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Excess mortality in men compared with women following a hip fracture. National analysis of comedications, comorbidity and survival

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Abstract

Introduction: osteoporosis is a common disease, and the incidence of osteoporotic fractures is expected to rise with the growing elderly population. Immediately following, and probably several years after a hip fracture, patients, both men and women, have a higher risk of dying compared to the general population regardless of age. The aim of this study was to assess excess mortality following hip fracture and, if possible, identify reasons for the difference between mortality for the two genders.
Methods: this is a nationwide register-based cohort study presenting data from the National Hospital Discharge Register on mortality, comorbidity and medication for all Danish patients (more than 41,000 persons) experiencing a hip fracture between 1 January 1999 and 31 December 2002. Follow-up period was until 31 December 2005.
Results: we found a substantially higher mortality among male hip fracture patients than female hip fracture patients despite men being 4 years younger at the time of fracture. Both male and female hip fracture patients were found to have an excess mortality rate compared to the general population. The cumulative mortality at 12 months among hip fracture patients compared to the general population was 37.1% (9.9%) in men and 26.4% (9.3%) in women. In the first year, the risk of death significantly increased for women with increasing age (hazard ratio, HR: 1.06, 95% confidence interval, CI: 1.06–1.07), the number of comedications (HR 1.04, 95% CI 1.03–1.05) and the presence of specific Charlson index components and medications described below. For men, age (HR 1.07, 95% CI 1.07–1.08), number of comedications (HR 1.06, 95% CI 1.04–1.07) and presence of different specific Charlson index components and medications increased the risk. Long-term survival analyses revealed that excess mortality for men compared with women remained strongly significant (HR 1.70, 95% CI 1.65–1.75, P < 0.001), even when controlled for age, fracture site, the number of medications, exposure to drug classes A, C, D, G, J, M, N, P, S and for chronic comorbidities.

Conclusion: excess mortality among male patients cannot be explained by controlling for known comorbidity and medications. Besides gender, we found higher age and multimorbidity to be related to an increased risk of dying within the first year after fracture; acute complications might be one of the explanations. This study emphasises the need for particular rigorous postoperative diagnostic evaluation and treatment of comorbid conditions in the male hip fracture patient.

Background

The incidence of osteoporotic hip fractures is expected to increase over the next decades as the elderly population increases [1]. Most cases of hip fractures arise in an individual with underlying—often asymptomatic—bone fragility who is exposed to low-impact trauma. This places the frail geriatric patient with high risk of falling at a particularly increased risk of hip fractures [2].

Previous studies have found excess mortality in hip fracture patients in the immediate post-fracture period [3]. Old age is a risk factor for death within the first year after a hip fracture [4–8], as is—for unknown reasons—male gender [4, 7, 9, 10].

Crude mortality rates following hip fractures demonstrate a gender bias favouring women regardless of age during hospitalization. The mortality rate in men has been found in several studies to be almost twice that in women during the first year after the fracture. Male gender has been shown to be predictive of high risk of postoperative complications such as chest infections and heart failure [8].

Though there is substantial evidence supporting the benefit of treatment of osteoporosis, several studies report low treatment rates at a maximum of 20–30% [11–13]. Especially for men, osteoporosis seems to be substantially underdiagnosed and undertreated [14, 15]. Recent studies indicate that a second osteoporotic fracture and elevated mortality following hip fracture could potentially be prevented if anti-osteoporotic medications were initiated [12, 15–17].

The aim of this study was to assess excess mortality following hip fracture and, if possible, identify the reasons why men are at greater risk than women of dying if they suffer a fracture of the hip.

Methods

In Denmark, the National Hospital Discharge Register (NHDR) maintains a complete record of hospitalizations and outpatient appointments in the country including data on diagnoses linked with civil registry numbers. Using the NHDR, we identified all men and women born before 1945 who sustained fractures of the proximal femur (ICD-10 codes S720, S721, S722 or S723) between 1 January 1999 and 31 December 2002. For patients experiencing more than one hip fracture, survival analyses were conducted only for the period following the index fracture.

Information about date of death was available up to the end of 2005, providing at least 3 years of post-fracture mortality observations in all patients. For comorbidity, we retrieved all diagnoses for hospital treatment in the last 3 years preceding the index fracture and calculated the individual disease constituents of the International Clasification of Diseases 10th Revision (ICD-10) modified Charlson comorbidity index. Data on all prescriptions dispensed from Danish pharmacies are collected in the National Prescription Database. We retrieved information about all prescriptions redeemed in the last year before fracture and calculated 1-year cumulative exposure in defined daily doses (DDD), both for the Anatomical Therapeutical Chemical Classification System (ATC) [18] main categories and for key individual drug families.

The primary outcome was all-cause mortality. Rates were calculated in absolute numbers and the standardised mortality ratio (SMR) was calculated relative to the death rates in the general population as observed number of deaths divided by expected numbers of deaths, using age- and sex-specific mortality data from the National Bureau of Statistics for the years 2001–05. When excess mortality in men compared with women was limited to a certain time period, e.g. in the first months following fracture, mortality at that point in time was to be used in explanatory binary logistic regression analysis to select a parsimonious subset of covariates for Cox regression analysis. A subgroup analysis for patients >75 years of age was prespecified. If mortality significantly differed by fracture type, this should also be accommodated in the Cox analysis. In an additional post hoc analysis, we specifically identified diagnosis of bone metastasis (ICD-10 code C795) assigned from 6 months before the hip fracture to 6 months after the hip fracture and considered hip fractures in these patients potentially pathological/metastatic. We used SPSS version 14.0.

Results

Demographics and comorbidities

Men with hip fracture were significantly more likely to suffer from most comorbidities included in the Charlson index [19] (Table 1). This was especially pronounced for malignancy, cardiac heart failure, chronic obstructive pulmonary disease (COPD) and all forms of arterial disease. Women outnumbered men in collagen disorders.

Table 1. Demographics and comorbidities for patients born in 1945 or earlier with incident hip fracture in Denmark 1999–2002

	Women (N=30,755)	Men (N=11,321)	P
Age	81.7 ± 8.9	78.1 ± 10.0	<0.001
Mortality			
3 months	15.3%	23.9%	<0.001
12 months	26.4%	37.1%	<0.001
36 months	46.3%	57.1%	<0.001
Loaction of index fracture			
Femoral neck	18,298 (59%)	6,396 (56%)	<0.001
Pertrochanteric	9,596 (31%)	3,747 (33%)	
Subtrochanteric	1,484 (5%)	655 (6%)	
Diaphyseal	1,377 (4%)	523 (5%)	
Hospital-treated chronic comorbidity in the last 3 years (Charlson index components)			
Cerebrovascular disease	2,650 (8.6%)	1,347 (11.9%)	<0.001
Any malignancy	1,860 (6.0%)	1,021 (9.0%)	<0.001
Metastatic solid tumour	232 (0.8%)	126 (1.1%)	<0.01
Congestive heart failure	1,793 (5.8%)	903 (8.0%)	<0.001
COPD	1,692 (5.5%)	933 (8.2%)	<0.001
Dementia	1,309 (4.3%)	506 (4.5%)	0.34
DM w/o complications	1,018 (3.3%)	477 (4.2%)	<0.001
DM with complications	327 (1.1%)	265 (2.3%)	<0.001
Ulcer disease	951 (3.1%)	356 (3.1%)	0.78
Peripheral vascular disease	800 (2.6%)	530 (4.7%)	<0.001
Myocardial infarction	710 (2.3%)	424 (3.7%)	<0.001
Connective tissue diseases	635 (2.1%)	104 (0.9%)	<0.001
Moderate or severe renal disease	160 (0.5%)	135 (1.2%)	<0.001
Hemiplegia	61 (0.2%)	31 (0.3%)	0.16
Moderate or severe liver disease	32 (0.1%)	29 (0.3%)	<0.001
AIDS	0 (0.0%)	2 (0.0%)	0.07

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus.

Medications

Based on cumulative doses, male hip fracture patients had greater exposure to most classes of drugs in the year preceding fracture than was the case for women (Table 2). The difference was pronounced for anti-thrombotics, insulin, anti-epileptic drugs and angiotensin-converting enzyme (ACE) inhibitors. Overall exposure to cardiovascular drugs was greater in women based on more widespread use of thiazide diuretics. There was no gender difference in exposure to oral glucocorticoids. Women were more likely to receive anti-depressants and anti-osteoporotic medications.

Absolute mortality rates by sex

Cumulative mortality was significantly lower for women: 15.3% at 3 months, 26.4% at 12 months and 46.3% at 36 months. Corresponding numbers for men were 23.9%, 37.1% and 57.1%, resulting in a male/female risk ratio of 1.6, 1.4 and 1.2 after 3, 12 and 36 months, respectively (Table 1). In patients aged >75 years, men had higher mortality than women only in the first year following fracture. For both genders, absolute mortality rates were highest in the older subset of patients.

Excess mortality

The increased mortality observed in this study was particularly pronounced in men and younger patients (<75 years) leading to reduced life expectancy compared with the general population. The 12-month SMR was 7.9 in men and 7.3 in women among the younger patients. Excess mortality was less pronounced in patients aged >75 years; SMR was 3.3 in men and 2.6 in women.

Mortality and fracture type

Mean survival was slightly longer after femoral neck (3.5 years, 95% confidence interval, CI: 3.5–3.6) and diaphyseal fracture (3.8 years, 95% CI 3.7–3.9) compared with pertrochanteric (3.3 years, 95% CI 3.3–3.4) or subtrochanteric fracture (3.4 years, 95% CI 3.3–3.5).

Identification of predictors of 1-year mortality in each gender (stepwise logistic regression)

Women

The risk of death increased with increasing age (hazard ratio, HR: 1.06, 95% CI 1.06–1.07), the number of medications (HR 1.04, 95% CI 1.03–1.05) and by the presence of any of the following Charlson index components: COPD, cardiac failure, dementia, diabetes with complications, hemiplegia, malignancy, metastatic solid tumour, liver disease (moderate or severe) and renal disease. The use of drugs affecting the digestive system (A), cardiovascular system (C), antibiotics (J) and nervous system (N) was associated with increased risk of death while exposure to drug classes D (dermatology), G (urogenital, including sex hormones), M (musculoskeletal, including anti-resorptives), P (anti-parasite drugs, includes quinine used for restless legs) and S (sensory system) was weakly but significantly associated with decreased risk of death at 1 year. In contrast, cerebrovascular disease (P = 0.99) or prior myocardial infarction (P = 0.54) did not influence mortality in this multivariate model.

Men

Age (HR 1.07, 95% CI 1.07–1.08), number of comedications (HR 1.06, 95% CI 1.04–1.07), COPD, cardiac failure, dementia, malignancy, metastatic solid tumour, liver disease (moderate or severe) and renal disease were all indicative of increased risk of death at 1 year. This also held true for myocardial infarction, ulcer disease and rheumatic/collagen disorders, but not for cerebrovascular disease (P = 0.51). The use of drug classes A (digestive system) and N (nervous system) was associated with increased risk of death, while D (dermatology), G (urogenital), M (musculoskeletal) and S (sensory system) were weakly associated with decreased risk. Mortality was slightly higher after pertrochanteric or subtrochanteric fracture (HR 1.10, 95% CI 1.01–1.19).

Table 2. Comparison of medication use prior to hip fracture, men versus women. Any use: redeemed at least one prescription in the 12 months preceding the index fracture. Annual DDD: cumulative exposure in defined daily doses (DDD) in the past year divided by population size. Example: if 10% of the group redeemed prescriptions for one tablet daily, the average annual DDD for the population for that medication would be 36.5

		Any use in last year		P	Average cumulative DDD use in last year		P
		Women ($N = 30,755$)	Men ($N = 11,321$)		Women ($N = 30,755$)	Men ($N = 11,321$)	
A	Digestive system	16,053 (52.2%)	5,641 (49.8%)	<0.001	129.1 ± 231.0	125.5 ± 225.2	0.14
	Insulin	749 (2.4%)	411 (3.6%)	<0.001	6.8 ± 50.7	10.8 ± 67.2	<0.001
	Oral antidiabetics	1,481 (4.8%)	623 (5.5%)	<0.01	15.4 ± 88.4	15.1 ± 82.3	0.75
	Thiamine	1,869 (6.1%)	642 (5.7%)	0.12	7.7 ± 37.5	6.8 ± 34.4	<0.05
B	Blood	9,440 (30.7%)	3,639 (32.10%)	<0.01	90.1 ± 172.0	91.8 ± 169.6	0.38
	Anti-thrombotics	6,622 (21.5%)	2,768 (24.5%)	<0.001	57.3 ± 128.1	64.4 ±134.4	<0.001
	B12	2,229 (7.2%)	677 (6.0%)	<0.001	25.0 ± 101.5	20.3 ± 90.0	<0.00
C	Cardiovascular	18,504 (60.2%)	6,079 (53.7%)	<0.01	383.8 ± 579.1	380.3 ± 649.1	0.60
	Cardiac glycosides	3,209 (10.4%)	1,057 (9.3%)	<0.01	16.4 ± 54.5	15.2 ± 55.2	<0.05
	Loop diuretics	8,188 (26.6%)	3,081 (27.2%)	0.22	148.6 ± 395.8	167.7 ± 451.7	<0.001
	Thiazide diuretics	6,471 (21.0%)	1,569 (13.9%)	<0.001	65.9 ± 161.4	39.5 ± 125.1	<0.001
	Beta blockers	3,352 (10.9%)	1,076 (9.5%)	<0.001	17.6 ± 65.3	15.5 ± 61.8	<0.01
	ACE inhibitors	2,698 (8.8%)	1,240 (11.0%)	<0.001	27.9 ± 119.2	37.5 ± 144.3	<0.001
D	Dermatological drugs	5,794 (18.8%)	2,528 (22.3%)	<0.001	15.9 ± 70.4	24.3 ± 102.4	<0.001
G	Urogenital and sex hormones	3,614 (11.8%)	1,370 (12.1%)	0.32	17.6 ± 70.8	23.8 ± 84.4	<0.001
	Oestrogen therapy (+/− progest)	1,539 (5.0%)			10.8 ± 56.3		
H	Hormones and related	5,393 (17.5%)	1,360 (12.0%)	<0.001	35.2 ± 104.5	25.0 ± 97.3	<0.001
	Oral glucocorticoids	2,572 (8.4%)	951 (8.4%)	0.90	18.0 ± 78.7	19.5 ± 87.8	0.09
J	Antibiotics	13,156 (42.8%)	4,299 (38.0%)	<0.001	10.6 ± 29.1	10.2 ± 31.8	0.19
L	Anti-neoplastic	464 (1.5%)	151 (1.3%)	0.20	3.1 ± 30.2	2.4 ± 24.6	<0.05
M	Musculoskeletal	9,747 (31.7%)	3,132 (27.7%)	<0.001	43.3 ± 103.8	37.4 ± 97.2	<0.001
	Anti-resorptives	1,813 (5.9%)	211 (1.9%)	<0.001	4.9 ± 30.3	1.4 ± 15.2	<0.001
N	Nervous system	23,874 (77.6%)	7,639 (67.5%)	<0.001	328.7 ± 411.9	264.3 ± 407.0	<0.001
	Anti-epileptics	1,345 (4.4%)	750 (6.6%)	<0.001	8.1 ± 55.0	15.9 ± 82.9	<0.001
	Anti-depressants	8,449 (27.5%)	2,415 (21.3%)	<0.001	71.5 ± 155.3	55.9 ± 139.4	<0.001
P	Anti-parasite drugs	2,016 (6.6%)	582 (5.1%)	<0.001	1.4 ± 7.5	1.1 ± 6.6	<0.001
R	Respiratory system	8,539 (27.8%)	3,182 (28.1%)	0.49	81.2 ± 299.5	114.6 ± 380.5	<0.001
S	Sensory system	1,822 (5.9%)	556 (4.0%)	<0.001	19.4 ± 96.8	16.3 ± 89.3	<0.01

Long-term survival analysis (Cox model)—effect of gender and covariates

Cox proportional hazards models were defined based on observed deaths in the follow-up period, terminating observations on the day of death or on 31 December 2005, whichever was earlier (Figure 1). The covariates identified by the logistic regresssion analysis above were entered as independent variables. The greater mortality for men compared with women remained strongly significant (HR 1.70, 95% CI 1.65–1.75, $P < 0.001$; Figure 1, top panel) even when controlled for age, fracture site, the number of medications, exposure to drug classes A, C, D, G, J, M, N, P, S and for the chronic comorbidities COPD, cardiac failure, dementia, hemiplegia, malignancy (with or without metastasis), mild or severe liver disease, renal failure, myocardial infarction, ulcer disease and rheumatic/collagen disorders.

The most powerful baseline risk factors for death in women were, in descending order, metastatic solid tumours, severe or moderate renal disease, severe liver disease and COPD. In men, strong risk factors were severe liver disease, mild liver disease, metastatic solid tumour and other malignancies. In contrast, the influence of a diagnosis of cardiac failure only had a modest effect on survival though it should be borne in mind that the analysis was adjusted for medications, including the use of diuretics and ACE inhibitors.

Bone metastasis

Few fractures occurred in patients with bone metastases. Thus, 0.5% of women and 1.2% of men with hip fractures were diagnosed with bone metastases. While the risk of death was increased threefold in patients with bone metastases (HR 3.00, 95% CI 2.60–3.38, $P < 0.001$), this did not account for the difference in survival between men and women (men vs women HR 1.69, 95% CI 1.64–1.74, $P < 0.001$, after adjustment for presence of bone metastases).
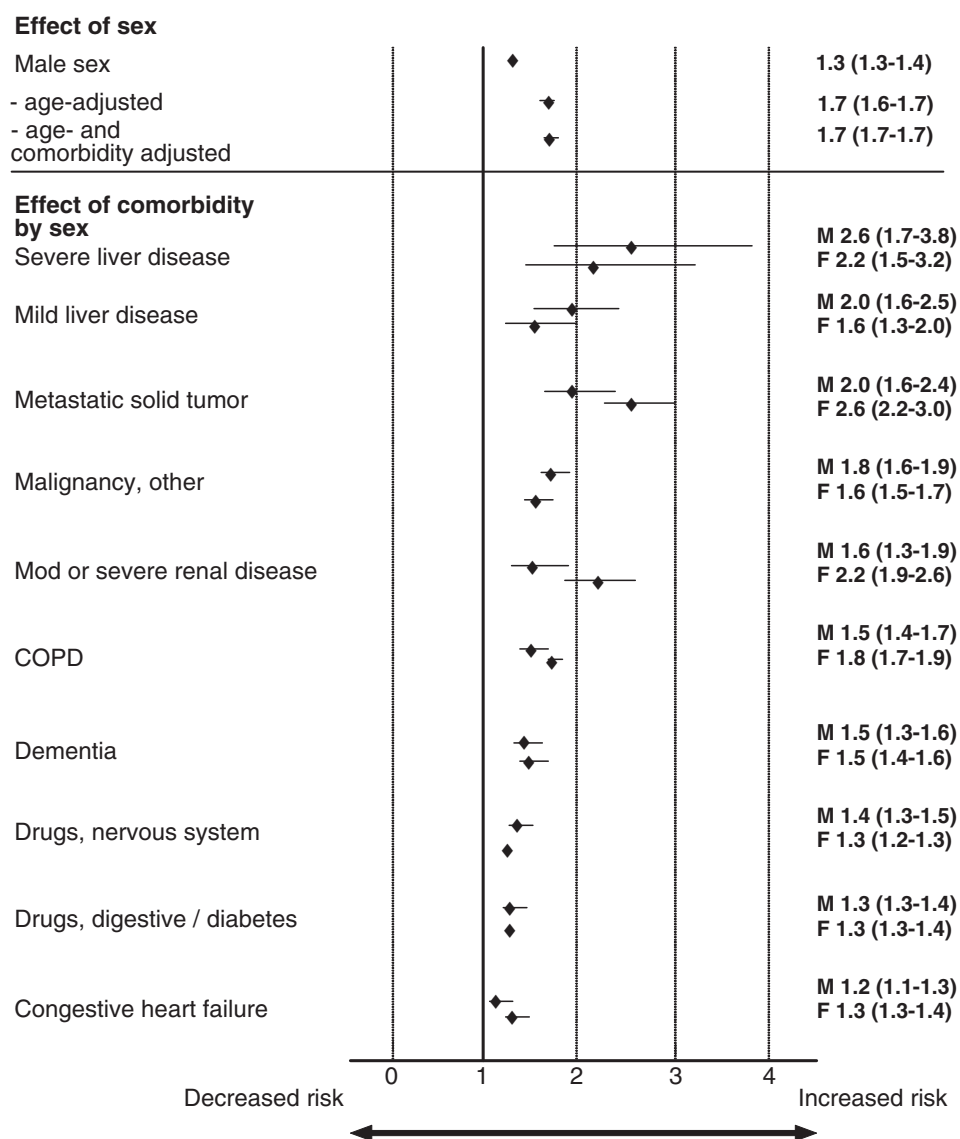
Discussion

Hip fracture, defined as any fracture of the femur between the articular joint of the hip and 5 cm below the distal point of the minor trochanter, is most common in older persons [16].

The most important strength of this register-based nationwide study is the complete capture of hip fractures, deaths and emigration provided by the registers.

Figure 1. Forrest plot of risk factors for death, Cox proportional hazards model. Hazard ratios and 95% confidence intervals. Upper part of figure shows influence of male sex on mortality, with and without adjustment for age and comorbidity. Cox proportional hazards model incorporating fracture site, the number of comedications, exposure to drug classes A, C, D, G, J, M, N, P, S (please see table 2 for explanation of drug classes) and the following chronic comorbidities: COPD, cardiac failure, dementia, hemiplegia, malignancy (with or without metastasis), mild or severe liver disease, renal failure, myocardial infarction, ulcer disease and rheumatic / collagen disorders. Variables for this analysis were selected by stepwise logistic regression. Lower part shows influence of individual risk factors for death with a comparison of effect size between men and women.

Our study confirmed a substantially higher mortality among male hip fracture patients compared to women, even when controlling for age, fracture site, number of medications and chronic comorbidity. In other words, male gender is in itself a risk factor for dying within the first year after a hip fracture. Unsurprisingly, both male and female hip fracture patients were found to have an excess mortality rate compared to the general population. The excess mortality in men was particularly pronounced in the first 3 months following fracture. This gender difference persisted for up to 36 months after the fracture for patients >75 years. Adjusting risks for age further increased the gender difference in

mortality, as men were on average 4 years younger at the time of fracture.

We confirmed a higher prevalence of chronic comorbidity preceding the fracture in men compared with women. The study revealed only minor differences in the impact of the type of comorbidity on survival between the sexes, which could be spurious due to small effects and multiple tests. Thus, while rare in both men and women, liver disease was more common in men and also appeared to less strongly affect survival in women. In contrast, renal disease reduced survival to a greater extent in women than in men. Though malignancy was common in both men and

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women, disseminated malignancy was slightly more prevalent in men. The impact of malignancy on survival was also gender specific. Thus, the effect of metastatic solid tumours on mortality seemed greater in women than in men despite similar 5-year survival rates for prostate and breast cancer [20].

Being male was a strong risk factor for death after fracture, with an impact comparable to a chronic comorbidity such as COPD. Such unexplained excess mortality in male patients has also been found in other acute medical conditions, most notably stroke [21]. We noted that women used a greater number of medications, whereas cumulative doses were higher in men for most ATC groups. The use of anti-epileptic drugs, a risk factor for fractures [22, 23], was 50% more prevalent in men than in women. We demonstrated that the prevalence of exposure to systemic glucocorticoids did not differ between women and men, though there was a weak, non-significant trend towards higher doses in men. Women were more likely to receive anti-osteoporosis medications, but the influence of male sex on mortality remained unattenuated by incorporating these differences in medication use into the survival analysis.

There is a remarkable discrepancy among health and mortality between the two genders. In almost all developed countries, women live longer than men, while men in general are physically stronger, report better health and have fewer disabilities. In Denmark, women live almost 5 years longer than men, but the number of years lived without disabilities is almost the same for both genders [24]. It seems that male excess mortality is caused by acute complications, which was also suggested in a recent Finnish study [25]. The present study confirms a trend towards both greater comorbidity and use of fewer medications—albeit at higher doses—in men. Taken together, it might be that some comorbid conditions in men are underdiagnosed and thereby undertreated, leading to more acute postoperative complications that might be fatal.

Contrary to our expectations, the marked difference in mortality does not appear to result from widespread presence of terminal or end-stage comorbid conditions in the male hip fracture patient.

It is a limitation that we were unable to examine the weight of comorbidities that had been treated by the family physician without hospital contacts. We were, however, able to capture all prescriptions whether issued by a hospital department, a practising specialist or the family physician, independent of insurance arrangements. This provides an indirect capture of many additional common diseases such as medically treated type II diabetes, hypertension, epilepsy and depression. However, if a diagnosis of type II diabetes or hypertension is less likely to be made in men than in women, a systematic bias towards lower prevalences and stronger effect sizes may be induced. In the present study, however, the tendency was for higher prevalence and—with the exception of liver disease—smaller effect sizes in men. Alcohol abuse could not be assessed in this study but could contribute to ex-

cess mortality, perhaps especially in younger men. Tobacco smoking has been shown to be an independent risk factor for hip fracture in both genders probably due to both direct and indirect biological effects [26]. In our study, we found a higher number of males suffering from COPD, which is related to tobacco smoking. In recent years, the use of tobacco has been reduced in Denmark, but for 2003, the Danish National Board of Health estimates 66.8% of men and 73% of women to be non-smokers [27]. An additional limitation is that trauma mechanism codes had not yet been introduced into the register, preventing us from distinguishing high energy hip fractures (traffic accidents) from low energy fractures (falls).

Reducing the risk of osteoporotic fractures calls for a combination of primary, secondary and tertiary preventive approaches. Many hip fracture patients are frail geriatric patients with multimorbidity—some 30% of Danish hip fracture patients are nursing home residents [28] and, therefore, in many countries, it is considered appropriate to have coordinated multidisciplinary teams assist in both the screening and the management of hip fracture patients during hospital stay. Different models of orthogeriatric services are being developed around the world and a cross-border template might be possible.

A hip fracture precipitating the diagnosis of osteoporosis is no guarantee of adequate treatment as several studies have found low prescription rates for anti-osteoporotic therapy in fracture patients as well as low compliance. Thus, in 2004, only 9.2% of women and 4.1% of men who suffered a hip fracture in Denmark began anti-osteoporotic therapy within the first year post-fracture. For the period 1997–2004, fracture patients persisted with anti-osteoporotic therapy for a median of 2.8 years for daily alendronate and 3.8 years for once-weekly alendronate [17].

The low prescription rates of anti-osteoporotic therapy both prior to and after an osteoporotic fracture might be due to the shared responsibility for the treatment between different clinical specialities.

Failure to diagnose and treat osteoporosis may leave the patient at an elevated risk of a second fracture, complications and even death [29, 30]. This fact has necessitated the establishment of fracture liaison services to diagnose the condition and to initiate and monitor the treatment [13].

In conclusion, using national health register data, this study confirms that mortality post-hip fracture is substantially higher in men than in women, despite men being on average 4 years younger at the time of fracture. This excess mortality is not explained by the slightly higher prevalence of chronic comorbidities in male fracture patients, nor by differences in comedications. The greatest difference between mortality in the two genders was observed in the first weeks following fracture.

This study further emphasises the need for particular rigorous acute diagnostic evaluation of the male hip fracture patient more prone to acute postoperative complications and risk of mortality.

Key points

- Mortality in the ageing hip fracture patients.
- All Danish hip fracture patients in 1999–2004 included.
- Higher mortality among male hip fracture patients.
- Analyses of gender and age-related comorbidity.
- Register-based cohort study showing higher mortality than general population.

Conflicts of interests

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