LUND UNIVERSITY

Hip fracture, mortality risk, and cause of death over two decades

von Friesendorff, M.; McGuigan, F. E.; Wizert, A.; Rogmark, C.; Holmberg, A. H.; Woolf, A. D.; Åkesson, Kristina

Published in:
Osteoporosis International

DOI:
10.1007/s00198-016-3616-5

2016

Document Version:
Peer reviewed version (aka post-print)

Link to publication

Citation for published version (APA):
von Friesendorff, M., McGuigan, F. E., Wizert, A., Rogmark, C., Holmberg, A. H., Woolf, A. D., & Åkesson, K. (2016). Hip fracture, mortality risk, and cause of death over two decades. *Osteoporosis International*, *27*(10), 2945-2953. https://doi.org/10.1007/s00198-016-3616-5

Total number of authors:
7

General rights
Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.
• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: https://creativecommons.org/licenses/

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

HIP FRACTURE, MORTALITY RISK AND CAUSE OF DEATH OVER TWO DECADES

My von Friesendorff[1], MD, PhD, Fiona E McGuigan[1], PhD, Alicja Wizert[2], MSc, Cecilia Rogmark[1], MD, PhD, Anna H Holmberg[1], MD, PhD, Anthony D Woolf [3], BSc, MBBS, FRCP, Kristina Akesson[1], MD, PhD

[1]Dept of Clinical Sciences Malmö, Clinical and Molecular Osteoporosis Research Unit, Lund University, and Dept of Orthopedics Malmö, Skåne University Hospital, Malmö, Sweden; [2]ERC Syd - Epidemiology and Register Centre South, Skåne University Hospital, Lund, Sweden; [3]Dept of Rheumatology Royal Cornwall Hospital, UK

Correspondence to:

Kristina Akesson, MD, PhD
Lund University
Dept of Clinical Sciences Malmö
Skåne University Hospital
Dept of Orthopedics
S-205 02 Malmö, Sweden
E-mail: **kristina.akesson@med.lu.se**
Telephone +46 40 331000
Fax +46 40 336200

Conflict of interest: My von Friesendorff, Fiona E McGuigan, Alicja Wizert, Cecilia Rogmark, Anna H Holmberg, Anthony D Woolf, and Kristina Akesson declare that they have no conflicts of interest.

ABSTRACT

Purpose: Hip fractures are associated with increased mortality, particularly short term. In this study with a two decade follow-up, we examined mortality and cause of death compared to the background population.

Methods: We followed 1013 hip fracture patients and 2026 matched community controls for 22 years. Mortality, excess mortality and cause of death were analysed, stratified for age and sex. Hazard ratio (HR) was estimated by Cox regression. A competing risk model was fitted to estimate HR for common causes of death (CVD, cancer, pneumonia) in the short-term and long-term (>1 year).

Results: For both sexes and at all ages, mortality was higher in hip fracture patients across the observation period with men losing most life years (p <0.001). Mortality risk was higher for up to 15 years (women (**RR 1.9 [95% CI 1.7-2.1**]); men (RR **2.8 [2.2-3.5])**) and until end of follow-up ((RR **1.8[1.6-2.0]);** (RR **2.7 [2.1-3.3**])). Excess mortality by time intervals, censored for first year, was evident in women (<80 yrs, up to 10 yrs; >80 yrs, for 5 yrs) and in men <80 yrs throughout. CVD and pneumonia were predominant causes of death in men and women with an associated higher risk in all age-groups. Pneumonia caused excess mortality in men over the entire observation period.

Conclusion: In a remaining lifetime perspective, all-cause and excess mortality after hip fracture was higher even over two decades of follow-up. CVD and pneumonia reduce life expectancy for the remaining lifetime and highlights the need to further improve post-fracture management.

Key words: Hip fracture; mortality, cause of death, sex, age

Mini Abstract:

Men and women with hip fracture have higher short term mortality. This study investigated mortality risk over two decades post-fracture; excess mortality remained high in women up to 10 years and in men 20 years. CVD and pneumonia were leading causes of death with a long term doubling of risk.

INTRODUCTION

Hip fracture at any age is the most severe fracture attributable to bone fragility and predominantly affects an already frail population. The burden on health care and society is very high [1]. Despite an apparent decrease in the incidence of hip fracture in some countries [2-5], the lifetime risk of sustaining a hip fracture continues to be high in Scandinavia [6]. Hip fracture is associated with high mortality, multi-cause morbidity and loss of functional independence [7-9], although immediate peri-operative management and surgical outcome has improved over the past decade [10].

After hip fracture, the early mortality within 1 to 3 months and up to one year in both men and women is well described and universal [11-14], with excess mortality most pronounced in men [14-19]. Although early mortality is high, the majority of patients do survive the first year, hence a longer term perspective is essential, yet less well studied. Of the limited reports extending to 5-years post-fracture, a higher mortality rate, most pronounced in men and in the oldest, is noted [14,15,18,20-25]. Critically, information on age-specific mortality 10-years or more after presenting with a hip fracture is scarce, in part due to difficulties obtaining continuous long term data, including validated cause of death. Furthermore, a hip fracture will not routinely be included as a contributing cause of death beyond one year [16,21,26-29]. Moreover, in the elderly identifying the proportion of mortality risk attributable to the hip fracture per se becomes problematic with the progression of time. However, fracture attributable risk can be addressed if the hip fracture cohort is compared to that of the background population; whereby mortality in the background population can be assumed to result from causes other than hip fracture [30]. In addition, analyses stratifying for age (since fractures occur from younger than fifty to older than ninety) and sex are instrumental to correctly estimating excess mortality in meaningful time-intervals. Neglecting this may give estimates that are too conservative in older individuals and misleadingly high in those who are younger [14].

In the immediate post-operative period, complications leading to death are well known [31]. For those who survive beyond the first 3 or even 12 months, the causes of early mortality following hip fracture are predominantly cardiovascular disease and pneumonia [20,32-34]. Subsequently there is a large gap in our knowledge in terms of mortality and cause of death for those men and women surviving longer term after a hip fracture and whether this group continues to differ from the background population, information that is essential for estimates of health and social care utilization. To address this gap in knowledge we have used a hip fracture cohort of 1013 patients and 2026 matched controls followed for their remaining life time or up to 22-years (the end of the study).

In previous studies we reported on fracture risk and long term survival after hip fracture in women [35] and men [36], but without comparison to controls or addressing causes of death.

The aim of this study was to address these gaps in knowledge; (i) describing mortality and the causes of death in male and female patients presenting with a hip fracture using a two decade post-fracture perspective and (ii) comparing these with the background population over the same time frame.

MATERIALS AND METHODS

The present study utilizes the two cohorts of prospectively followed consecutive female [35] and male [36] hip fracture cases and now with added matched controls, from Malmö, Sweden. In a catchment area of ~260,000 the department of Orthopedics Malmö, Skåne University Hospital, is the only unit treating hip fractures [37].

The cases, identified through the radiology department, were all adults (>20 yrs) who sustained a low-energy trauma hip fracture (the index hip fracture) during the two-year inclusion period (1984-1985). This study design has the advantage of individual fracture verification compared to registry studies, while similarly no individual medical information are available. As previously reported in detail [35], hip fracture was defined as any fracture of the proximal femur ranging from femoral neck to the subtrochanteric region, fractures caused by high energy (n=16) or pathological (n=14) were excluded. We identified 1013 cases (757 women, 256 men) after excluding 16 individuals for which no matching controls could be identified.

The admission date for each hip fracture case served as index date for the controls, which were randomly selected through Statistics Sweden (SCB). Controls were living in the catchment area when their corresponding case sustained the index fracture. No exclusion criteria were applied. Controls were sex- and age- (year and month) matched. Where possible, two controls (or one weighted) were coupled to each case using the random sampling technique, giving 2026 controls. The hip fracture cases and their corresponding controls were subsequently individually followed until death or December 2005, i.e., 22-years. Three controls were followed until their date of emigration.

The study was approved by the Local Ethics Committee, Lund University, Sweden and complies with ethical principles of the Declaration of Helsinki.

Mortality and Cause of Death

Using the unique Swedish personal identification number, date and cause of death (International Classification of Diseases, v8-10) for every individual were obtained from the National Board of Health and Welfare, Sweden which validates all data; >99% of all Swedish subjects receive a diagnosis [38]. We report cause of death according to major disease categories (Supplementary-Table 1).

Statistical analysis

All data was analysed separately for women and men and stratified by age. Age-groups and time-intervals used were dependent on the statistical model applied, and to ensure that the closely matched subjects were included in the same group. Descriptive data and survival analyses include all available matched cases and controls; weighted controls were removed before analysis (table 2). For all other analyses, initial matching of cases and controls was removed and replicate controls deleted.

For the results presented in tables 1 - 2 and Figures 1 - 3 the study population was stratified into age-groups <75, 75-84 and ≥85 yrs at inclusion. These groups were chosen since the 75-84y group captures mean age at hip fracture in the cohort and allows comparison with published studies. For the data in Figure 2 two subsets were used, <80 yrs at inclusion and ≥80 yrs (the approximate median age at inclusion). This ensured a sufficient sample size in each age-group. In Supplementary-Table 2 descriptive data are reported in 5-yr age-bands, except those <50 yrs (n=21). Cumulative survival was estimated using the Kaplan-Meier method (figure 1). Follow-up was from the date of the index hip fracture until date of death (event) or end of follow-up (censored).

The relative mortality (i.e. risk compared to the controls) was estimated using Cox regression. In the first instance, for age-groups <75, 75-84 and ≥85 yrs the mortality from inclusion to end of follow-up; for 1-, 5-, 10- and 15-years, risk is presented as Hazard Ratio (HR) with 95% confidence interval (CI); end of follow-up is presented as Rate Ratio (RR) (Table 2). Additional analyses (Figure 2) for estimating time-specific risk were also performed, to evaluate the change in death risk [38]. For individuals <80 yrs or >80 yrs at inclusion, time-specific risk ratios (RR) for the fracture variable adjusted for age were calculated for each of 5 time-intervals: [0, 3 months], [3 months, 1-year], [1-year, 5-years], [5-years, 10-years] and (10-years, 22-years i.e. end of follow-up]. Within each time-interval, events (and censored observations) occurring *before* the specified start-time were excluded; those occurring *after* the specified end-time were censored. The resulting 20 subsets each had a Cox model fitted. The assumption of proportional hazard was tested using Schoenfeld residuals. In most time-intervals there was insufficient evidence of non-proportional hazards and the global test did not indicate any statistically significant deviation from proportionality.

The causes of death registered for cases and controls (Figure 3) are presented as proportion within each age-group. For the most common causes of death we estimated the risk of death for a hip fracture patient compared to controls. We also calculated the risk of death from each of the studied diseases in a competing risks setting. For this (table 3) Fine and Gray models [40] were used to estimate the relative risk (with fracture and age included as covariates) in two time-intervals [0 - 1 year] and [1 – 22 years] censoring for the high first year mortality.

Analyses were performed using SPSS v17.0 (SPSS Inc.), STATISTICA 7.1 (StatSoft Inc.) and R (R foundation for statistical computing, Vienna, Austria). Significance was set at $p<0.05$.

RESULTS

Men were younger when they fractured than women ($p<0.001$), clearly demonstrated by the fact that 25% of men compared to 8.5% of women sustained their hip fracture before age 65 (data not shown). Fracture cases and age-matched controls, distributed according to the age-groups <75, 75-84 and ≥85 yrs are presented in Table 1A.

In women, mortality was higher in those with hip fracture compared to controls ($p<0.001$) as was the cumulative mortality (Table 1B; Figure 1A). This elevated mortality can be clearly seen in all age bands (Supplementary-Table 2A). As expected, the median time-to-death was age-dependent, significantly shorter in cases than controls and with the longest survival times in the lower age-group (p for all <0.001) (Table 1B; Figure 1A). As seen in Supplementary-Table 2A, none of the female cases (n=64) below age 65 died within the first 3 months. Overall, for women after a hip fracture the incidence of death at the end of the study equates to 142 per 1000 person-years compared to 96 per 1000 person-years in the background population.

In men, mortality was similarly higher compared to controls ($p<0.001$), as was the cumulative mortality (Table 1B; Figure 1B) and apparent in all age bands (Supplementary-Table 2B). Again, as expected the median time-to-death was age-dependent and significantly shorter in cases than controls. None of the male cases (n=36) below age 60 died within the first year (Supplementary-Table 2B). In men, the incidence of death equates to 168 in cases vs. 88 per 1000 person-years in controls.

The consequence of this shorter time-to-death is emphasized when presented as loss of potential lifetime. For the age-groups (<75, 75-84 and ≥85 yrs), the absolute number of life-years lost was 6.4, 3.2 and 1.9 respectively in

female hip fracture cases and 8.5, 2.7 and 2.4 yrs in males. In relative terms, life-expectancy was 36%, 39% and 45% shorter in women and 55%, 57% and 90% shorter in men compared to controls.

Within 1 year the proportion dead was 21% for women with a hip fracture and 6% for controls (Supplementary-Table 2A). Translated into an age adjusted risk estimate, this corresponds to an almost 5 times higher overall risk of a woman dying within the first year after a hip fracture (HR 4.6 [3.5-6.1]) (Table 2). Furthermore, the age-stratified analysis shows that in all three age-groups, mortality risk was more than doubled for at least 10-yrs post hip fracture, and remained at least 50% higher for the duration of the observation period (at 22-yrs RR 1.8 [1.6-2.0]).

To confirm these findings, ensuring the PH assumptions were met, we also calculated time-specific RR's censored for the observed high early mortality, across five time-intervals. For women younger than 80y when they fractured, excess mortality was evident for up to 10-years post-fracture (i.e. within the intervals 1-5 years and 5-10 years). For women older than 80y, it was evident for up to 5-years post-fracture (Figure 2).

Males had an even higher mortality during the first year post fracture compared to their controls (31% vs 8%) corresponding to an almost 6 times higher risk of dying within the first year after a hip fracture (HR 5.7 [3.7-8.9]) (Table 2). But, the age-stratified analysis demonstrated that the one-year mortality risk was highest in the oldest age-group (men ≥85 yrs), with a 9-fold risk increase. Beyond the first year, overall the relative risk of dying remained almost 3 times higher up to 10-years post-fracture and was more than doubled for the remaining observation period (at 22-yrs RR 2.7 [2.1-3.3]). Evaluation of excess mortality in the five time-intervals (and censored for the first year) showed that for men younger than 80y when they fractured, excess mortality persisted over the entire period although became less pronounced with time (RR 2.7 – 1.5) (Figure 2).

Cause of death after hip fracture

The underlying causes of death were diverse. Figure 3 illustrates the percentage distribution of the recorded causes of death within each age-group (<75, 75-84 and >85 yrs) for women and men, cases and controls.

The most common causes of death in women, both fracture cases and controls, were cardiovascular disease (CVD), pneumonia and cancer, with CVD being the dominant cause in all age-groups. Risk of death from each of these diseases in a competing risks setting and compared to the background controls was calculated. Within the

first year, the risk of a woman with a hip fracture dying from one of these three causes was 3-4 fold higher than the background controls (Table 3). Thereafter (between 1 and 22 years) the risk was not substantially different for hip fracture cases and controls. We also report 5-year risk to facilitate comparison with other studies (and reflecting median survival after hip fracture in our cohort), but not considering competing risks. Compared to controls, at 5-years the risk of death from these causes was 2-3 fold higher (CVD 1.8 [1.5-2.1]; pneumonia 2.5 [1.6-3.8] and cancer 1.5 [1.0-2.2]).

As for women, the most common causes of death in men, both fracture cases and controls, were CVD, pneumonia and cancer (Figure 3). Considering competing risks, within the first year, CVD and pneumonia was associated with a 4-5 fold risk increase for deaths among hip fracture cases (Table 3). For the interval 1- 22 years the risk from pneumonia continued to be significantly increased, while for CVD and cancer the risk degraded to that of the background controls. For the purpose of comparison with other studies (and because of the high early male mortality), we also report relative risks (but not considering competing risks) at 2- and 5-years. During the first 2-years following hip fracture the relative risk of dying from CVD was more than doubled in male cases (RR 2.7 [1.6-4.4]), and at 5-years it was 50 % higher. In addition to CVD, pneumonia, was elevated at 5-years (2.8 [1.6-4.9]).

DISCUSSION

In this study, men and women who had sustained a hip fracture during the mid-nineteen eighties were followed for their remaining lifetime and compared with the background population to describe the long-term influence of age at fracture on mortality and cause of death. Age stratification demonstrated that among fracture patients mortality was high in women over 85 and men over 75. Few of these individuals were still alive 5-years after their fracture. Those surviving beyond 10-years were predominantly the youngest when they fractured their hip and the largest proportion were women. Even accounting for the high early mortality, excess mortality was evident among these younger individuals, persisting up to 10-years in women and 22 in men. Regarding the common causes of death, after the first year they did not differ from the background population, with the exception of pneumonia which continued to be higher in men over the entire follow-up. Age at hip fracture is the most important predictor also of long-term mortality, where the very elderly only survive for a very short time [11,12,20,23,24,31,34]. However, if the fracture occurred before age 75 the reduction in life expectancy was substantial, equivalent to six years in women and eight for men. Our study highlights the importance of also paying particular attention to relatively

younger patients at the clinic, although since life expectancy has increased the definition of relatively younger may shift upwards in chronological age, an issue for future studies.

Among the published data, the lack of uniform study design has made it difficult to establish the true mortality risk associated with hip fracture [12,15,18,27,28,34,41,42]. When evaluating mortality beyond 10-15 years, all observations are driven by the longer survival of the relatively younger women (<75) and men (<65-70) and furthermore, hip fracture studies with extensive follow-up are complicated by mortality risk not being constant over time (for patients or controls). To address these issues, in our study we used Cox regression within specific time-frames and censoring for earlier mortality to model this non-constant risk. By doing so we could show that, regardless of age, a woman who has fractured her hip fracture has a higher mortality risk than equivalently aged women from the background population, across the whole of follow-up. For men under age 80, mortality is elevated for the remainder of their life. This applies also to the oldest men, although their remaining lifetime is short, with almost all dead by one year.

Given that mortality is increased among hip fracture patients, we asked what accounts for this higher mortality. Cardiovascular disease was the most common cause of death. We report that compared to the background population, the mortality risk attributable to CVD was consistently elevated among hip fracture patients, but mainly over the early part of the observation period with a sustained two to three-fold higher risk over the first five years and fifty percent higher risk thereafter in both sexes. This is keeping with the reported association between CVD risk and hip fracture [19,31,32,43,44]. Remarkably, pneumonia, so common post-operatively as a cause of premature death [31,34,42] continued to be fatal for men, for up to 10 years, with a three-fold higher mortality risk at all time-points. Conversely, death from cancer was similar between patients and controls, with the exception of an associated higher risk in women over the first year despite presenting with a non-pathological hip fracture. Apart from these three most common causes of death, we reviewed all major- and sub-groups; beyond the first year the cause of death became proportionally more similar among patients and controls with passage of time i.e. the risk related to a specific cause is attenuated. This indicates that the cause of death was less affected than mortality per se with time after hip fracture, compared to the background population; most likely a reflection of the incipient frailty that afflicts the fracture patient earlier than controls for the early years post-fracture.

Recognition of the high short term mortality has already led to increased awareness and optimized management from the fracture event to post-operative care. The findings of this study are also clinically relevant, highlighting as it does that those surviving beyond a year ought to receive additional long term medical attention including therapy to reduce re-fracture risk, since there is great potential for life years lost or gained. Such preventive measures need individualisation, factoring in age and sex, but will bring with it health benefits to the individual while reducing the burden on healthcare and society. Prediction of post-fracture survival in the short and long term is also of surgical interest since modern treatment algorithms suggest different implants e.g. arthroplasty or internal fixation, depending on the remaining lifespan.

Strengths and limitations

The study has several strengths: the length of follow-up; the large number of hip fractures; completeness of data; the consecutive and limited inclusion period; and closely matched controls in terms of age and geography. The birth-date-based personal identification number allowed for 100% retrieval of fracture and mortality data with validated diagnoses [38,46] and no loss-to-follow-up. Consequently, this is the most comprehensive study to report on mortality and cause of death over the remaining lifespan in hip fracture patients compared with the background population. While the overall findings are likely to be applicable to Scandinavia, they will require confirmation in other studies of a correspondingly long duration. Similarly, given that life expectancy has increased, those who fracture in 2016 are likely to be different to those who fractured during the nineteen eighties.

We acknowledge limitations; ideally the number of controls matched with the younger hip fracture age-group would have been larger, since these individuals are likely to be heterogeneous with some biologically younger and some older. The lack of data on co-morbidities is regrettable, but this information is not systematically available through medical records and if collected retrospectively, not fully reliable or comprehensive over a long follow-up; hence it was not part of the planned analysis. For this study, chronological age is therefore considered a relevant proxy. We assume that the co-morbidities influencing early deaths may be similar to other studies [12,13,15,29,34] since, in agreement with other reports, the within one-year mortality was also high [11,12,20,23,24,34]. Patients or controls may have had a previous hip fracture, but presumably this should not skew the results significantly. Bias resulting from secular changes occurring over time is minimised in this study as, unlike the extended inclusion of register studies, here a 2-year inclusion is used. We believe that, as far as is possible, the design of this study minimises potential inaccuracies in the estimation of adverse outcomes occurring many years after the initial event and through including also time framed analyses.

In conclusion, this study with a remaining lifetime perspective, demonstrated that all-cause mortality and excess mortality in patients presenting with a hip fracture was higher in both men and women even over two decades of follow-up and was age-dependent. Cardiovascular disease and pneumonia represent a threat to life expectancy over the post-fracture lifetime. The observed age related influence on mortality highlights the necessity to tailor patient care and post-fracture management to improve life expectancy.

Acknowledgements

This work was supported by grants from the Swedish Research Council (K2009-53X-14691-07-3, K2010-77PK-21362-01-2), FAS (Grant 2007-2125), Greta and Johan Kock Foundation, A Påhlsson Foundation, A Österlund Foundation, King Gustav V and Queen Victoria Foundation, Malmö University Hospital Research Foundation, Research and Development Council of Region Skåne, Sweden and the Swedish Medical Society.

We thank Professor Jonas Ranstam and Mr Jan-Åke Nilsson for statistical advice and Dr Jack Besjakov for access to radiography files.

Authors' roles: Study design and study conduct: KÅ and MvF. Data collection: MvF. Data analysis: MvF, FEMG, AW. Data interpretation: MvF, FEMG, CR, AHH, ADW, KÅ. Drafting manuscript: MvF, FEMG, KÅ. Revising manuscript content: MvF, FEMG, CR, AW, AHH, ADW, KÅ. Approving final version of manuscript: MvF, FEMG, CR, AW, AHH, ADW, KÅ. KÅ takes responsibility for the integrity of the data analysis.

REFERENCES

1. Borgstrom F, Johnell O, Kanis JA, Jonsson B, Rehnberg C (2006) At what hip fracture risk is it cost-effective to treat? International intervention thresholds for the treatment of osteoporosis. Osteoporos Int 17: 1459-1471.
2. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB (2009) Incidence and mortality of hip fractures in the United States. JAMA 302: 1573-1579.
3. Leslie WD, O'Donnell S, Jean S, Lagace C, Walsh P, et al. (2009) Trends in hip fracture rates in Canada. JAMA 302: 883-889.
4. Rogmark C, Sernbo I, Johnell O, Nilsson JA (1999) Incidence of hip fractures in Malmo, Sweden, 1992-1995. A trend-break. Acta Orthop Scand 70: 19-22.
5. Ahlborg HG, Rosengren BE, Jarvinen TL, Rogmark C, Nilsson JA, Sernbo I, Karlsson MK Prevalence of osteoporosis and incidence of hip fracture in women - secular trends over 30 years. BMC Musculoskelet Disord 11: 48.
6. Karampampa K, Ahlbom A, Michaelsson K, Andersson T, Drefahl S, Modig K (2015) Declining incidence trends for hip fractures have not been accompanied by improvements in lifetime risk or post-fracture survival--A nationwide study of the Swedish population 60 years and older. Bone 78: 55-61.
7. Cooper C, Campion G, Melton LJ, 3rd (1992) Hip fractures in the elderly: a world-wide projection. Osteoporos Int 2: 285-289.
8. Johnell O, Kanis JA (2004) An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. Osteoporos Int 15: 897-902.
9. Melton LJ, 3rd (1993) Hip fractures: a worldwide problem today and tomorrow. Bone 14 Suppl 1: S1-8.
10. Leonardsson O, Garellick G, Karrholm J, Akesson K, Rogmark C (2012) Changes in implant choice and surgical technique for hemiarthroplasty. 21,346 procedures from the Swedish Hip Arthroplasty Register 2005-2009. Acta Orthop 83: 7-13.
11. Empana JP, Dargent-Molina P, Breart G (2004) Effect of hip fracture on mortality in elderly women: the EPIDOS prospective study. J Am Geriatr Soc 52: 685-690.
12. Farahmand BY, Michaelsson K, Ahlbom A, Ljunghall S, Baron JA (2005) Survival after hip fracture. Osteoporos Int 16: 1583-1590.
13. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK (2003) The components of excess mortality after hip fracture. Bone 32: 468-473.
14. Omsland TK, Emaus N, Tell GS, Magnus JH, Ahmed LA, et al. (2014) Mortality following the first hip fracture in Norwegian women and men (1999-2008). A NOREPOS study. Bone 63: 81-86.
15. Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, et al. (2004) Mortality after osteoporotic fractures. Osteoporos Int 15: 38-42.
16. Pande I, Scott DL, O'Neill TW, Pritchard C, Woolf AD, Davis MJ (2006) Quality of life, morbidity, and mortality after low trauma hip fracture in men. Ann Rheum Dis 65: 87-92.
17. Trombetti A, Herrmann F, Hoffmeyer P, Schurch MA, Bonjour JP, Rizzoli R (2002) Survival and potential years of life lost after hip fracture in men and age-matched women. Osteoporos Int 13: 731-737.
18. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C (2009) Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int 20: 1633-1650.
19. Koh GC, Tai BC, Ang LW, Heng D, Yuan JM, Koh WP (2013) All-cause and cause-specific mortality after hip fracture among Chinese women and men: the Singapore Chinese Health Study. Osteoporos Int 24: 1981-1989.
20. Panula J, Pihlajamaki H, Mattila VM, Jaatinen P, Vahlberg T, Aarnio P, Kivela SL (2011) Mortality and cause of death in hip fracture patients aged 65 or older: a population-based study. BMC Musculoskelet Disord 12: 105.
21. Forsen L, Sogaard AJ, Meyer HE, Edna T, Kopjar B (1999) Survival after hip fracture: short- and long-term excess mortality according to age and gender. Osteoporos Int 10: 73-78.

22. Magaziner J, Lydick E, Hawkes W, Fox KM, Zimmerman SI, Epstein RS, Hebel JR (1997) Excess mortality attributable to hip fracture in white women aged 70 years and older. Am J Public Health 87: 1630-1636.
23. Luthje P, Helkamaa T, Kaukonen JP, Nurmi-Luthje I, Kataja M (2011) A long-term follow-up of 221 hip fracture patients in southeastern Finland: Analysis of survival and prior or subsequent fractures. Arch Gerontol Geriatr.
24. Gronskag AB, Romundstad P, Forsmo S, Langhammer A, Schei B (2011) Excess mortality after hip fracture among elderly women in Norway : The HUNT study. Osteoporos Int.
25. Michaelsson K, Nordstrom P, Nordstrom A, Garmo H, Byberg L, Pedersen NL, Melhus H (2014) Impact of hip fracture on mortality: a cohort study in hip fracture discordant identical twins. J Bone Miner Res 29: 424-431.
26. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR (2009) Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 301: 513-521.
27. Schroder HM, Erlandsen M (1993) Age and sex as determinants of mortality after hip fracture: 3,895 patients followed for 2.5-18.5 years. J Orthop Trauma 7: 525-531.
28. Vestergaard P, Rejnmark L, Mosekilde L (2007) Increased mortality in patients with a hip fracture-effect of pre-morbid conditions and post-fracture complications. Osteoporos Int 18: 1583-1593.
29. Kannegaard PN, van der Mark S, Eiken P, Abrahamsen B (2010) Excess mortality in men compared with women following a hip fracture. National analysis of comedications, comorbidity and survival. Age Ageing 39: 203-209.
30. Frost SA, Nguyen ND, Center JR, Eisman JA, Nguyen TV (2013) Excess mortality attributable to hip-fracture: a relative survival analysis. Bone 56: 23-29.
31. Ekstrom W, Samuelsson B, Ponzer S, Cederholm T, Thorngren KG, Hedstrom M (2015) Sex effects on short-term complications after hip fracture: a prospective cohort study. Clin Interv Aging 10: 1259-1266.
32. Sennerby U, Melhus H, Gedeborg R, Byberg L, Garmo H, et al. (2009) Cardiovascular diseases and risk of hip fracture. JAMA 302: 1666-1673.
33. Tosteson AN, Gottlieb DJ, Radley DC, Fisher ES, Melton LJ, 3rd (2007) Excess mortality following hip fracture: the role of underlying health status. Osteoporos Int 18: 1463-1472.
34. Wehren LE, Hawkes WG, Orwig DL, Hebel JR, Zimmerman SI, Magaziner J (2003) Gender differences in mortality after hip fracture: the role of infection. J Bone Miner Res 18: 2231-2237.
35. von Friesendorff M, Besjakov J, Akesson K (2008) Long-term survival and fracture risk after hip fracture: a 22-year follow-up in women. J Bone Miner Res 23: 1832-1841.
36. von Friesendorff M, McGuigan FE, Besjakov J, Akesson K (2011) Hip fracture in men-survival and subsequent fractures: a cohort study with 22-year follow-up. J Am Geriatr Soc 59: 806-813.
37. Jonsson B, Gardsell P, Johnell O, Redlund-Johnell I, Sernbo I (1994) Remembering fractures: fracture registration and proband recall in southern Sweden. J Epidemiol Community Health 48: 489-490.
38. National Board of Health and Welfare E, Sweden (2006) Causes of death: The National Board of Health and Welfare, Sweden.
39. Grambsch PM, Therneau TM (1994) Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 81: 515-526.
40. Fine JP, Gray RJ (1999) A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association 94: 496-509.
41. Haentjens P, Johnell O, Kanis JA, Bouillon R, Cooper C, et al. (2004) Evidence from data searches and life-table analyses for gender-related differences in absolute risk of hip fracture after Colles' or spine fracture: Colles' fracture as an early and sensitive marker of skeletal fragility in white men. J Bone Miner Res 19: 1933-1944.
42. Roche JJ, Wenn RT, Sahota O, Moran CG (2005) Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study. BMJ 331: 1374.

43. Hofbauer LC, Brueck CC, Shanahan CM, Schoppet M, Dobnig H (2007) Vascular calcification and osteoporosis--from clinical observation towards molecular understanding. Osteoporos Int 18: 251-259.
44. Persy V, D'Haese P (2009) Vascular calcification and bone disease: the calcification paradox. Trends Mol Med 15: 405-416.
45. Bliuc D, Alarkawi D, Nguyen TV, Eisman JA, Center JR (2015) Risk of subsequent fractures and mortality in elderly women and men with fragility fractures with and without osteoporotic bone density: the Dubbo Osteoporosis Epidemiology Study. J Bone Miner Res 30: 637-646.
46. Rosvall M, Chaix B, Lynch J, Lindstrom M, Merlo J (2006) Similar support for three different life course socioeconomic models on predicting premature cardiovascular mortality and all-cause mortality. BMC Public Health 6: 203.

Table 1 Baseline characteristics and survival of hip fracture patients and their age matched controls

		Patients n=1013	**Controls n=2026**
A) Subjects		Number	Number
Women	All	757	1514
	Mean age (SD)	79.6 (9.8)	79.6 (9.8)
	Median age (range)	81.0 (32-97)	81.0 (32-97)
	<75 yrs	192 (25%)	384 (25%)
	75-84 yrs	317 (42%)	634 (42%)
	≥85 yrs	248 (33%)	496 (33%)
Men	All	256	512
	Mean age (SD)	73.9 (12.3)	73.9 (12.3)
	Median age (range)	76.3 (33-95)	76.3 (33-95)
	<75 yrs	121 (47%)	242 (47%)
	75-84 yrs	94 (37%)	188 (37%)
	≥85 yrs	41 (16%)	82 (16%)
B) Survival (years)		Median (95% CI)	Median (95% CI)
Women	All	4.9 (4.4-5.4)	7.8 (7.3-8.3)
	<75 yrs	11.4 (8.8-14.0)	17.8 (16.6-19.1)
	75-84 yrs	5.0 (4.4-5.7)	8.2 (7.6-8.8)
	≥85 yrs	2.3 (1.8-2.8)	4.2 (3.8-4.6)
Men	All	3.7 (2.7-4.7)	7.5 (6.5-8.4)
	<75 yrs	7.0 (5.6-8.4)	15.5 (13.7-17.3)
	75-84 yrs	2.0 (0.97-3.1)	4.7 (3.8-5.6)
	≥85 yrs	0.23 (0.11-0.35)	2.6 (2.1-3.2)

Table 2. Risk of death for hip fracture patients compared to matched controls

Age at inclusion	Patients	Controls	1 year	5 year	10 year	15 year	End of follow-up (22-years)
A) Women							
<75yr	192	**380**	**4.2 (1.6-10.9)**	**2.9 (1.9-4.5)**	**2.4 (1.8-3.3)**	**2.2 (1.6-2.9)**	**1.9 (1.5-2.5)**
75-84yr	317	**624**	**6.9 (4.2-11.4)**	**2.2 (1.8-2.8)**	**1.9 (1.6-2.3)**	**1.8 (1.5-2.1)**	**1.8 (1.5-2.1)**
≥85yr	248	**467** [a]	**3.7 (2.6-5.3)**	**1.9 (1.6-2.5)**	**1.8 (1.5-2.2)**	**1.8 (1.5-2.2)**	**1.9 (1.5-2.2)**
All	757	**1471**	**4.6 (3.5-6.1)**	**2.2 (1.9-2.5)**	**1.9 (1.7-2.2)**	**1.9 (1.7-2.1)**	**1.8 (1.6-2.0)**
B) Men							
<75yr	121	**238**	**4.1 (1.8-9.7)**	**3.5 (2.1-5.7)**	**3.1 (2.1-4.6)**	**3.2 (2.2-4.5)**	**2.9 (2.0-3.9)**
75-84yr	94	**186**	**5.4 (2.9-10.1)**	**2.8 (1.9-4.1)**	**2.3 (1.7-3.2)**	**2.3 (1.7-3.3)**	**2.4 (1.7-3.3)**
≥85yr	41	**65** [b]	**9.1 (3.5-23.9)**	**3.4 (1.8-3.4)**	**3.3 (1.8-5.9)**	**3.3 (1.8-5.9)**	**3.3 (1.8-5.9)**
All	256	**489**	**5.7 (3.7-8.9)**	**3.1 (2.4-4.1)**	**2.7 (2.2-3.4)**	**2.8 (2.2-3.5)**	**2.7 (2.1-3.3)**

Cox regression analysis was used to calculate risk of death (in hip fracture patients compared to matched controls). Reported at 1-, 5- 10- and 15 years (Hazard Ratio with 95% CI); at end of follow-up (Rate Ratio with 95% CI).

[a] One control age 93 emigrated at 3 yrs. [b] One control age 86 emigrated at 3.2 yrs and one control age 87 yr emigrated at >20yrs

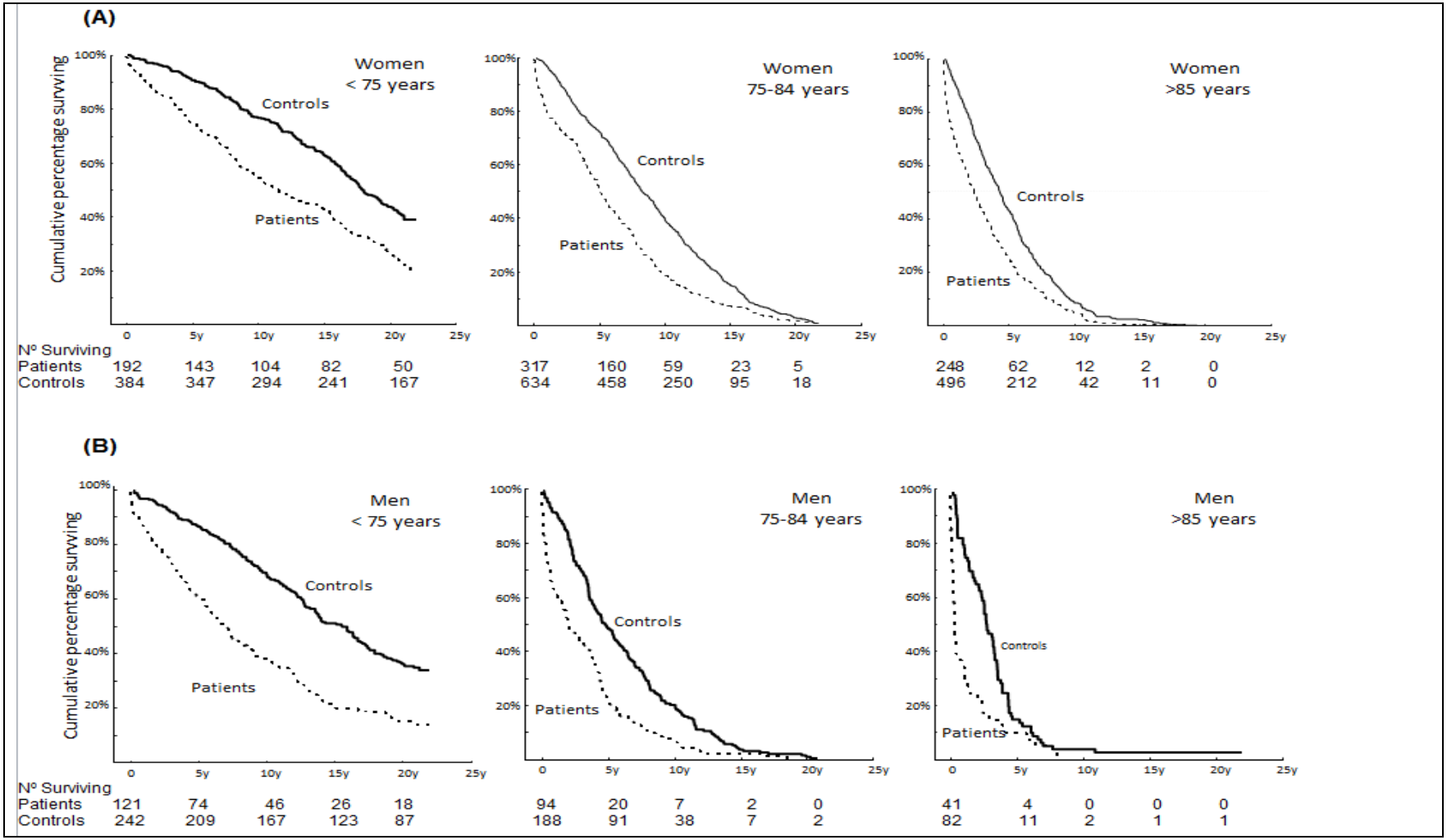
Table 3. Risk of a hip fracture patient dying from the three most common causes of death; CVD, cancer or pneumonia within the first 12 months and from 1year until end of follow-up

A) Women	Cardiovascular Disease		Cancer		Pneumonia	
	Events (n)	RR (95% CI)	Events (n)	RR (95% CI)	Events (n)	RR (95% CI)
Between 0-1 year	84	3.6 (2.5-5.1)	18	4.2 (1.8-9.6)	20	3.4 (1.6-7.1)
Between 1-22 years	291	1.1 (0.98-1.3)	55	0.75 (0.55-1.0)	50	1.1 (0.77-1.5)

B) Men	Cardiovascular Disease		Cancer		Pneumonia	
	Events (n)	RR (95% CI)	Events (n)	RR (95% CI)	Events (n)	RR (95% CI)
Between 0-1 year	27	3.8 (2.0-7.2)	6	1.9 (0.61-5.8)	17	4.7 (1.9-11.3)
Between 1-22 years	66	0.92 (0.69-1.2)	18	0.59 (0.35-0.98)	20	2.1 (1.2-3.7)

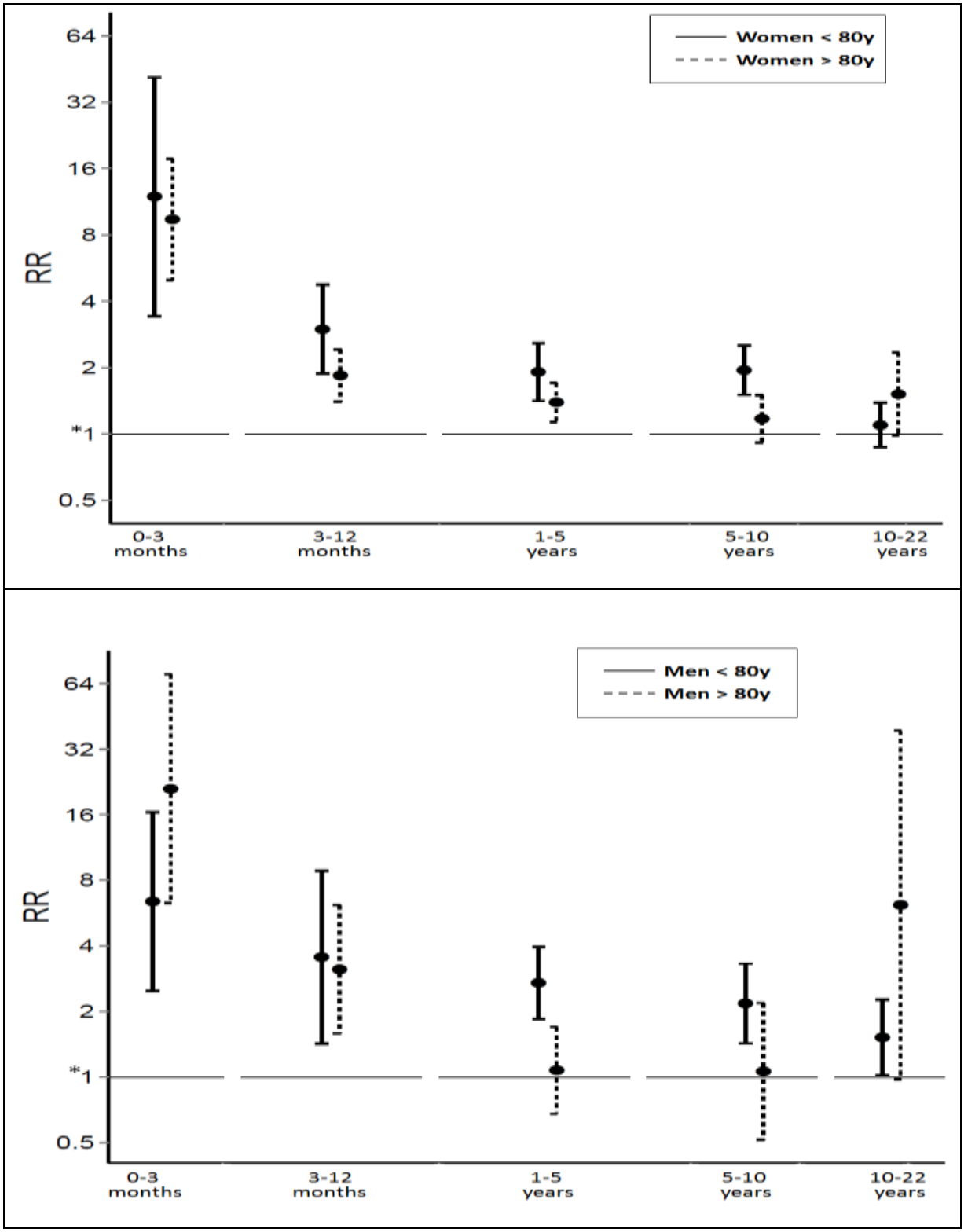
Fine and Gray models were used to calculate risk of death (RR and 95% CI (including fracture and age as covariates)) for a hip fracture patient compared to controls from each of these diseases in a competing risks setting. Events (and censored observations) occurring before the specified start-time were excluded; those occurring after the specified end-time were censored. [40]

Figure 1 Cumulative percentage surviving across follow-up. Women (A) and men (B) with hip fracture compared to matched controls



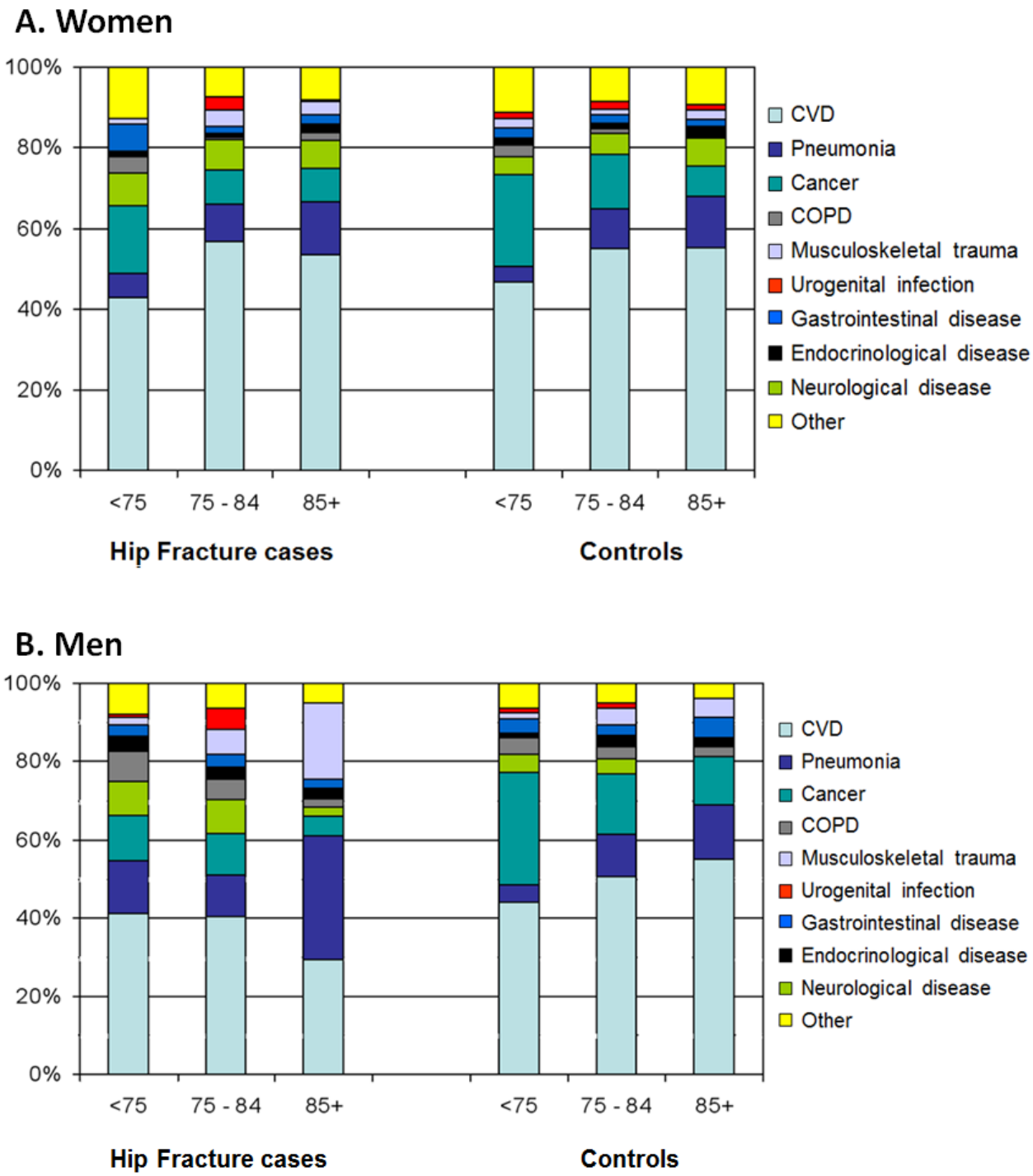
Survival was assessed using the Kaplan-Meier method and the figure shows cumulative % survival and underneath includes absolute numbers surviving. Follow-up continued until "date of death" or "alive at the end of follow-up".

Figure 2 Hip fracture and associated excess mortality in those above or below age 80 yrs. The relative risk (RR) is hip fracture compared to controls (*RR=1.0 controls)



The hip fracture patients and their controls were followed until death or December 2005, i.e. 22-years. Cox Proportional Hazards model with a time interaction was used to calculate hazard ratio (95% CI's) in individuals below and above 80y at inclusion. Within each time-interval, events (and censored observations) occurring before the specified start-time were excluded from; those occurring after the specified end-time were censored. Wide CI's for the HR in the later time intervals is a consequence of the small number of men >80 at inclusion that lived up to 10 years post fracture.

Figure 3 Cause of death (proportional distribution by age-group) in hip fracture patients and **controls at the end of the observation period**



Each column illustrates the % distribution of the various recorded causes of death. It can be seen that cardiovascular disease, pneumonia and cancer are the most common causes of death in women (patients and controls) and men (patients and controls) across all age groups.

SUPPLEMENTARY TABLE 1 ICD (8, 9, 10) Codes for major causes of death
Supplementary Table 1A: ICD (8, 9, 10) Codes for major causes of death – major groups

A) Major causes of death (MAJOR GROUPS)	
Infectious disease	ICD 10 – A00-B99, ICD 9 and 8 – 000-136 and 460-486
Cancer	ICD10 – C00-D48 excludes D10-D36, ICD 9 and 8 – 140-239
Endocrinological diseases	ICD 10 – E00-E90, ICD 9 and 8 – 240-279
Psychiatric diseases	ICD 10 – F00-F99, ICD 9 and 8 – 290-319 (excludes 290)
Neurological disease	ICD 10 – G00-G99, ICD 9 and 8 – 320-358 and 290
Cardiovascular disease	ICD10 – I00-I99, ICD9 and 8 – 390-459
Chronic obstructive pulmonary disease	ICD 10 – J40-J47, ICD 9 and 8 – 490-496
Pneumonia and upper respiratory tract infection	ICD 10 - J00-J22, ICD 9 and 8 – 460-466 and 480-486
Digestive system diseases	ICD 10 – K00-K93, ICD 9 and 8 – 520-577
Musculoskeletal disorders, excluding trauma	ICD 10 – M00-M99, ICD 9 and 8 – 710-738
Genitourinary diseases	ICD 10 – N00-N99 (*excludes N60-N64*), ICD 9 and 8 – 580-629 (*excludes 610-611*)
External causes	ICD 10 – S00-T98 and V01-Y98, ICD 9 and 8 – 800-999
Trauma, musculoskeletal	ICD 10 – S00-S99 and T00-T14, ICD 9 and 8 – 800-959
Other diseases	Remaining ICD codes
B) Major causes of death (SUB-GROUPS)	
Breast cancer	ICD 10 – C50, ICD 9 and 8 – 174
Lung cancer	ICD 10 – C34, ICD 9 and 8 – 162
Prostate cancer	ICD 10 – C61, ICD 9 and 8 – 185
Digestive system cancer	ICD 10 – C15-C26, ICD 9 and 8 – 150-159
Diabetes Mellitus	ICD 10 – E10-E14, ICD 9 and 8 – 250
Dementia	ICD 10 – F1-F3 and G30, IUC 9 and 8 – 290
Alcohol related diseases	ICD 10 – F10 and G31.2, ICD 9 and 8 – 291 and 303
Coronary heart disease	ICD 10 – I20-I25, ICD9 and 8 – 410-414
Stroke	ICD 10 – I60-I69, ICD 9 and 8 – 430-438
Urinary tract infection	ICD 10 – N10, N12, N13.6, N15, N30, N34 and N39.0, ICD 9 and 8 – 590 and 595
Road traffic accidents	ICD 10 – V01-V99, ICD 10 – E807-E846
Falls	ICD 10 – W00-W19, ICD 9 and 8 – E880-E888
Suicide	ICD 10 – X60-X84, ICD 9 and 8 – E950-E959

SUPPLEMENTARY TABLE 2A

Cumulative mortality followed **until death or end of follow-up December 2005 (i.e. for up to 22-yrs)** in **women** with hip fracture and age matched controls.

AGE	AT INCLUSION		DEAD 3 MONTHS		DEAD 1 YR		DEAD 5 YRS		DEAD 10 YRS		DEAD 15 YRS		DEAD END OF STUDY		YEARS OF FOLLOW-UP	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
<50	8 (1)	16 (1)	-	-	-	-	1 (13)	1 (6)	2 (25)	1 (6)	3 (38)	1 (6)	5 (63)	1 (6)	15.4 (6.7)	20.0 (4.5)
50-54	8 (1)	16 (1)	-	-	-	-	1 (13)	-	1 (13)	1 (6)	2 (25)	2 (13)	5 (63)	3 (19)	16.6 (6.8)	19.9 (3.7)
55-59	22 (3)	43 (3)	-	-	1 (5)	-	2 (9)	1 (2)	5 (23)	2 (5)	7 (32)	3 (7)	12 (55)	7 (16)	16.4 (6.7)	20.0 (3.3)
60-64	26 (3)	53 (4)	-	-	1 (4)	-	3 (12)	1 (2)	6 (23)	6 (11)	8 (31)	12 (23)	13 (50)	23 (43)	16.2 (6.7)	17.9 (4.6)
65-69	41 (5)	82 (5)	2 (5)	1 (1)	3 (7)	1 (1)	9 (22)	11 (13)	18 (44)	22 (27)	25 (61)	36 (44)	34 (83)	52 (63)	11.8 (7.1)	14.5 (6.7)
70-74	87 (12)	174 (12)	5 (6)	-	8 (9)	6 (3)	33 (38)	23 (13)	56 (64)	58 (33)	65 (75)	89 (51)	80 (92)	143 (82)	8.8 (6.7)	13.4 (6.3)
75-79	155 (21)	309 (20)	10 (6)	1 (0)	30 (19)	7 (2)	66 (43)	59 (19)	119 (77)	154 (50)	139 (90)	243 (79)	151 (97)	301 (97)	6.9 (5.3)	10.2 (5.4)
80-84	162 (21)	325 (22)	17 (10)	2 (1)	37 (23)	15 (5)	91 (56)	117 (36)	139 (86)	230 (71)	155 (96)	296 (91)	162 (100)	323 (99)	5.3 (4.6)	7.6 (4.9)
85-89	163 (22)	326 (22)	27 (17)	6 (2)	49 (30)	28 (9)	118 (72)	161 (49)	153 (94)	290 (89)	161 (99)	315 (97)	163 (100)	326 (100)	3.7 (3.6)	5.5 (3.8)
≥90	85 (11)	170 (11)	18 (21)	6 (4)	33 (39)	28 (16)	68 (80)	123[a] (72)	83 (98)	164 (96)	85 (100)	170 (100)	85 (100)	170 (100)	2.5 (2.6)	3.6 (2.8)
TOTAL	757	1514	79 (10)	16 (1)	162 (21)	85 (6)	392 (52)	497 (33)	582 (77)	928 (61)	650 (86)	1167 (77)	710 (94)	1349 (89)	6.6 (6.3)	9.2 (6.6)

Mortality is reported in numbers and percentage (%).
Average length of follow-up is reported in years and standard deviation (SD)
[a]One control aged 93 emigrated at 3 yr

SUPPLEMENTARY TABLE 2 B
Cumulative mortality followed **until death or December 2005 (i.e. for up to 22-yrs)** in **men** with hip fracture and age matched controls.

AGE	AT INCLUSION		DEAD 3 MONTHS		DEAD 1 YR		DEAD 5 YRS		DEAD 10 YRS		DEAD 15 YRS		DEAD END OF STUDY		YEARS OF FOLLOW-UP	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
<50	13 (5)	26 (5)	-	-	-	-	3 (23)	1 (4)	5 (38)	2 (8)	7 (54)	3 (12)	8 (62)	5 (19)	13.2 (8.1)	19.6 (4.6)
50-54	8 (3)	16 (3)	-	-	-	-	-	-	1 (13)	1 (6)	2 (25)	3 (19)	3 (38)	5 (31)	18.7 (4.8)	18.6 (4.7)
55-59	15 (6)	30 (6)	-	1 (3)	-	1 (3)	4 (27)	1 (3)	7 (47)	2 (7)	10 (67)	6 (20)	12 (80)	8 (27)	11.5 (7.0)	18.5 (5.1)
60-64	20 (8)	38 (7)	1 (5)	-	1 (5)	1 (3)	6 (30)	2 (5)	14 (70)	8 (21)	17 (85)	14 (37)	18 (90)	22 (58)	8.4 (5.8)	15.8 (6.2)
65-69	21 (8)	42 (8)	1 (5)	-	4 (19)	-	10 (48)	6 (14)	14 (67)	16 (38)	19 (90)	23 (55)	20 (95)	37 (88)	7.0 (6.2)	12.6 (5.9)
70-74	44 (17)	90 (18)	8 (18)	1 (1)	11 (25)	6 (7)	24 (55)	23 (26)	34 (77)	46 (51)	40 (91)	70 (78)	43 (98)	82 (91)	5.7 (5.7)	10.2 (6.3)
75-79	41 (16)	83 (16)	6 (15)	3 (4)	12 (29)	5 (6)	33 (80)	34 (41)	37 (90)	58 (70)	39 (95)	76 (92)	41 (100)	82 (99)	3.9 (4.3)	7.4 (5.2)
80-84	53 (21)	105 (21)	12 (23)	3 (3)	23 (43)	11 (10)	41 (77)	63 (60)	50 (94)	92 (88)	53 (100)	105 (100)	53 (100)	105 (100)	2.9 (3.2)	4.9 (3.6)
85-89	26 (10)	52 (10)	13 (50)	-	18 (69)	9 (17)	23 (88)	47[a] (90)	26 (100)	50 (96)	26 (100)	51 (98)	26 (100)	52[b] (100)	1.5 (2.4)	3.1 (3.0)
>=90	15 (6)	30 (6)	8 (53)	2 (7)	10 (67)	9 (30)	14 (93)	24 (80)	15 (100)	30 (100)	15 (100)	30 (100)	15 (100)	30 (100)	1.1 (1.7)	2.9 (2.3)
TOTAL	256	512	49 (19)	10 (2)	79 (31)	42 (8)	158 (62)	201 (39)	203 (79)	305 (60)	228 (89)	381 (74)	239 (93)	428 (84)	5.6 (6.3)	9.3 (7.2)

Mortality is reported in numbers and percentage (%).
Average length of follow-up is reported in years and standard deviation (SD)
[a]One control aged 86 emigrated at 3.2 yrs [b]One control aged 87 emigrated at >20 yrs