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Excess mortality attributable to hip-fracture: A relative survival analysis

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ABSTRACT

Introduction: Individuals with hip fracture are at substantially increased risk of mortality. The aim of this study was to estimate the excess mortality attributable to hip fracture in elderly men and women.
Methods: The Dubbo Osteoporosis Epidemiology Study was designed as a prospective epidemiologic investigation, in which more than 2000 men and women aged 60+ as of 1989 had been followed for 21 years. During the follow-up period, the incidence of atraumatic hip fractures was ascertained by X-ray reports, and mortality was ascertained by the New South Wales Birth, Death and Marriage Registry. Relative survival ratios were estimated by taking into account the age-and-sex specific expected survival in the general Australian population from 1989 to 2010.
Results: During the follow-up period 151 women and 55 men sustained a hip fracture. Death occurred in 86 (57%) women and 36 (66%) men. In women, the cumulative relative survival post hip-fracture at 1, 5 and 10 years was 0.83 (95% confidence interval (CI) 0.76–0.89), 0.59 (95% CI 0.48–0.68), and 0.31 (95% CI 0.20–0.43), respectively; in men, the corresponding estimates of relative survival were: 0.63 (95% CI 0.48–0.75), 0.48 (95% CI 0.32–0.63), and 0.36 (95% CI 0.18–0.56). On average post hip-fracture women died 4 years earlier (median: 4.1, inter-quartile range (IQR) 1.7–7.8) and men died 5 years earlier (median = 4.8, IQR 2.4–7.0) than expected. For every six women and for every three men with hip fracture one extra death occurred above that expected in the background population.
Conclusion: Hip fracture is associated with reduced life expectancy, with men having a greater reduction than women, even after accounting for time-related changes in background mortality in the population. These data underscore that hip fracture is an independent clinical risk factor for mortality.

Introduction

Hip fracture is a relatively common and serious clinical outcome of osteoporosis. From the age of 60, the remaining lifetime risk of hip fracture for men and women is 5% and 10%, respectively [1]. In women the lifetime risk of hip fracture is equivalent to or even higher than that of breast cancer [2,3]. Apart from hip fracture, all other osteoporotic fractures, including vertebral fracture, are associated with increased risk of mortality [4–8]. However, the excess is greatest following hip fracture [5,9,10]. Approximately 20% of women with a hip fracture have died within a year following the event [5], which is equivalent to the risk of mortality from breast cancer. Although data in men have been limited, recent studies [5] have shown that the one-year risk of mortality after a hip fracture was 37%, which is 1.8-fold higher than that in women.

There are considerable discussions about whether hip fracture is causally related to, or indirectly associated with, mortality. While it is well known that major osteoporotic fractures, including hip fracture, increase the risk of mortality [9], fracture is rarely documented as the cause of death. Therefore, it is difficult to make a cause-and-effect inference on the association between osteoporotic fracture and mortality. It can however be hypothesized that the excess deaths are due to two sources: one due to fracture per se and the other one due to other causes. Therefore, if the expected background mortality rate reflects the effect of "other causes" it is possible to estimate the excess of mortality due to hip fracture.

Life expectancy in the general population continually improves over time. For example, in Australia a 60-year old woman in 1970 was expected on average to live another 26.1 years, but a women of the same age in 2000 was expected to live another 32.3 years. Thus,

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if a woman with hip fracture died at the age of 60 in 2000 it would be considered less favorable (i.e. more years of life lost) than her counterpart who died at the age of 60 in 1970. Previous studies of post fracture mortality have largely ignored this time-related increase in life-expectancy.

In recent years, with the further development of survival analysis techniques [11] it is possible to estimate the relative survival of patients with hip fracture by taking into account the background expected survival [12]. The aims of this study were therefore: (a) to estimate the relative survival among men and women following a hip fracture; and (b) to estimate the excess mortality due to factors among elderly women and men with hip fracture, such as prior fracture, comorbid status and lifestyle factors such as history of smoking.

Materials and methods

Setting and subjects

This study was part of an on-going longitudinal Dubbo Osteoporosis Epidemiology Study (DOES), for which details of protocol and study design have been previously described [13,14]. Briefly, in 1989, all men and women aged 60 or above (as of 1989) living in Dubbo, a city of approximately 32,000 people 400 km north west of Sydney (Australia), were invited to participate in an epidemiological study. At that time, the population comprised 1581 men and 2095 women aged >60 years, of whom 98.6% were Caucasian and 1.4% were indigenous Aboriginal. These individuals were then invited to participate in DOES. This study was approved by the St Vincent's Campus Research Ethics Committee and informed written consent has been obtained from each participant.

Fracture ascertainment

Because Dubbo City is relatively isolated in terms of health care, with only two major hospitals in the region, it is possible to have a complete ascertainment of fractures in the city. Low-trauma fractures occurring during the study period were identified in residents of the Dubbo local government area through radiologist's reports from the only two centers providing X-ray services as previously described [13,14]. Fractures were only included if the report of fracture was definite and, on interview, had occurred with minimal or no trauma, including a fall from standing height or less. If study participants were unavailable for interview following fracture, relatives were contacted to obtain the circumstances related to the fracture event. Fractures clearly caused by major trauma such as motor vehicle accidents were excluded from the analysis. Fractures were classified as follows: hip, clinical vertebral, forearm and others. Other fractures included: clavicle, ribs, sternum, upper arm (including humerus and scapula), pelvis, and lower limb (including distal femur). Fractures of digits, face and skull were excluded from the analysis.

Mortality ascertainment

The incidence of mortality was ascertained through the Birth, Death and Marriage Registry of New South Wales. Mortality was also recorded by the study nurse coordinators located in Dubbo up to November 30, 2010. The date of death was then corroborated with the list of deaths from the Birth, Deaths and Marriage Registry of New South Wales. Causes of deaths were not collected.

Bone mineral density

Lumbar spine and femoral neck bone density was measured at baseline and at follow-up visits (average interval 2.2 years) by dual X-ray absorptiometry (DXA) using a LUNAR DPX or Prodigy densitometer (GE-LUNAR, Madison USA). A qualified technologist using a standard protocol performed the measurements. Daily quality control of both densitometers occurred throughout the study period. At our institution the coefficient of variance (CV) was between 1.5% and 2.0% at the femoral neck and lumbar spine, respectively, for the DPX [15].

Ascertainment of co-morbidity and smoking status

A structured questionnaire was used to obtain data concerning concomitant illnesses of participants. These co-morbidity data were reduced into a Charlson Comorbidity Index [16] as follows:

$$\begin{aligned}&(\text{acute myocardial infarction} + \text{congestive heart failure}\\&\quad + \text{peripheral vascular disease} + \text{cerebral vascular disease}\\&\quad + \text{dementia} + \text{chronic pulmonary disease} + \text{rheumatologic disease}\\&\quad + \text{peptic ulcer disease} + \text{diabetes} + \text{mild liver disease}) * 1\\&\quad + (\text{hemiplegia/paraplegia} + \text{renal disease}\\&\quad + \text{diabetes with chronic complications} + \text{malignancy}) * 2\\&\quad + (\text{moderate or severe liver disease}) * 3 + (\text{metastatic solid tumor}\\&\quad + \text{HIV/AIDS}) * 6.\end{aligned}$$

Smoking status was obtained by self report and categorized as pack-years. Smoking status was categorized based on the number of pack-years. However, "smoker" was defined as an individual who had smoked one pack-year (even if the smoker had recently given up smoking).

Relative survival

Relative survival ratio (RSR) is defined as the observed survival in the study group (where all deaths from any cause are considered an event) divided by the expected survival in the background [general] population of the same age, sex and calendar period. Expected survival was estimated using the Ederer II method [11] from Australian population lifetables stratified by age, sex and calendar period. Lifetable data was obtained from the Human Mortality Database [17]. At the time of analysis (November 2010), lifetable data were only available up until 2007, therefore, expected survival for the period 2008 to 2010 were based on 2007 data. The cumulative relative survival function, $r(t)$, is defined as [18]:

$$r(t) = \frac{S_O(t)}{S_P(t)}. \quad (1)$$

Where $S_O(t)$ denotes observed survival in the hip fracture group, and $S_P(t)$ is the background or expected survival [19]. Thus, relative survival ratio provides a measure of the excess mortality associated with hip fracture [11].

Excess mortality related to factors among the study participants was estimated using a modified Poisson regression model as suggested by Dickman [11]. This model incorporates, in our case, the assessment of potential risk factors for death in the fracture group (i.e. age, sex, prior fracture status, smoking status and co-morbidity status), while accounting for the expected mortality in the background population of a similar age, sex and calendar period. The estimate obtained is referred to as "excess mortality ratio" (EMR) [11]. In initial analyses we found no dose-dependent association between the number of co-morbidities and mortality; therefore, we decided to present the co-morbidity data in a stratified form (e.g. present or absent).

Results

Characteristics of study participants

During the follow-up period up, 206 individuals (of which, 155 women) had sustained a hip fracture. The rate of mortality among hip fracture patients was 57% in women (n = 86) and 66% in men (n = 36). Women and men who died following hip fracture were older, and had lower body weight than those who survived after a hip fracture (Table 1). Moreover, femoral neck BMD in both women and men who died was lower than survivors. There was no significant difference in comorbidity and smoking prevalence between survivors and non-survivors. However, a greater number of women who died following hip fracture had a history of previous non-hip osteoporotic fracture.

Relative survival

Relative survival ratios (RSR) for 1, 5 and 10-year survival post fracture are presented in Table 2. In women, RSR following hip fracture ranged from 0.90 (95% CI 0.77–0.96) in those aged 60–79 after 1 year, to 0.14 (95% CI 0.03–0.37) in those with a history of prior fracture after 10 years. In men, RSR following hip fracture ranged from, 0.80 (95% CI 0.58–0.92) in men aged 60–79 after 1 year, to 0.22 (95% CI 0.09–0.75) in men aged 80+ after 10 years.

The gender-related difference in RSR was most pronounced during the first 5 years after fracture, but tended to converge after 8 years (Fig. 1). It is perhaps expected that the RSR reduced (e.g. risk of mortality increased) with age and this was independent of the duration after fracture. Moreover, individuals with a prior fracture and/or smoking were associated with reduced RSR with time (Fig. 2).

Table 1
Baseline characteristics of women and men with hip-fracture between 1989 and 2010.

Characteristic	Follow-up status		P-value
	Deceased	Alive	
Women (n = 151)	(n = 86)	(n = 65)	
Age, mean (SD), years	83 (7)	79 (9)	0.027
Weight, mean (SD), kg	58 (12)	63 (12)	0.028
Height, mean (SD), cm	156 (7)	159 (8)	0.046
BMI, mean (SD), kg/m^2	24 (4)	25 (5)	0.150
Lumbar spine BMD, mean (SD), g/cm^2	0.94 (0.20)	1.01 (0.19)	0.014
Femoral neck BMD, mean (SD), g/cm^2	0.67 (0.12)	0.72 (0.11)	0.022
Smoking status, no. (%)			0.620
Never smoked	59 (69)	47 (72)	
Current/previously smoked	27 (31)	18 (28)	
Co-morbidity status, no. (%)			0.600
No co-morbidity	46 (53)	32 (49)	
One or more	40 (47)	33 (51)	
Prior fracture, no. (%)			0.380
None	55 (64)	46 (71)	
One or more	31 (36)	19 (29)	
Follow-up, median (IQR), years	2 (1–6)	3 (1–5)	0.340
Men (n = 55)	(n = 36)	(n = 19)	
Age, mean (SD), years	82 (8)	76 (7)	0.006
Weight, mean (SD), kg	76(12)	74 (14)	0.510
Height, mean (SD), cm	172 (7)	174 (8)	0.250
BMI, mean (SD, kg/m^2	26 (3)	24 (4)	0.130
Lumbar spine BMD, mean (SD), g/cm^2	1.17 (0.17)	1.18 (0.27) (0.27(0.27)	1.000
Femoral neck BMD, mean (SD), g/cm^2	0.78 (0.11)	0.81 (0.19)	0.240
Smoking status, no. (%)			0.560
Never smoked	16 (44)	10 (53)	
Current/previously smoked	20 (56)	9 (47)	
Co-morbidity status, no. (%)			0.390
No co-morbidity	11 (31)	8 (42)	
One or more	25 (69)	11 (58)	
Prior fracture, no. (%)			0.920
None	28 (78)	15 (79)	
One or more	8 (22)	4 (21)	
Follow-up, median (IQR), years	1 (1–3)	5 (2–6)	0.002

Table 2
Cumulative relative survival of women and men at 1, 5 and 10 years following hip fracture, stratified by age group and prior fracture status.

	Relative survival ratio (95% confidence interval)		
	1 year	5 years	10 years
All women (n = 151)	0.83 (0.76–0.89)	0.59 (0.48–0.68)	0.31 (0.20–0.43)
Age group			
60–79	0.90 (0.77–0.96)	0.70 (0.53–0.83)	0.47 (0.28–0.64)
80+	0.80 (0.70–0.87)	0.51 (0.38–0.64)	0.18 (0.07–0.34)
Prior fracture			
Yes	0.73 (0.57–0.84)	0.40 (0.23–0.58)	0.14 (0.03–0.37)
No	0.88 (0.79–0.94)	0.66 (0.54–0.76)	0.37 (0.24–0.51)
Smoking			
Never	0.84 (0.75–0.90)	0.62 (0.49–0.73)	0.33 (0.20–0.48)
Current/previous	0.82 (0.68–0.92)	0.51 (0.33–0.67)	0.26 (0.10–0.47)
Comorbid disease			
None	0.84 (0.73–0.91)	0.55 (0.39–0.67)	0.25 (0.11–0.42)
One or more	0.83 (0.71–0.90)	0.63 (0.49–0.76)	0.37 (0.21–0.54)
All men (n = 55)	0.63 (0.48–0.75)	0.48 (0.32–0.63)	0.36 (0.18–0.56)
Age group			
60–79	0.80 (0.58–0.92)	0.70 (0.45–0.87)	0.52 (0.24–0.77)
80+	0.48 (0.29–0.65)	0.26 (0.10–0.48)	0.22 (0.46–0.85)
Prior fracture			
Yes	0.60 (0.28–0.82)	0.37 (0.11–0.65)	0.41 (0.66–1.12)
No	0.63 (0.46–0.77)	0.51 (0.33–0.69)	0.33 (0.13–0.72)
Smoking			
Never	0.71 (0.49–0.86)	0.49 (0.27–0.70)	0.44 (0.19–0.71)
Current/previous	0.54 (0.34–0.71)	0.46 (0.25–0.68)	0.30 (0.09–0.75)
Comorbid disease			
None	0.68 (0.42–0.86)	0.39 (0.15–0.64)	0.44 (0.17–0.72)
One or more	0.59 (0.41–0.74)	0.52 (0.32–0.71)	0.34 (0.14–0.59)

Relative excess mortality

Excess mortality ratio (EMR) was estimated for subgroups stratified by age, sex, prior fracture, comorbid status, current or prior smoking and mortality is shown in Table 3 and Fig. 3. Excess mortality was observed in older age groups (EMR = 2.82, 95% CI 1.7–4.6), among men (EMR = 1.68, 95% CI 1.1–2.7), in those with a history of prior non-hip fracture (EMR = 1.65, 95% CI 1.1–2.6), and a history of smoking (EMR = 1.41, 95% CI 0.9–2.2). The presence of at least one comorbid condition did not significantly increase the risk of mortality (EMR = 0.85, 95% CI 0.6–1.3) compared with those with no documented comorbid conditions. On average women died 4 years (median = 4.1, inter-quartile range (IQR) 1.7–7.8), and men died 5 years (median = 4.8, IQR 2.4–7.0) earlier than expected.

We next addressed the question of how many deaths were attributable to hip fracture? For approximately every 6 women (95% CI 4–9) with a hip fracture, there was one extra death in the first year following the fracture. In men this excess was greater: for every 3 men (95% CI 2–4) with a hip fracture there was one extra death during the first year after the fracture. However, this attributable fraction (also referred to as "number needed to harm") was not constant across subgroups. For instance, in women with a history of non-hip osteoporotic fracture, one extra death will occur in every 4 women following a hip fracture. In smoking men, one extra death will occur in every 2 hip fractures over five years. Thus, smoking contributes substantially to the excess post-hip fracture mortality in men. The excess of mortality related to these lifestyle factors would suggest a potential independent effect on mortality — above that attributable to the hip fracture event alone.

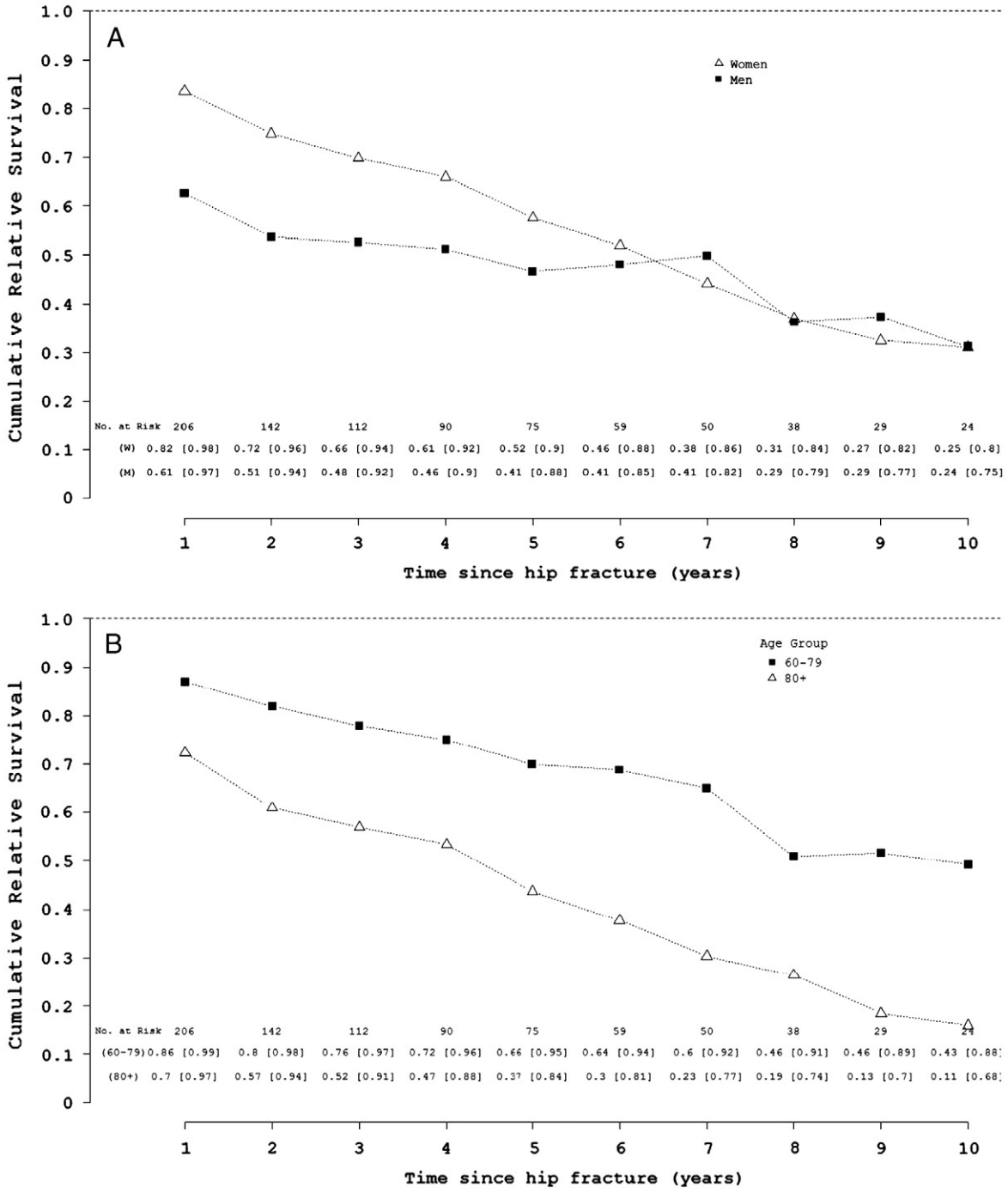

Fig. 1. Plots of relative survival following hip fracture comparing women and men (panel A) and age groups (panel B). Observed survival and [expected survival] added to the bottom of each plot.

Discussion

In this elderly population with hip fracture, the risk of mortality was higher than that expected from the background population of similar age and calendar period. Men had a higher risk and greater excess of mortality than women. More importantly, we found that co-morbidity was not significantly associated with reduced survival among hip fracture, suggesting that hip fracture is probably causally related to mortality.

The relative survival of patients with a hip fracture has been reported previously [4,5,20]. Our estimates of relative survival in this study are comparable with those of previous studies which also used the relative survival technique [9,20]. For instance, the Rochester Epidemiology Project reported a 5-year RSR of 0.82 (95% CI 0.77–0.87) (women and men combined) post hip fracture. A hospital registry based hip fracture study, that compared women aged 70 or older post fracture, with a group of women from a population-based aging study [21], found an overall excess of 1-year mortality of 4 per 100 fractures, or an NNH of 25. Importantly, our data show an excess of mortality following hip fracture in men to that expected in the background population of men of a similar age and calendar period. Greater risk of mortality among men when compared to women has been previously described by Kannegaard [22].

It is interesting that there was no significant effect of co-morbidity on the post-hip fracture relative survival. This finding is consistent with a previous report [23], but is inconsistent with a previous study

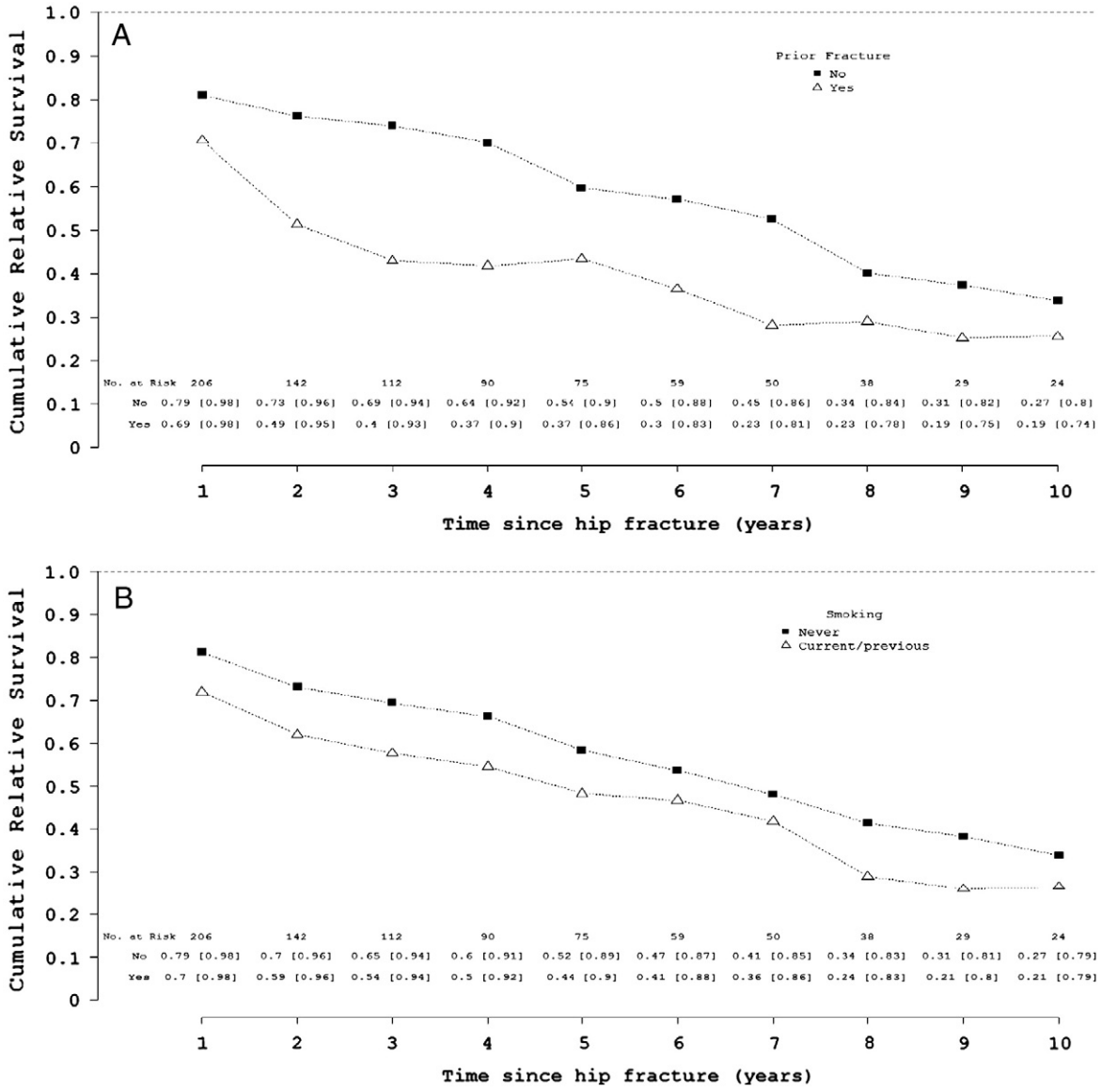

Fig. 2. Plots of relative survival following hip fracture comparing prior fracture status (panel A), and history of smoking (panel B). Observed survival and [expected survival] added to the bottom of each plot.

Table 3
Effect of age, sex, history of prior fracture, comorbid disease and smoking status on excess of mortality in women and men with hip-fracture between 1989 and 2010.

	Excess mortality ratio (95% CI)		P-value[a]
	Crude	Adjusted[a]	
Age group			
60–79	1.0 (reference)	1.0 (reference)	
80+	2.54 (1.6–4.1)	2.82 (1.7–4.6)	<0.001
Sex			
Female	1.0 (reference)	1.0 (reference)	
Male	1.30 (0.8–2.1)	1.68 (1.1–2.7)	0.034
Prior fracture			
No	1.0 (reference)	1.0 (reference)	
Yes	2.10 (1.3–3.3)	1.65 (1.1–2.6)	0.029
Comorbidity disease			
None	1.0 (reference)	1.0 (reference)	
One or more	0.86 (0.6–1.3)	0.85 (0.6–1.3)	0.477
Smoking status			
Never	1.0 (reference)	1.0 (reference)	
Current/previous	1.47 (0.9–2.3)	1.41 (0.9–2.2)	0.128

[a] Adjusted for age and sex.

which suggested that comorbidity was associated with an increased risk of mortality [24]. Taken together, it seems clear that comorbidity does not contribute significantly to the excess mortality following a hip fracture. The present study further showed that even after adjusting for time-related increase in life expectancy in the general population, hip fracture patients, particularly men, still had greater risk of mortality than the general population. These facts collectively suggest that hip fracture is probably causally related to reduced survival in the elderly population. Nevertheless, it is not clear about the underlying mechanism for the relationship between hip fracture and mortality.

The relevance of this study's finding can be appreciated within the context of the global burden of hip fracture. It has been estimated that in the year 2000, approximately 1.5 million hip fractures occurred world-wide in women and men, aged 60 or older (422,000 men and 1.1 million women) [25]. With the upper confidence intervals of our estimates of the number needed to harm, we estimated that world-wide, an extra of 120,000 women and 105,000 men would have died within the first-year following a hip fracture. The additional significance of these estimates is that although fracture in men accounts for only a-third of the incidence of hip fracture, the mortality from men accounted for half of excess deaths following a hip fracture.

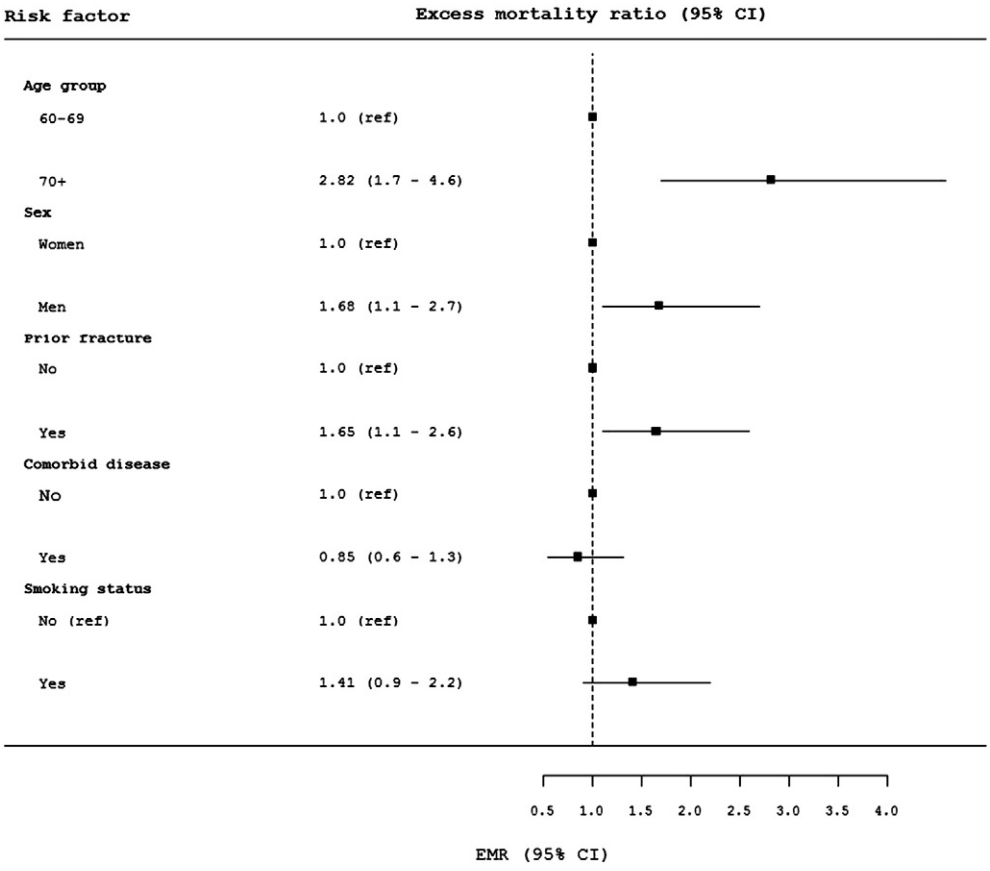

Fig. 3. Effect of age, sex, history of prior fracture, comorbid disease and smoking status on excess of mortality in women and men with hip-fracture. All estimates are adjusted for age and sex.

An important strength of this study is that the results were derived from a long-term population-based osteoporosis epidemiology study. The study included both men and women, and was able to compare the relative survival between sexes. Furthermore, by applying relative survival technique and by accounting for the expected mortality in the background population of a similar age, sex and calendar period, we have addressed the proportion of mortality attributable to osteoporotic hip fracture. The Dubbo population is highly representative of the Australian population. Our preliminary analysis (not reported) has shown that the rate of mortality among non-fracture individuals in the Dubbo Study was almost identical to that of the general population. However, the sample size (e.g., the number of hip fracture cases) in the study was relatively modest, which limited our ability to examine factors with low effect sizes. Importantly, we did not have information of smoking and prior fracture status of the background population, and a lack of accounting for these factors could introduce bias in our results. However, the relative survival curves for the Dubbo population and Australian population are almost identical, which is reassuring that bias was not a real problem.

The finding that a large excess mortality occurred within the first 5 years after a fracture has important clinical implication. Bisphosphonates are considered first-line treatment of osteoporosis, and recent evidence suggest that the bisphosphonates as a group could reduce the risk of mortality among men and women with a fracture [26,27]. In a large randomized controlled trial, zoledronic acid treatment was shown to reduce the risk of post-hip-fracture mortality by 28%, when given within 90-days post hip surgery [28]. Interestingly, only a small part of the benefit of reducing death post fracture is thought to be attributable to preventing re-fracture. Nevertheless, our finding, together with evidence from clinical trials, suggest that the first 5 years, particularly the first year, after fracture is perhaps the ideal time for intervention to reduce the risk of mortality among hip fracture patients.

In conclusion, hip fracture is associated with reduced life expectancy even after accounting for time-related changes in background mortality in the population, with men having a greater reduction than women. These data underscore that hip fracture is an independent clinical risk factor for mortality.

Acknowledgments

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Conflicts of interest

Professor J. A. Eisman received support from the MBF Living Well Foundation; the Ernst Heine Foundation; and untied grants from Amgen, Merck Sharp & Dohme, Sanofi-Aventis, Servier, and Novartis. Professor T. V. Nguyen is supported by a senior fellowship from the Australian National Health and Medical Research Council, and has served as a consultant or speaker for Merck Sharp & Dohme, Sanofi-Aventis, Servier, Roche, and Novartis.

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