Persistence of Excess Mortality Following Individual Nonhip Fractures: A Relative Survival Analysis

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Context: Little is known about long-term excess mortality following fragility nonhip fractures.

Objective: The study aimed to determine which fracture was associated with excess mortality and for how long the postfracture excess mortality persisted.

Design, Setting, and Patients: This nationwide registry-based follow-up study included all individuals in Denmark aged 50+ years who first experienced fragility fractures in 2001 and were followed up for up to 10 years for their mortality risk.

Main Outcome Measure: The contribution of fracture to mortality at precise postfracture time intervals was examined using relative survival analysis, accounting for time-related mortality changes in the background population.

Results: There were 21,123 women (aged 72 ± 13 years) and 9481 men (aged 67 ± 12 years) with an incident fragility fracture in 2001, followed by 10,668 and 4745 deaths, respectively. Excess mortality was observed following all proximal and lower leg fractures. The majority of deaths occurred within the first year after fracture, and thereafter excess mortality gradually declined. Hip fractures were associated with the highest excess mortality (33% and 20% at 1 year after fracture in men and women, respectively). One-year excess mortality after fracture of a femur or pelvis was 20% to 25%; vertebrae, 10%; humerus, rib, or clavicle, 5% to 10%; and lower leg, 3%. A significant although smaller excess mortality was still observed until 10 years for hip fractures and ~5 years after femur, other proximal, and lower leg fractures.

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Abbreviation: NHDR, Danish National Hospital Discharge Register.

Conclusion: This study highlights the important contribution of a wide variety of fragility fractures to long-term excess mortality and thus the potential for benefit from early intervention. (***J Clin Endocrinol Metab*** **103: 3205–3214, 2018)**

Fragility fracture represents a major public health problem globally. Hip (1–8) and clinical vertebral (2, 3, 9–12) fractures have been consistently associated with a two- to sixfold increased mortality risk, independent of the contributing effects of aging and comorbidities. However, long-term follow-up studies have provided conflicting results for length of time the excess mortality persists after a hip fracture (1, 5, 6, 13–15). The extent of any increased mortality risk associated with fractures other than hip and vertebral fractures remains controversial. Importantly, to date no study has been conducted to determine long-term excess mortality attributable to individual nonhip fractures accounting for time-related mortality changes, even though these fractures represent more than two-thirds of all fragility fractures (10).

Relative survival analysis is a modern statistical approach initially used in oncology research to determine long-term excess mortality attributable to a specific cancer by comparing the mortality rate observed in a cancer population with the expected mortality rate in a comparative noncancer population (16). The analysis is based on the hypothesis that the excess deaths are due to two sources: the cancer or disease of interest *per se* and other causes. Assuming that the expected background mortality rate reflects the effect of "other causes," excess mortality derived from relative survival analysis is considered a good measure of mortality attributable to the disease of interest (16). The analysis, accounting for time-related mortality changes in the background population, is particularly useful in examination of the impact of a disease on mortality at precise time intervals.

To examine the potential effect of a specific fracture on mortality risk, the population-based study must be both large enough and has the ability to capture and follow all the subjects long enough to obtain their long-term mortality risk. The analysis should be robust to differentiate the risk of mortality attributable to a fracture from the risk due to other causes. The Danish national register is a unique population-based data source for which information on health care utilization and diagnoses is systematically obtained for the entire country, providing an excellent representative study population with minimal risk of selection bias and loss to follow-up as well as sufficient size for this type of analysis (17).

We thus conducted a relative survival analysis to determine (1) which fragility fracture is associated with excess mortality and (2) how long the postfracture excess mortality persists.

Methods and Materials

Study design

This nationwide registry-based follow-up study included all individuals aged 50+ years who experienced an incident fragility fracture in Denmark between 1 January 2001 and 31 December 2001. This was not a clinical trial. The Danish National Hospital Discharge Register (NHDR) was used to identify participants with a diagnosis of an index fracture at one of the following sites: hip (International Statistical Classification of Diseases and Related Health Problems, Tenth Version, code: S72.0-2), femur (nonhip) (S72.3-9), vertebrae (S22.0–S22.1, S32.0–S32.2, S32.7, S32.8, T08.x), clavicle (S42.0), rib (S22.3-4), humerus (S42.x), forearm (S52.x), hand (S62.0-4, S62.8), finger (S62.5-7), pelvis (S32.3-5), knee (S82.0), lower leg (S82.2-8), ankle (S82.5-6), foot (S92.0-3, S92.7, S92.9), and toe (S92.4-5). The NHDR has national coverage of both inpatient and outpatient contacts since 1995, with excellent, complete medical records and precise diagnoses (18, 19). The concordance between fracture reports in the NHDR and patient files was documented as 97% (19).The study (Statistics Denmark project nos. 703381 and 706667) was subject to approval and monitoring by the National Board of Health, the Danish Data Protection Agency, and Statistics Denmark.

Individuals with a fragility fracture between 1996 and 2000 at age 45+ years were excluded to avoid potential bias that the incident fracture analyzed in 2001 was a second fracture that may have adversely affected mortality (9).The analyses did not include individuals who had sustained fractures due only to traffic accidents in 2001. The initial incident fracture was defined as the first fracture reported in 2001. When more than one fracture was reported during one event, only the more serious fracture was considered. Individual types of fracture included hip, femur, pelvis, vertebrae, clavicle, rib, and humerus (*i.e.*, proximal fractures) and forearm, knee, lower leg, ankle, hand, fingers, foot, and toes (*i.e.*, distal fractures). Comorbidities at the time of the initial fracture were reported using the updated Charlson comorbidity index, which has been shown to be more appropriate for use with administrative data (20).

Death of the study participants was ascertained from the Danish Register on Causes of Death until 31 December 2011. The follow-up time was calculated from time of the first diagnosis of an incident fracture to either date of death or 31 December 2011. The first primary cause of death was also documented for our patients with a fracture and for all individuals aged 50 years or older in 2001 in Denmark, using the International Statistical Classification of Diseases and Related Health Problems, Tenth Version, classification system.

Statistical analysis

Statistical analyses were carried out separately for women and men to address (1) age-standardized mortality incidence following a specific fracture, (2) excess mortality associated with a fracture, and (3) length of time during which postfracture excess mortality persisted.

The mortality incidence rate following specific types of fractures was estimated for 100 person-years of follow-up assuming a Poisson distribution. The age-standardized postfracture mortality incidence rates were calculated using the direct standardization method (21). The direct standardization method uses weights from a reference general Danish population of the same age, sex, and calendar period (22) to compute the weighted average of age group–specific estimates in the fracture cohort.

Excess mortality attributable to a fracture, defined as 1 minus its relative survival ratio, can be interpreted as the proportion of patients who would die of this particular fracture (16). The relative survival ratio is a ratio of observed survival in the fracture population to expected survival in a similar nonfracture population (16). The observed survival is the probability that a patient with a specific fracture survived from all-cause deaths. The expected survival is the survival probability of similar individuals, ideally from a comparative nonfracture population but more practically from the general population of the same age, sex, and calendar period as the fracture cohort (16, 23).The expected survival was estimated using the Ederer II method (23) from the Danish population life tables stratified by sex, age, and calendar period from the Human Mortality Database (22). An excess mortality of zero for a specific fracture indicates the mortality rate observed in the population of patients with this particular fracture type does not differ from that in a comparative background population, suggesting no excess mortality attributable to this fracture type.

The length of time for which any postfracture mortality persisted was assessed using an interval-specific excess mortality for 1-year intervals after a fracture (*i.e.*, an annual excess mortality). An annual excess mortality of zero for a fracture suggests that there is no longer any excess mortality for that fracture type for that particular year. Persistence of postfracture excess mortality was defined as the interval between the fracture time and the last year for which the observed mortality in the fracture population was still significantly higher than the expected survival rate (*i.e.* the last year the 95% CI of the annual excess mortality did not include a reference unity of zero). For instance, if the excess mortality was 8% (95% CI: 1%, 15%) at year 3 and 5% (95% CI: −2%, 12%) at year 4 after a pelvis fracture, the conclusion would be that excess mortality persisted for 3 years after the pelvis fracture.

All analyses were carried out using Stata MP 13 (StataCorp, College Station, TX) and SAS 9.4 (SAS Institute, Inc., Cary, NC). A level of 0.05 was considered statistically significant.

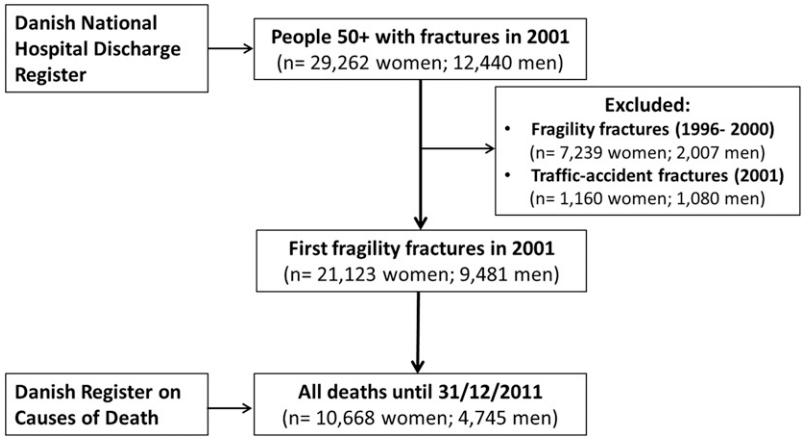

Figure 1. Flowchart of follow-up.

Results

The study included 21,123 women and 9481 men who experienced an incident fragility fracture in the year 2001 at an average age (mean ± SD) of 72 (±13) and 67 (±12) years, respectively (Fig. 1). None of these subjects experienced any fragility fracture between 1996 and 2000 or fractures related solely to traffic accidents in 2001. A third of women and a half of men in the study population sustained a first fragility fracture between 50 and 64 years of age. Forearm, hip and humerus fractures together contributed 63% and 42% of total fractures in women and men, respectively (Table 1). Hip fractures occurred late (81 ± 9 years in women vs 78 ± 11 years in men; $P < 0.001$), whereas peripheral fractures, such as hand, finger, foot, and toe fractures, were diagnosed at a mean age of 60 years. Patients with a fracture who eventually died during the study period were more likely to have a higher Charlson comorbidity index and more comorbidities reported at fracture time, especially congestive heart failure, dementia, and chronic pulmonary disease, than those alive until the end of 2011 (Table 1).

Absolute mortality rates according to fracture type

During an average follow-up period of 7.2 (±4.0) years (7.1 ± 4.1 years in women vs 7.3 ± 3.9 years in men), 10,668 women (51%) and 4745 men (50%) died (Fig. 1). Overall, patients with a fracture had a higher mortality incidence than the Danish general population aged 50 years or older in 2001 (Table 2). There were four more deaths following a fragility fracture in men than in women for every 100 person-years of follow-up (95% CI: 3.7, 4.4) after difference in age at fracture was taken into consideration. Moreover, postfracture mortality rates were higher in men than in women for all fracture types, though the differences following a clavicle, rib, lower leg, foot, or toe fracture did not achieve statistical significance.

As expected, hip, femur, and pelvis fractures were associated with the highest mortality incidence, even after accounting for difference in age at fracture (Table 2). The age-standardized mortality incidences following specific fracture types varied greatly, from 20 deaths per 100 person-years (95% CI: 19, 21) following a hip fracture to 7 deaths per 100 person-years (95% CI: 6, 8) after a

Table 1. Characteristics of the Study Population at Time of Fracture

	Women		Men	
	Alive	Dead	Alive	Dead
	(n = 10,455)	(n = 10,668)	(n = 4736)	(n = 4745)
Comorbidities at fracture time				
Charlson comorbidity index[a]	0 (0–0)	0 (0–2)	0 (0–0)	0 (0–2)
0	9233 (88.3)	6714 (62.9)	4310 (91.0)	2682 (56.5)
1–2	1137 (10.9)	2936 (27.5)	378 (8.0)	1374 (29.0)
3–4	70 (0.7)	691 (6.5)	39 (0.8)	434 (9.1)
5+	15 (0.1)	327 (3.1)	9 (0.2)	255 (5.4)
Specific comorbidities				
Congestive heart failure	90 (0.9)	1111 (10.4)	60 (1.3)	619 (13.1)
Dementia	37 (0.4)	883 (8.3)	21 (0.4)	349 (7.4)
Chronic pulmonary disease	362 (3.5)	991 (9.3)	130 (2.7)	614 (12.9)
Rheumatologic disease	211 (2.0)	408 (3.8)	33 (0.7)	91 (1.9)
Mild liver disease	56 (0.5)	103 (1.0)	36 (0.8)	142 (3.0)
Diabetes with chronic complications	66 (0.6)	214 (2.0)	47 (1.0)	194 (4.1)
Hemiplegia or paraplegia	13 (0.1)	35 (0.3)	11 (0.2)	30 (0.6)
Renal disease	19 (0.2)	108 (1.0)	11 (0.2)	108 (2.3)
Any malignancy, including leukemia and lymphoma	456 (4.4)	1123 (10.5)	118 (2.5)	605 (12.8)
Moderate or severe liver disease	4 (0.04)	22 (0.2)	6 (0.1)	56 (1.2)
Metastatic solid tumor	12 (0.1)	213 (2.0)	6 (0.1)	135 (2.9)
AIDS/HIV	0 (0.0)	0 (0.0)	1 (0.02)	7 (0.2)
Fracture types				
Any fracture	10,455	10,668	4736	4745
Proximal fractures				
Hip	724 (6.9)	3885 (36.4)	235 (5.0)	1722 (36.3)
Femur	75 (0.7)	248 (2.3)	33 (0.7)	102 (2.1)
Pelvis	100 (1.0)	398 (3.7)	40 (0.8)	106 (2.2)
Vertebrae	223 (2.1)	470 (4.4)	186 (3.9)	252 (5.3)
Clavicle	138 (1.3)	181 (1.7)	184 (3.9)	147 (3.1)
Rib	116 (1.1)	128 (1.2)	253 (5.3)	194 (4.1)
Humerus	1106 (10.6)	1353 (12.6)	276 (5.8)	520 (10.9)
Distal fractures				
Forearm	3839 (36.7)	2409 (22.6)	733 (15.5)	538 (11.4)
Knee	152 (1.5)	71 (0.7)	63 (1.3)	47 (1.0)
Lower leg	626 (6.0)	384 (3.6)	383 (8.1)	201 (4.2)
Ankle	872 (8.3)	302 (2.8)	416 (8.8)	226 (4.8)
Hand	785 (7.5)	306 (2.9)	500 (10.6)	235 (5.0)
Fingers	573 (5.5)	207 (1.9)	745 (15.7)	247 (5.2)
Foot	655 (6.3)	246 (2.3)	363 (7.7)	133 (2.8)
Toes	471 (4.5)	80 (0.7)	326 (6.9)	75 (1.6)

Data presented as number (%) unless otherwise indicated.

[a]Data presented as median (interquartile range).

lower leg fracture in men. Comparable rates in women were 13 deaths per 100 person-years (95% CI: 12, 13) and 6 deaths per 100 person-years (95% CI: 5, 7) following hip and lower leg fractures, respectively. The lowest mortality rate was found for hand, finger, foot, and toe fractures. Over the 10 year follow-up, there were overall increased age-standardized mortality incidences for every fracture type. However, for the majority of distal fractures, there was no excess mortality when mortality rates in the general population were considered for each individual calendar year (Fig, 2 and relative survival analysis below).

Approximately 65% of deaths occurred within 5 years after fracture, ranging from ~75% to 80% after hip, femur, or pelvis fracture to 40% to 50% after a peripheral fracture (Supplemental Table 1). The most common causes of death included cardiac (30% in patients with a fracture and 24% in the general population), malignant (16% and 14%, respectively), and respiratory (10% and 18%, respectively) diseases (Table 3). Compared with the general population aged 50 years or older in 2001 who died between 1 January 2001 and 31 December 2011, fracture subjects were more likely to have cardiovascular disorders or external causes of

Table 2. Mortality Incidence by Sex

Fracture Types	Women					Men				
	Age at Fracture (y)	Number of Deaths	Follow-up (person-y)	Crude Mortality Incidence (95% CI)	Age-Standardized Mortality Incidence (95% CI)	Age at Fracture (y)	Number of Deaths	Follow-up (person-y)	Crude Mortality Incidence (95% CI)	Age-Standardized Mortality Incidence (95% CI)
General population[a]		1,045,880	28,760,930	3.64 (3.63, 3.64)			1,010,630	24,458,382	4.13 (4.12, 4.14)	
Any fracture	72 (13)	10,668	153,595	6.9 (6.8, 7.1)	6.7 (6.6, 6.8)	67 (12)	4745	66,935	7.1 (6.9, 7.3)	10.7 (10.4, 11.0)
Proximal fractures										
Hip	81 (9)	3885	20,068	19.4 (18.8, 20.0)	12.7 (12.1, 13.3)	78 (11)	1722	6613	26.0 (24.8, 27.3)	20.3 (19.2, 21.4)
Femur	78 (12)	248	1540	16.1 (14.2, 18.2)	11.8 (10.2, 13.7)	71 (13)	102	660	15.5 (12.7, 18.8)	16.7 (13.6, 20.4)
Pelvis	81 (11)	398	2357	16.9 (15.3, 18.6)	11.0 (9.7, 12.4)	73 (12)	106	733	14.5 (12.0, 17.5)	16.0 (13.1, 19.4)
Vertebrae	75 (12)	470	4094	11.5 (10.5, 12.6)	9.4 (8.5, 10.3)	68 (12)	252	2853	8.8 (7.8, 10.0)	12.5 (10.9, 14.2)
Clavicle	70 (14)	181	2206	8.2 (7.1, 9.5)	9.0 (7.7, 10.4)	64 (12)	147	2496	5.9 (5.0, 6.9)	10.8 (8.9, 12.9)
Rib	70 (13)	128	1754	7.3 (6.1, 8.7)	8.3 (6.9, 9.8)	64 (11)	194	3514	5.5 (4.8, 6.4)	9.2 (7.8, 10.8)
Humerus	73 (11)	1353	17,434	7.8 (7.4, 8.2)	6.6 (6.3, 7.0)	69 (12)	520	4714	11.0 (10.1, 12.0)	12.5 (11.4, 13.6)
Distal fractures										
Forearm	70 (11)	2409	52,741	4.6 (4.4, 4.8)	4.6 (4.5, 4.8)	65 (11)	538	10,084	5.3 (4.9, 5.8)	7.6 (6.9, 8.3)
Knee	67 (11)	71	1977	3.6 (2.9, 4.5)	4.1 (3.2, 5.2)	66 (11)	47	890	5.3 (4.0, 7.0)	6.5 (4.8, 8.7)
Lower leg	67 (12)	384	8226	4.7 (4.2, 5.2)	6.0 (5.4, 6.7)	62 (10)	201	5000	4.0 (3.5, 4.6)	6.9 (5.7, 8.2)
Ankle	64 (11)	302	10,730	2.8 (2.5, 3.2)	4.3 (3.8, 4.9)	63 (10)	226	5501	4.1 (3.6, 4.7)	6.4 (5.5, 7.5)
Hand	66 (11)	306	9899	3.1 (2.8, 3.5)	4.2 (3.7, 4.7)	62 (11)	235	6383	3.7 (3.2, 4.2)	6.9 (5.9, 7.9)
Fingers	65 (12)	207	7058	2.9 (2.6, 3.4)	4.4 (3.8, 5.0)	61 (10)	247	9103	2.7 (2.4, 3.1)	6.6 (5.6, 7.7)
Foot	64 (11)	246	8158	3.0 (2.7, 3.4)	4.8 (4.2, 5.5)	60 (8)	133	4526	2.9 (2.5, 3.5)	5.1 (4.0, 6.3)
Toes	60 (9)	80	5352	1.5 (1.2, 1.9)	3.6 (2.7, 4.7)	59 (8)	75	3865	1.9 (1.6, 2.4)	4.3 (3.1, 5.9)

Age-standardized mortality incidence was estimated by the direct standardization method using the Danish general population of the same age, sex, and calendar period. Rates and incidence are presented as numbers of deaths per 100 person-years. Age at fracture is presented as mean (SD).

[a]Included all individuals aged 50+ years in 2001 in Denmark with follow-up time calculated as a sum of person-years lived, obtained from the Human Mortality Database (22).

morbidity and mortality (including falls) as the first primary cause of death. More deaths in patients with a fracture, especially in those with a hip fracture, had the first primary cause of death documented as "Diseases of the musculoskeletal system" (1.6% and 0.5% of the first primary causes of death in women and men who sustained a hip fracture, respectively, vs 0.2% and 0.1% in the general population).

Excess mortality following a fragility fracture

One-year excess mortality following a specific fracture is demonstrated in Fig. 2A and 2B for proximal and distal fractures, respectively. In general, postfracture excess mortality in men was higher than in women, though the difference became evident only for hip fractures (excess mortality, 33% in men vs 20% in women; $P = 0.002$) and humerus fractures (12% in men vs 5% in women; $P = 0.03$).

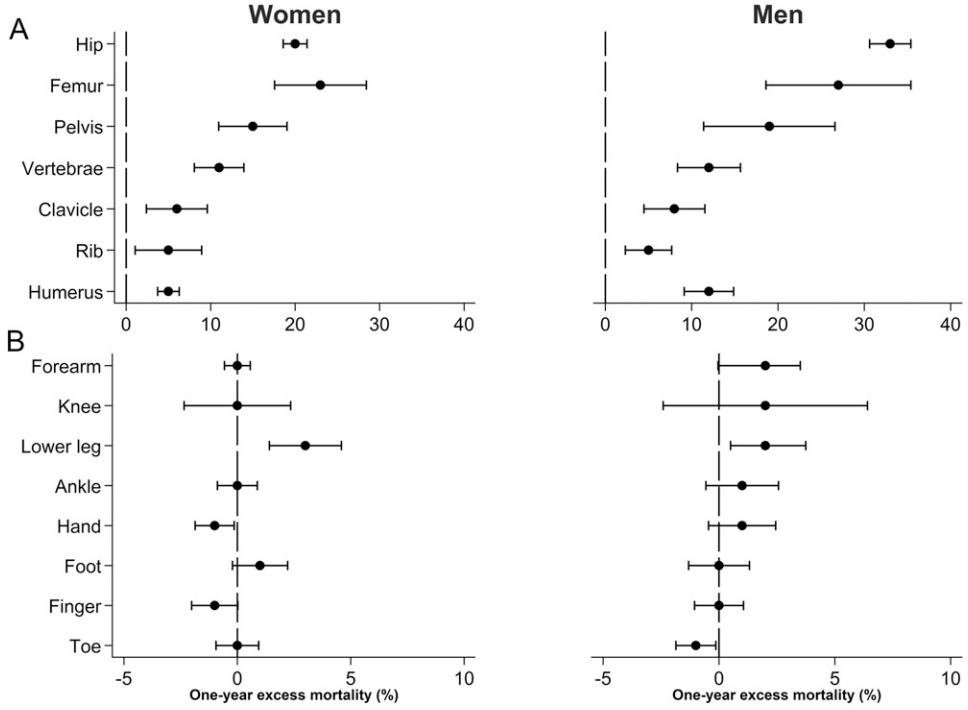

Figure 2. Excess mortality 1 year after individual types of fragility fracture: (A) proximal fractures and (B) distal fractures.

Table 3. Primary Causes of Death

		Women				
	General Population[a] (n = 291,565)	Any Fracture (n = 10,668)	Hip (n = 3885)	Vertebrae (n = 470)	Proximal (n = 2308)	Distal (n = 4005)
Diseases of the circulatory system	69,853 (24.0)	3409 (32.0)	1296 (33.4)	134 (28.5)	721 (31.2)	1258 (31.4)
Diseases of the respiratory system	52,135 (17.9)	1084 (10.2)	399 (10.3)	57 (12.1)	247 (10.7)	381 (9.5)
Abnormal clinical and laboratory findings, not elsewhere classified	49,286 (16.9)	719 (6.7)	265 (6.8)	32 (6.8)	173 (7.5)	249 (6.2)
Neoplasm	39,436 (13.5)	1707 (16.0)	453 (11.7)	73 (15.5)	391 (16.9)	790 (19.7)
Infectious diseases	9696 (3.3)	147 (1.4)	50 (1.3)	9 (1.9)	30 (1.3)	58 (1.4)
Diseases of the digestive system	8610 (3.0)	508 (4.8)	163 (4.2)	26 (5.5)	122 (5.3)	197 (4.9)
Endocrine diseases	8255 (2.8)	407 (3.8)	155 (4.0)	27 (5.7)	94 (4.1)	131 (3.3)
Diseases of the genitourinary system	4879 (1.7)	176 (1.6)	63 (1.6)	10 (2.1)	45 (1.9)	58 (1.4)
Mental disorders	4584 (1.6)	672 (6.3)	277 (7.1)	32 (6.8)	138 (6.0)	225 (5.6)
Diseases of the nervous system	4281 (1.5)	332 (3.1)	137 (3.5)	10 (2.1)	75 (3.2)	110 (2.7)
External causes of morbidity and mortality	3937 (1.4)	664 (6.2)	396 (10.2)	23 (4.9)	116 (5.0)	129 (3.2)
Diseases of the blood and immune disorders	1417 (0.5)	61 (0.6)	26 (0.7)	4 (0.9)	8 (0.3)	23 (0.6)
Diseases of the musculoskeletal system	503 (0.2)	122 (1.1)	62 (1.6)	11 (2.3)	16 (0.7)	33 (0.8)
Not registered	34,693 (11.9)	660 (6.2)	143 (3.7)	22 (4.7)	132 (5.7)	363 (9.1)

(*Continued*)

Significant excess mortality was observed following essentially all proximal and lower leg fractures for both sexes, with the magnitude gradually declining after the first year after fracture. By contrast, the observed mortality following other distal fractures, such as forearm, hand, finger, knee, ankle, foot, or toe fractures, did not differ from the expected survival in the comparative background population, suggesting that these distal fractures were not associated with an increased risk of mortality. As expected, hip fractures were associated with the highest excess mortality, with a 1-year excess mortality of 33% in men and 20% in women. For nonhip fractures, excess mortality at 1 year after fracture was 20% to 25% after femur or pelvic fractures; 10% after vertebral fractures; 5% to 10% after humerus, rib, or clavicle fractures; and 3% after lower leg fractures. There was also a nonsignificant 2% excess mortality 1 year after a forearm or knee fracture in men. These percentages equated to ~33 extra deaths 1 year after fracture for an average 100 men with a hip fracture compared with 100 equivalently aged men without a fracture. The comparable number of excess deaths in 100 women with hip fracture was 20. By contrast, only two and three additional deaths were observed at 1 year after fracture in 100 men and 100 women, respectively, with a lower leg fracture.

For all fracture types, excess mortality increased with increasing age (Supplemental Table 2). However, excess mortality after clavicle, rib, or lower leg fractures was evident only for elderly patients after the age of 70 years.

Persistence of excess mortality after fracture

The number of years with persistent excess mortality varied by fracture type (Fig. 3).The study suggests that excess mortality persisted for more than 10 years following a hip fracture for both men and women. In addition, the observed mortality following a proximal fracture remained significantly higher than the expected mortality in the comparative, matched general population for approximately 5 years after fracture, varying from 3 years after a rib fracture to 6 to 7 years after a vertebral or humerus fracture. Lower leg fracture was associated with excess mortality for 4 years after fracture. Interestingly, there was little difference in length of postfracture excess mortality between men and women. The difference in length of post–pelvis fracture excess mortality between men (~3 years after fracture) and women (7 years) may reflect fewer men with pelvis fractures (146 men vs 498 women).

In addition to cardiovascular diseases reported in almost a third of all deaths, the causes of early mortality, defined as deaths within 1 year after fracture, differed from those of late mortality ≥5 years after a fracture (Supplemental Table 3). Malignancy (~20% to 25% of early mortality vs 10% to 15% of late mortality) and external causes of morbidity and mortality (~25% to 30% and 10% of early mortality following hip and nonhip fractures, respectively, vs 2% to 3% of late mortality) were much more commonly reported as the cause of death within 1 year after fracture. By contrast, diseases of the respiratory system were more likely to be reported for late mortality (~10% to 15% of late mortality vs 7% of early mortality).

Discussion

There is still controversy regarding whether a nonhip nonvertebral fracture is associated with excess mortality

Table 3. Primary Causes of Death (Continued)

	Men				
General Population[a] (n = 262,761)	Any Fracture (n = 4745)	Hip (n = 1722)	Vertebrae (n = 252)	Proximal (n = 1069)	Distal (n = 1702)
63,047 (24.0)	1425 (30.0)	551 (32.0)	66 (26.2)	307 (28.7)	501 (29.4)
48,382 (18.4)	536 (11.3)	217 (12.6)	44 (17.5)	135 (12.6)	140 (8.2)
38,931 (14.8)	210 (4.4)	71 (4.1)	10 (4.0)	45 (4.2)	84 (4.9)
39,384 (15.0)	957 (20.2)	270 (15.7)	37 (14.7)	242 (22.6)	408 (24.0)
9537 (3.6)	50 (1.1)	16 (0.9)	4 (1.6)	6 (0.6)	24 (1.4)
7562 (2.9)	277 (5.8)	74 (4.3)	20 (7.9)	64 (6.0)	119 (7.0)
4899 (1.9)	150 (3.2)	42 (2.4)	9 (3.6)	35 (3.3)	64 (3.8)
5267 (2.0)	94 (2.0)	38 (2.2)	8 (3.2)	20 (1.9)	28 (1.6)
2732 (1.0)	238 (5.0)	67 (3.9)	13 (15.2)	64 (6.0)	94 (5.5)
3311 (1.3)	125 (2.6)	56 (3.3)	3 (1.2)	27 (2.5)	39 (2.3)
5042 (1.9)	397 (8.4)	261 (15.2)	15 (6.0)	66 (6.2)	55 (3.2)
1171 (0.4)	18 (0.4)	5 (0.3)	3 (1.2)	4 (0.4)	6 (0.4)
208 (0.1)	24 (0.5)	9 (0.5)	6 (2.4)	3 (0.3)	6 (0.4)
33,288 (12.7)	244 (5.1)	45 (2.6)	14 (5.6)	51 (4.8)	134 (7.9)

Data are presented as number of deaths (% of total deaths). Proximal fractures included clavicle, rib, humerus, femur, and pelvis. Distal fractures included forearm, knee, lower leg, ankle, hand, foot, fingers, and toes.

[a]Included all individuals aged 50+ years in 2001 in Denmark who died between 1 January 2001 and 31 December 2011.

and, more importantly, how long any excess mortality persists following a specific fracture. We determined excess mortality following specific fracture types in a nationwide representative cohort using a robust analysis method accounting for time-related mortality changes in a matched reference population. The whole-nation cohort included all individuals in Denmark with a fragility fracture during 2001 who had not had a prior fracture in the preceding 5 years and who were followed up for up to 10 years for their risk of mortality. We

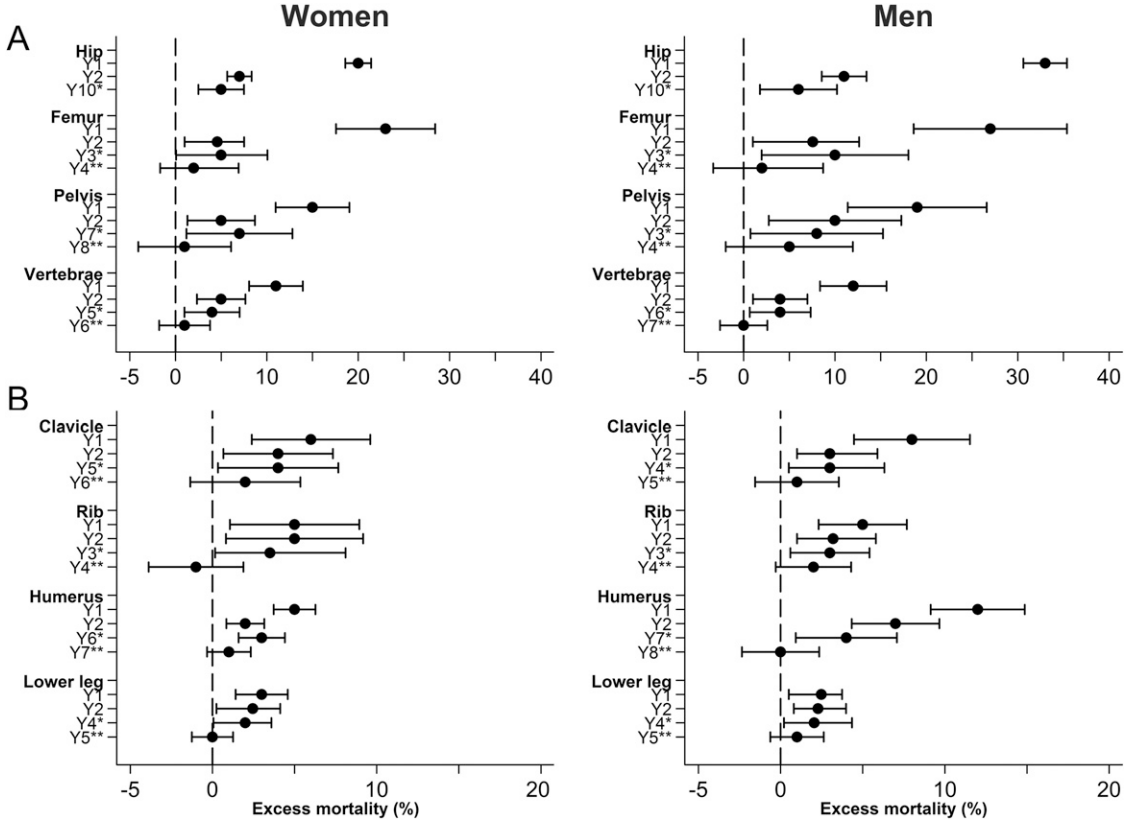

Figure 3. Persistent excess mortality after individual types of fragility fracture: (A) proximal fractures and (B) distal fractures. *The last year postfracture excess mortality was still evident; **The first year postfracture excess mortality was no longer evident.

hypothesized that more severe fractures were associated with excess mortality, with the length of the excess mortality being fracture-type specific. The study findings are consistent with the hypothesis, suggesting excess mortality was associated with virtually all proximal and lower leg fractures. Excess mortality remained evident for more than 10 years after a hip fracture and for ~5 years following a proximal nonhip or lower leg fracture, ranging from 3 years following a rib fracture to about 6 to 7 years following a vertebral or humerus fracture.

Our findings of long-term excess mortality after hip fractures are in line with the majority of (7, 8, 13–15) but not all (1, 5, 6) other studies of hip fracture mortality. The reasons why excess mortality persists years after a fragility hip fracture are not clear. The long-term post–hip fracture excess mortality might be related to underlying prefracture conditions (5, 11), postfracture pneumonia (8), or cardiovascular events (8, 24) or to the fracture event itself (7). In addition, the inflammatory effect found after a hip fracture (25, 26) might have a role in triggering frailty in these patients, leading to long-term effects on survival.

The novelty of our study is the ability to quantify not only the magnitude but also the length of excess mortality following individual nonhip fractures for which data are scarce. Our findings confirm other studies that vertebral (2, 3, 9–12), humerus (2–4, 11, 27, 28), rib (2, 11), and pelvis fractures (2, 11, 29) are associated with increased mortality risk. Mortality risk has not been examined separately for a clavicle fracture, though a group of clavicle, scapula, and sternum fractures was reportedly associated with increased mortality risk in a large population-based study in Olmsted County in the United States (2). Elderly patients with a fracture of the tibia or fibula above the ankle also had an associated fourfold increased mortality risk within the first 90 days and a 10% increased risk after 1 year compared with their matched nonfracture controls (30).

The impact of forearm fractures on mortality nevertheless remains controversial. We found that a forearm fracture was not associated with excess mortality, though a nonsignificant excess mortality of 2% was noted in men within 1 year after fracture. A follow-up study using a health care database of 14,000 Canadians with a forearm fracture (3) also reported an increased mortality risk within 1 year after a wrist fracture for men (relative risk: 1.5; 95% CI: 1.2, 1.9) but not women (relative risk: 0.8; 95% CI: 0.7, 1.0). Forearm fractures have not been associated with increased mortality in other studies (2, 4, 11, 28), although increased risk of mortality has been noted in special subgroups, such as those aged 70+ years at fracture (3, 30, 31) and those who then suffered a subsequent fracture (10).

This study addressed the length of excess mortality following a nonhip fracture, accounting for time-related mortality risk in the comparative background population. Other studies have found long-term increased mortality risk up to 5 (2) to 10 years (12) after a new clinical vertebral fracture, 3 (32) to 5 years (33) after a pelvis fracture, or 5 years after a humerus fracture (2, 27, 28); however, all these analyses assumed that mortality risk was proportional over time. By contrast, a few studies have shown excess mortality was no longer evident after 2 (29), 8 (34), or 12 months (2) after pelvis fracture. Some reasons for these discrepancies include differences in analysis approach (2) and study participants (29, 34). The standardized mortality ratio approach averages mortality rates over long time intervals (such as 5-year and >5-year intervals) to compute average excess mortality after 1 postfracture year (2). As a result, these analyses are not able to account for time-related changes, making them far less robust than the relative survival analysis for examination of excess mortality at precise intervals after a low-frequency fracture (16). Other studies demonstrating only short-term increased mortality either included different types of pelvis fracture (*e.g.*, minor fracture of the coccyx or ischium and unspecified fracture of the pelvis) (34) or recruited patients who had experienced a fracture at much older ages (88 years in women and 87 years in men) than our patients (81 years in women, 73 years in men) (29).

Few studies have examined potential causes of long-term excess mortality following nonhip fractures. The most common primary causes of death for our subjects with a fracture, including diseases of the circulatory or respiratory system and neoplasm, were similar to those reported in an Australian fracture population, even though respiratory disorders were more likely to be reported as cause of death in Australian subjects with a fracture (26%) (9) than ours (10%). Interestingly, there appeared to be a difference in the current study between early (mortality within 1 year after fracture) and late (≥5 years after fracture) mortality. Malignancy and "external cause" were more often recorded for early mortality, whereas respiratory disease was more often recorded for mortality ≥5 years after fracture. Cardiac causes remained the most common recorded cause for both early and late mortality. These findings deserve further exploration. The postulated pathways for excess mortality after a nonhip fracture include rapid bone loss (35) and reduced muscular strength (36), which have been independent predictors for long-term mortality risk following both clinical vertebral and nonhip nonvertebral fractures as a group. Vertebral fracture was also associated with 25% increased risk of incident cardiovascular

events (24) and deteriorating functional capacity (12), which itself may elevate the risk of mortality.

The results of the current study should be viewed in the context of its strengths and limitations. Our data were collected from a nationwide registry that captures virtually all fracture-related diagnoses in the whole country with very precise diagnoses (18, 19) and has a low likelihood of selection bias or misclassification (19). Our large study sample of >30,000 individuals with an initial fracture followed up for 10 years was robust enough to determine long-term excess mortality following specific fracture types in yearly intervals. No patient with a previous fracture within 5 years before the study entry point was included, making the clean sample powerful for examining excess mortality following an incident fracture. The relative survival analysis is well recognized as a rigorous method to identify the length of persistence of excess mortality because it can estimate excess mortality at specific time points after a fracture (16). The fact that cause-specific mortality data are not needed in a relative survival analysis makes it especially relevant for the examination of the fracture-mortality association because a fracture is rarely mentioned as a contributing cause of death (14, 37).

However, the study was not able to completely distinguish the effect of a fragility fracture on mortality from that of chronic diseases. Postfracture excess mortality was estimated using expected survival from the age-, sex-, and calendar year–matched Danish general population life table data from the Human Mortality Database (22). No comorbidity-specific life table data have been created in the Human Mortality Database (22), precluding complete adjustment for potential confounding effects of comorbidities. The potential age- and sex-related confounding effects of chronic diseases were at least partly accounted for in relative survival analysis, which estimates excess mortality (attributable to a fracture) under the assumption that the expected mortality from the comparative general population with the same age, sex, and calendar year reflects mortality due to reasons other than fracture (16). Our analyses were not able to exclude patients with bone metastases. Nevertheless, patients with any site metastasis comprised only 2% to 3% of total deaths during the study follow-up period, only a quarter of which would have been bone metastases (38), with even fewer responsible for the fracture itself. Excluding these few patients with bone metastases would thus not change the overall findings. Finally, the length of persistent excess mortality following pelvis fractures in men, with limited numbers of subjects and deaths over ongoing follow-up, might have been underestimated because of limited statistical power (39). Therefore, the length of persistent mortality in this study should be considered a minimum.

Thus, with use of a robust technique to examine mortality over time, excess mortality for ~5 years after fracture was found for virtually all proximal and lower leg fractures and for at least 10 years after hip fracture. This study highlights the important contributions of a wide variety of fragility fractures to long-term excess mortality and thus the potential for benefit from early intervention.

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