuals with any MOF as index fracture, the highest mortality was observed in those sustaining a subsequent hip fracture (HR 1.86 (95% CI 1.73 to 2.01) in women and HR 1.97 (95% CI 1.73 to 2.26) in men). Subsequent hip fractures resulted in the highest HRs for death across all index fracture types in both sexes. In women, the highest HR was observed in patients with an index wrist fracture and a subsequent hip fracture (HR 2.43 (95% CI 2.12 to 2.78)). In men, the highest HR was observed in patients with an index humerus fracture and a subsequent hip

Table 2 Study population characteristics stratified by sex and case status

	Women, N=859 496		Men, N=309 795	
	Fracture patients, N=78 137	Population controls, N=781 359	Fracture patients, N=28 166	Population controls, N=281 629
Age, years (median (Q1; Q3)	75.0 (68.0; 83.0)	75.0 (68.0; 83.0)	76.0 (69.0; 84.0)	76.0 (69.0; 84.0)
Age categorised, N (%)				
60–64	9743 (12.5)	95 036 (12.2)	4100 (14.6)	39 517 (14.0)
65–69	12 170 (15.6)	121 512 (15.6)	4707 (16.7)	47 329 (16.8)
70–74	13 103 (16.8)	130 817 (16.7)	4950 (17.6)	49 323 (17.5)
75–79	12 342 (15.8)	123 250 (15.8)	4370 (15.5)	43 883 (15.6)
≥80	30 779 (39.4)	307 867 (39.4)	10 039 (35.6)	100 274 (35.6)
CCI N (%)				
Myocardial infarct	2957 (3.8)	25 769 (3.3)	2250 (8.0)	19 621 (7.0)
Congestive heart failure	4326 (5.5)	35 691 (4.6)	3027 (10.7)	20 621 (7.3)
Peripheral vascular disease	4497 (5.8)	36 667 (4.7)	3109 (11.0)	21 222 (7.5)
Cerebrovascular disease	9374 (12.0)	74 703 (9.6)	5411 (19.2)	33 433 (11.9)
Dementia	5208 (6.7)	28 947 (3.7)	1999 (7.1)	8340 (3.0)
Chronic pulmonary disease	8894 (11.4)	65 959 (8.4)	3992 (14.2)	23 424 (8.3)
Rheumatic disease	3870 (5.0)	32 125 (4.1)	880 (3.1)	6776 (2.4)
Ulcer disease	2673 (3.4)	20 113 (2.6)	1371 (4.9)	7889 (2.8)
Mild liver disease	1200 (1.5)	7065 (0.9)	791 (2.8)	2459 (0.9)
Diabetes (without organ damage)	6294 (8.1)	53 568 (6.9)	3612 (12.8)	26 048 (9.2)
Diabetes (organ damage)	1831 (2.3)	13 714 (1.8)	1486 (5.3)	8973 (3.2)
Hemiplegia or paraplegia	232 (0.3)	1696 (0.2)	188 (0.7)	774 (0.3)
Moderate or severe renal disease	1953 (2.5)	14 803 (1.9)	1687 (6.0)	9894 (3.5)
Any malignancy	9790 (12.5)	84 904 (10.9)	4941 (17.5)	37 725 (13.4)
Moderate or severe liver disease	318 (0.4)	1290 (0.2)	313 (1.1)	696 (0.2)
Metastatic solid tumour	1280 (1.6)	8782 (1.1)	650 (2.3)	3106 (1.1)
AIDS/HIV	9 (0.0)	47 (0.0)	22 (0.1)	92 (0.0)

CCI, Charlson Comorbidity Index.

Table 3 Frequency of deaths and Hazard Ratios (HR) with 95% Confidence Intervals (CI) for each fracture site stratified by time and sex

	Women			Men		
Fracture site	**Fracture patients, N***	**Deaths, N**	**HR (95% CI)**	**Fracture patients, N***	**Deaths, N**	**HR (95% CI)**
MOF						
0–30 days mortality	78 137	2532	7.20 (6.82 to 7.59)	28 166	2115	12.71 (11.86 to 13.63)
31–60 days mortality	74 654	1350	3.97 (3.72 to 4.24)	25 702	920	6.36 (5.83 to 6.93)
61–90 days mortality	72 362	883	2.74 (2.54 to 2.96)	24 467	472	3.66 (3.28 to 4.08)
91–180 days mortality	70 547	1762	1.98 (1.88 to 2.08)	23 661	965	2.58 (2.40 to 2.78)
181–365 days mortality	66 008	2286	1.37 (1.31 to 1.43)	21 653	1352	2.00 (1.88 to 2.12)
Second year mortality	57 666	3582	1.28 (1.24 to 1.33)	18 243	1782	1.69 (1.60 to 1.78)
Third year mortality	43 086	2838	1.36 (1.30 to1.41)	12 922	1185	1.60 (1.50 to 1.71)
Fourth year mortality	30 041	1934	1.38 (1.31 to 1.45)	8617	769	1.62 (1.50 to 1.76)
≥ 5 year mortality	18 528	1463	1.41 (1.33 to 1.50)	5136	491	1.53 (1.39 to 1.69)
Clinical vertebral						
0–30 days mortality	6.726	239	7.48 (6.24 to 8.96)	5248	321	12.07 (10.08 to 14.45)
31–60 days mortality	6389	111	3.28 (2.63 to 4.08)	4859	160	6.90 (5.57 to 8.54)
61–90 days mortality	6177	81	2.85 (2.19 to 3.69)	4635	77	3.98 (3.01 to 5.25)
91–180 days mortality	5994	202	2.50 (2.12 to 2.93)	4496	152	2.34 (1.95 to 2.81)
181–365 days mortality	5521	224	1.49 (1.28 to1.72)	4104	240	2.26 (1.95 to 2.61)
Second year mortality	4732	338	1.44 (1.28 to 1.63)	3438	315	1.91 (1.68 to 2.17)
Third year mortality	3429	253	1.47 (1.28 to 1.68)	2421	191	1.67 (1.43 to 1.95)
Fourth year mortality	2277	168	1.51 (1.28 to 1.79)	1617	115	1.60 (1.30 to 1.97)
≥ 5 year mortality	1318	108	1.35 (1.09 to 1.66)	943	72	1.50 (1.17 to 1.92)
Hip						
0–30 days mortality	23 362	1780	10.9 (10.23 to 11.79)	11 730	1506	16.40 (15.00 to17.93)
31–60 days mortality	21 289	924	6.15 (5.66 to 6.69)	10 093	603	7.71 (6.91 to 8.61)
61–90 days mortality	20 106	564	3.89 (3.53 to 4.29)	9356	295	4.42 (3.84 to 5.09)
91–180 days mortality	19 272	945	2.40 (2.24 to 2.58)	8932	561	2.95 (2.67 to 3.24)
181–365 days mortality	17 645	1148	1.60 (1.50 to 1.70)	7.968	729	2.13 (1.96 to 2.31)
Second year mortality	15 110	1625	1.37 (1.30 to 1.45)	6559	881	1.68 (1.56 to 1.81)
Third year mortality	10 872	1284	1.49 (1.40 to 1.59)	4391	599	1.72 (1.57 to 1.88)
Fourth year mortality	7184	911	1.67 (1.55 to 1.79)	2764	375	1.73 (1.54 to 1.94)
≥ 5 year mortality	4158	627	1.66 (1.52 to 1.81)	1549	233	1.73 (1.50 to 2.00)
Humerus						
0–30 days mortality	16 393	376	6.33 (5.53 to 7.24)	5321	258	10.48 (8.66 to 12.69)
31–60 days mortality	15 794	202	3.51 (2.98 to 4.15)	4987	128	5.51 (4.38 to 6.93)
61–90 days mortality	15 401	132	2.28 (1.88 to 2.76)	4798	72	3.58 (2.71 to 4.73)
91–180 days mortality	15 082	324	1.98 (1.75 to 2.23)	4663	173	2.91 (2.44 to 3.45)
181–365 days mortality	14 226	422	1.45 (1.30 to 1.60)	4329	214	1.87 (1.61 to 2.17)

Continued

Table 3 Continued

Fracture site	Women			Men		
	Fracture patients, N*	Deaths, N	HR (95% CI)	Fracture patients, N*	Deaths, N	HR (95% CI)
Second year mortality	12 481	656	1.32 (1.21 to 1.43)	3697	355	1.98 (1.762 to 2.23)
Third year mortality	9409	537	1.43 (1.30 to 1.57)	2689	204	1.57 (1.34 to 1.83)
Fourth year mortality	6713	331	1.23 (1.09 to 1.38)	1846	160	1.83 (1.53 to 2.19)
≥ 5 year mortality	4166	303	1.46 (1.29 to 1.66)	1125	97	1.48 (1.18 to 1.87)
Wrist						
0–30 days mortality	33 007	232	2.24 (1.94 to 2.59)	6211	66	2.52 (1.90 to 3.34)
31–60 days mortality	32 424	152	1.44 (1.22 to 1.71)	6067	43	1.93 (1.38 to 2.70)
61–90 days mortality	31 870	129	1.32 (1.10 to 1.59)	5965	33	1.36 (0.94 to 1.97)
91–180 days mortality	31 355	346	1.28 (1.14 to 1.44)	5850	96	1.55 (1.251 to 1.94)
181–365 days mortality	29 674	534	0.99 (0.90 to 1.08)	5511	188	1.58 (1.35 to 1.85)
second year mortality	26 272	1041	1.12 (1.05 to 1.20)	4767	250	1.24 (1.08 to 1.42)
third year mortality	20 066	820	1.13 (1.05 to 1.22)	3583	207	1.39 (1.20 to 1.61)
fourth year mortality	14 352	564	1.11 (1.02 to 1.22)	2487	133	1.33 (1.11 to 1.60)
≥ 5 year mortality	9191	452	1.18 (1.06 to 1.30)	1572	96	1.27 (1.02 to 1.59)

*Individuals with a fracture who survived and were not censored at the start of the period. Risk of death following index fracture, compared to matched controls. Hazard ratios (HR) were estimated by Cox proportion hazards regression models, and estimates are presented with 95% confidence intervals (95% CI). HRs were adjusted for age and CCI comorbidities.

fracture (HR 2.69 (95% CI 2.04 to 3.54)) (figure 3). Similarly to the tendency observed following index fracture, the highest mortality was observed in the months immediately following a subsequent fracture (online supplemental table S1).

Mediation analysis

After removing duplicates, 242 different ICD-codes were registered in the fracture population within 6 months of the index date. A total of 155 ICD-codes were excluded, as these were assessed to not occur as consequences of fracture, and thus not explain the association between MOF and mortality. The remaining 87 ICD-10 codes were combined into 41 comorbidity categories. Based on 10 clinician ratings, 13 of these comorbidity categories were included in the mediation analyses (online supplemental table S2).

Overall, pneumonia was the most significant mediator across fracture types (table 4). The analysis showed that the proportion of excess mortality following MOF which could be explained by pneumonia was 21.85% (95% CI 19.95% to 23.74%) for women and 29.15% (95% CI 26.97% to 31.32%) for men. This trend occurred across all fracture types. In clinical vertebral fractures, dehydration also mediated a substantial part of the association with death (PE 15.02% (95% CI 10.24% to 19.80%) in women and PE 10.17% (95% CI 5.43% to 14.92%) in men). In hip fractures, the second largest proportion of the association was mediated by urinary tract infections (UTIs) in women (PE 18.40% (95% CI 16.83% to 19.98%)) and sepsis in men (PE 15.36% (95% CI 13.31% to 17.40%)). In humerus fractures, sepsis mediated the second largest proportion in both sexes (PE 17.36% (95% CI 9.30% to 25.43%) in women and PE 15.59% (95% CI 8.03% to 23.15%) in men). In wrist fractures, the association in women was, besides pneumonia, also mediated by UTIs, dehydration and fall tendency (PE 18.53% (95% CI 6.75% to 30.32%), PE 16.86% (95% CI 3.37% to 30.35%) and PE 15.35% (95% CI 7.70% to 23.00%), respectively). For wrist fractures in men, estimates were imprecise due to wide and insignificant CIs and low case numbers (table 4). We will, therefore, not conclude on these results. The full mediation analysis is presented in online supplemental table S3.

Sensitivity analysis

Analyses applying a 10-year exclusion period for MOFs prior to the index date displayed the same trends as the main analyses, however, with slightly inflated estimates (online supplemental tables S4–S7B file 1). Analyses using a 3-month grace period between index and subsequent fractures at the same site yielded results similar to the main analysis (data not shown). Analyses using the fracture hierarchy hip>clinical vertebral>humerus>wrist to categorise the index fracture also produced similar results compared with the main analyses (data not shown). Analysis stratifying the population on CCI score proved an excess mortality trend following fracture,

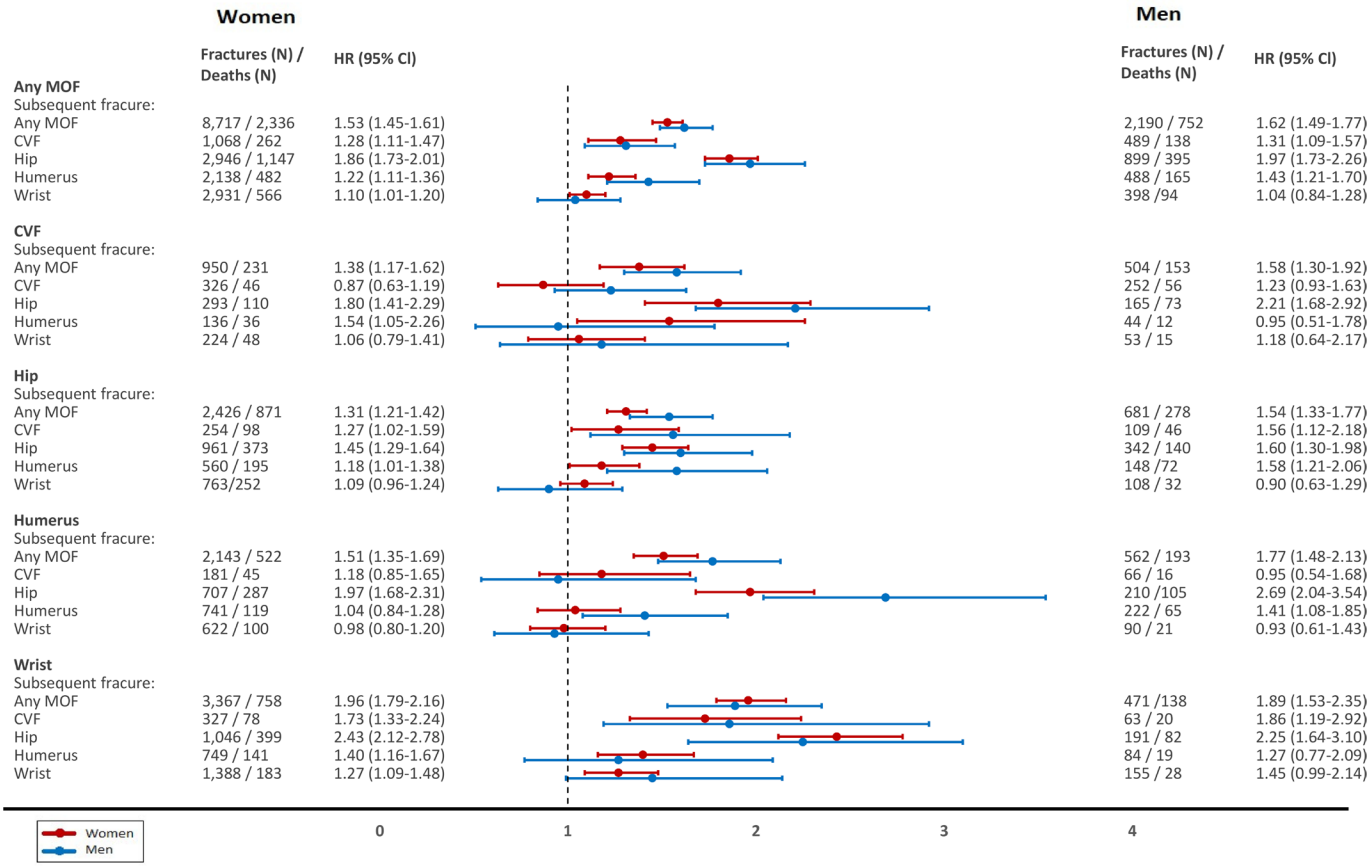

Figure 3 Forest plot of HR with 95% CI for mortality following subsequent fractures, by each initial fracture site and stratified by sex. HRs were adjusted for age and CCI comorbidities. Estimates are presented with 95% CI. CCI, Charlson Comorbidity Index; MOF, major osteoporotic fracture; CVF, clinical vertebral fracture.

with inflated estimates for CCI=0 compared with the main analysis, whereas estimates for CCI≥1 decreased compared with the main analysis (online supplemental tables S8–9).

DISCUSSION

Main findings

The results of this nationwide register-based cohort study showed that the highest relative mortality risk was observed within the first month following an osteoporotic hip fracture in both men and women. In patients sustaining a subsequent osteoporotic fracture, the highest relative mortality risk was also observed in the first month following a subsequent hip fracture. Overall, male fracture patients displayed higher HRs than female fracture patients. In subsequent fracture patients, a subsequent hip fracture resulted in the highest HRs in both sexes, although the index fracture types differed. Pneumonia proved to be the most significant mediator, contributing to the largest proportions of excess mortality following an osteoporotic fracture, but other factors also showed important mediating effects.

Excess mortality following index and subsequent fractures

In this study, the highest mortality risk following an index fracture was observed in the first month after fracture. Overall, male fracture patients displayed higher relative mortality risk than female fracture patients. In both sexes, the highest mortality risk was observed within the first month following a hip fracture (table 3). Our findings are in accordance with previous studies, and increased short-term mortality is well established in hip fractures. A meta-analysis by Haentjens *et al* indicated a relative hazard of 7.95 (95% CI 6.13 to 10.30) for men and 5.75 (95% CI 4.6 to 6.69) for women in the first 3 months following hip fracture, compared with controls,[30] and multiple other studies have reported high mortality immediately following fracture and decreasing over time.[1 31–33] Our results indicate that the excess mortality decreases in the years following index fracture for all fracture types, but continues to be elevated compared with the control population for the duration of the study period (table 3). Existing literature indicates that excess mortality may persist for many years after the fracture occurs.[1 34] However, other studies have reported that excess mortality does not persist after the first 6 months following fracture, as a large proportion of it may be

Table 4 The role of select mediators* on the association between fractures and mortality, for each fracture type stratified by sex

	Women						Men					
Fracture site and mediator	**Fracture patients, N**	**Mediator, N**	**HR TE† (95% CI)**	**HR CDE‡ (95% CI)**	**HR PE§ (95% CI)**	**PE, ¶% (95% CI)**	**Fracture patients, N**	**Mediator, N**	**HR TE† (95% CI)**	**HR CDE‡ (95% CI)**	**HR PE§ (95% CI)**	**PE,¶ % (95% CI)**
MOF												
Pneumonia	68 054	1867	3.52 (3.40 to 3.65)	2.97 (2.85 to 3.09)	1.19 (1.17 to 1.20)	21.85 (19.95 to 23.74)	22 361	1454	5.69 (5.42 to 5.98)	4.32 (4.08 to 4.58)	1.32 (1.29 to 1.35)	29.15 (26.97 to 31.32)
Clinical vertebral												
Dehydration	6376	144	3.14 (2.86 to 3.44)	2.82 (2.56 to 3.11)	1.11 (1.07 to 1.15)	15.02 (10.24 to 19.80)	4997	94	3.87 (3.54 to 4.24)	3.58 (3.25 to 3.94)	1.08 (1.04 to 1.12)	10.17 (5.43 to 14.92)
Pneumonia	5612	193	3.43 (3.11 to 3.79)	2.9 (2.65 to 3.31)	1.16 (1.09 to 1.23)	19.31 (11.55 to 27.06)	4226	243	4.48 (4.05 to 4.95)	3.48 (3.10 to 3.91)	1.29 (1.20 to 1.38)	28.77 (21.58 to 35.95)
Hip												
Urinary tract infection	17 836	1254	5.36 (5.13 to 5.61)	4.56 (4.34 to 4.79)	1.18 (1.16 to 1.19)	18.40 (16.83 to 19.98)	9582	634	6.58 (6.22 to 6.95)	5.90 (5.57 to 6.26)	1.11 (1.10 to 1.13)	12.07 (10.54 to 13.60)
Pneumonia	18 843	1072	4.91 (4.70 to 5.13)	3.80 (3.60 to 4.00)	1.29 (1.26 to 1.33)	28.46 (26.02 to 30.91)	8630	896	6.39 (6.02 to 6.78)	4.35 (4.04 to 4.68)	1.47 (1.41 to 1.52)	37.81 (34.79 to 40.84)
Sepsis	22 512	397	4.76 (4.57 to 4.94)	4.31 (4.13 to 4.50)	1.10 (1.08 to 1.12)	11.91 (9.84 to 13.97)	10 860	460	6.27 (5.96 to 6.60)	5.46 (5.17 to 5.77)	1.15 (1.13 to 1.17)	15.36 (13.31 to 17.40)
Humerus												
Pneumonia	14 537	338	2.67 (2.47 to 2.88)	2.23 (2.00 to 2.47)	1.20 (1.13 to 1.27)	26.56 (18.12 to 35.00)	4381	223	3.73 (3.36 to 4.13)	2.70 (2.35 to 3.11)	1.38 (1.26 to 1.50)	37.50 (28.47 to 46.54)
Sepsis	16 018	137	2.60 (2.43 to 2.78)	2.32 (2.10 to 2.56)	1.12 (1.06 to 1.18)	17.36 (9.30 to 25.43)	5042	107	3.51 (3.20 to 3.84)	3.12 (2.80 to 3.47)	1.13 (1.06 to 1.19)	15.59 (8.03 to 23.15)
Wrist												
Abnormal weight loss	32 609	65	1.18 (1.10 to 1.27)	1.17 (1.09 to 1.26)	1.01 (1.00 to 1.02)	4.76 (0.00 to 11.63)	6131	13	1.23 (1.08 to 1.40)	1.19 (1.04 to 1.37)	1.03 (0.98 to 1.08)	15.94 (0.00 to 59.16)
Urinary tract infection	30 036	374	1.18 (1.09 to 1.29)	1.15 (1.06 to 1.25)	1.03 (1.01 to 1.05)	18.53 (6.75 to 30.32)	5674	68	1.16 (1.00 to 1.35)	1.15 (0.99 to 1.33)	1.01 (0.99 to 1.04)	9.28 (0.00 to 100.00)
Dehydration	32 191	203	1.19 (1.10 to 1.28)	1.16 (1.07 to 1.25)	1.03 (1.01 to 1.05)	16.86 (3.37 to 30.35)	6026	54	1.21 (1.06 to 1.39)	1.19 (1.03 to 1.36)	1.02 (0.99 to 1.05)	10.84 (0.00 to 39.12)
Delirium	32 819	83	1.17 (1.09 to 1.26)	1.15 (1.07 to 1.24)	1.01 (1.00 to 1.03)	10.00 (1.36 to 18.65)	6134	26	1.17 (1.02 to 1.34)	1.14 (0.99 to 1.30)	1.03 (1.00 to 1.06)	18.71 (0.00 to 69.79)
Fall tendency	32 251	539	1.19 (1.10 to 1.28)	1.16 (1.08 to 1.25)	1.02 (1.02 to 1.03)	15.35 (7.70 to 23.00)	6046	107	1.20 (1.04 to 1.37)	1.15 (1.00 to 1.32)	1.04 (1.02 to 1.05)	22.65 (0.00 to 64.94)
Infection	32 704	79	1.18 (1.09 to 1.26)	1.17 (1.09 to 1.26)	1.01 (1.00 to 1.01)	3.42 (0.00 to 9.23)	6102	31	1.19 (1.04 to 1.36)	1.16 (1.01 to 1.33)	1.03 (1.00 to 1.06)	16.16 (0.00 to 100.00)
Pneumonia	30 187	316	1.20 (1.10 to 1.30)	1.15 (1.06 to 1.25)	1.04 (1.01 to 1.07)	22.44 (4.38 to 40.50)	5388	122	1.13 (0.95 to 1.33)	1.03 (0.87 to 1.23)	1.09 (1.01 to 1.17)	73.16 (0.00 to 100.00)

*This table includes select mediators, with only mediators with PE>15% shown. The full table is available in online supplemental table S3. HR were estimated by Cox regression models, and estimates are presented with 95% CI.
†HR of the TE (HR TE) was obtained by controlling for age and CCI comorbidities.
‡HR of the CDE (HR CDE) was obtained by controlling for age and CCI comorbidities and the potential mediating factor in question, which was included as a time-dependent variable.
§HR for the PE (HR PE)=HR TE/HR CDE.
¶PE=(HR TE-HR CDE/HR TE-1). PE is only presented if the direction of HR CDE and PE is the same. For the mediation analyses, CI was obtained by bootstrapping using 100 replicates. Individuals with preexisting conditions of the mediating factor in question were excluded in the analyses.
CCI, Charlson Comorbidity Index; CDE, controlled direct effect; MOF, major osteoporotic fracture; PE, proportion eliminated; TE, total effect.

explained by greater frailty or advanced age in the fracture population.[35 36]

In patients sustaining a subsequent osteoporotic fracture, the highest mortality risk was observed in the first 6 months after fracture occurrence in our study (online supplemental table S1). In general, knowledge of immediate excess mortality following subsequent fracture (within the first 6 months postfracture) is not well established. Increased long-term mortality has been observed in refracture patients in multiple studies.[37–39]

Fracture type combinations

In the analysis of different index and subsequent fracture type combinations, subsequent hip fracture had the highest HRs regardless of index fracture type (figure 3). Mortality risk was highest for men who sustained an index humerus fracture (HR 2.69 (95% CI 2.04 to 3.54)) and for women who sustained an index wrist fracture (HR 2.34 (95% CI 2.12 to 2.78)) prior to their subsequent hip fracture. This finding is consistent with that of Chen *et al*, who observed an increased mortality risk for both the combination of index humerus/subsequent hip fractures (HR 1.66 (95% CI 1.41 to 1.95)) and index wrist/subsequent hip fractures (HR 2.65 (95% CI 2.29 to 3.08)), with the wrist/hip combination resulting in the highest HR for all fracture types.[8] Chen *et al* also reported that subsequent hip fracture produced the highest HRs in combination with nearly all index fracture types,[8] which is in accordance with our findings. A possible explanation for the high HR resulting from the index wrist/subsequent hip fracture combination might be that wrist fractures alone result in a relatively limited excess mortality.[40] This may cause the excess mortality of a subsequent hip fracture to appear more pronounced when compared with those who only sustain a single wrist fracture. Additionally, subsequent wrist fractures produced the lowest HRs for mortality across multiple index fracture types for both sexes in our study (figure 3), and similar findings have been reported in other studies.[8 39]

Mediation of mortality risk

Prior studies have demonstrated that comorbidities significantly impact the excess mortality associated with fractures,[11–18] but studies examining perifracture or postfracture comorbidities have been mostly focused on hip fractures.[12 14 18] Of all the comorbidities included in this study as possible mediators, pneumonia proved to be the most significant mediator across all fracture types in both sexes (table 4). The proportion of mortality risk following MOF which hypothetically could be eliminated by preventing pneumonia was 21.85% (95% CI 19.95% to 23.74%) for women and 29.15% (95% CI 26.97% to 31.32%) for men, and some of the highest estimates were observed following hip fractures in both sexes (HR 28.46% (95% CI 26.02% to 30.91%) in women and HR 37.81% (95% CI 34.79% to 40.84%) in men) (table 4). In studies conducted by Whitney *et al* on the effect of incident respiratory disease following fractures in different study populations, pneumonia was shown to mediate 11.3%[41] and 15%[42] of the association between fractures and mortality in adults ≥65 years. Jang *et al* and Lv *et al* demonstrated an increased risk of mortality in hip fracture patients with postoperative pneumonia.[18 43] While the studies by Whitney *et al*[41 42] included study populations that were different from ours, they support that incident postfracture pneumonia mediates a significant proportion of the excessive mortality in fracture patients. A recent systematic review and meta-analysis by Gao *et al* showed that, while factors such as age, preexisting comorbidities, length of hospital stay, surgical delay and dependent function status has been linked to an increased risk of postoperative pneumonia in existing literature, fracture type has not (OR 0.96 (95% CI 0.69 to 1.35).[44] Targeted preventive measures may help mitigate the risk of pneumonia and, by extension, excess mortality following fracture. This should be considered in postfracture management.

Sensitivity analyses

Several sensitivity analyses were conducted in the study. Some resulted in minimal changes to the risk estimates, while applying a 10-year exclusion period for MOFs prior to index fracture resulted in slightly increased risk estimated that followed the same trends as the main analysis (online supplemental table S4–S7B). The last sensitivity analysis, in which the study population was stratified as either CCI score=0 or CCI score≥1, resulted in inflated estimates for the group with no CCI comorbidities, especially among men sustaining a hip fracture (online supplemental table S8), and decreased for the group with at least one CCI comorbidity prior to index fracture (online supplemental table S9). While this pattern is not unexpected, the authors do not have a definitive explanation for the magnitude of the increase in HR observed in patients with no comorbidity registered prior to index fracture, and advise caution when interpreting these results. Overall, the results display the same trends as those observed in the main analysis.

Strengths and limitations

This study had several strengths adding value to results and conclusions. First, the large sample size (n=1 169 291) added statistical strength to results. Second, the study sample was retrieved from nationwide Danish registers that cover all citizens in Denmark regardless of gender and socioeconomic status, thus adding to the generalisability of results and minimising the risk of selection bias. Third, this study performed mediation analyses examining the mediating role of postfracture comorbidities in the association between osteoporotic fractures and excess mortality. To the best of our knowledge, no studies have performed this analysis in a larger study population, thus adding novelty to results. Lastly, this study investigated excess mortality for MOFs which includes four fracture sites (fracture of hip, clinical vertebrae, humerus or wrist) which adds to the knowledge

base of the association between osteoporotic fractures and excess mortality, which has previously been examined primarily in hip fractures.[1]

Conversely, this study also had methodological limitations. First, the use of Danish register data eliminates the possibility to obtain information on potentially relevant confounders and covariates. These could for instance include body mass index or lifestyle factors such as level of physical activity, alcohol consumption, smoking habits, etc. The chance of unmeasured confounding should, therefore, be considered in the interpretation of results. However, our study did account for the effect of sex and age on mortality risk by stratifying analyses on sex and by adjusting for age in regression analyses. Second, the validity is unknown in the NPR of the ICD-10 coding of comorbidity variables used for mediation analyses as well as ICD-10 coding used in the outcome definition of MOF, which leaves risk of misclassification. However, the data quality of the NPR is overall estimated to be high and the register is acknowledged as a valuable data source for epidemiological research.[21] Lastly, it should be acknowledged that the underlying mechanisms of MOF cannot be asserted using the ICD-10 codes available in this study. This could possibly lead to the inclusion of fractures that are non-osteoporotic by nature. However, MOF is used as the outcome measure in this study as it is a well established concept which stems from the Fracture Risk Assessment Tool where it used as the endpoint of prediction,[45] and it continues to be used in research definitions of osteoporotic fractures.[46–48]

CONCLUSION

In conclusion, this study showed that mortality risk is highest in the months immediately after an osteoporotic fracture occurs, especially following hip fracture. This tendency was observed following both index and subsequent fractures in both sexes. The combination of index and subsequent fracture types was found to have a significant impact on the excess mortality, with subsequent hip fracture resulting in the highest HRs across all index fracture types in both sexes. In mediation analyses, pneumonia proved to be the most significant mediator across all fracture types and in both sexes. These findings could inform the development of clinical guidelines for the care of future osteoporotic fracture patients at risk of excess mortality.

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Contributors ERC, AC and KHR were responsible for the initial study concept. TGP was responsible for the statistical analysis in collaboration with SM. All authors contributed to the design and choice of methods. MKS and BA advised on clinically relevant aspects of the study. ERC and AC drafted the manuscript and conducted the initial interpretation of the data alongside KHR and TGP. All authors critically reviewed the manuscript multiple times for important intellectual content and have approved the final version for publication. ERC and AC contributed equally to this paper. KHR is guarantor and accepts final responsibility for the finished work, and controlled the decision to publish.

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