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

Peer-reviewed author version

Tran, Thach; Bliuc, Dana; Hansen, Louise; Abrahamsen, Bo; VAN DEN BERGH, Joop; Eisman, John A.; van Geel, Tineke; GEUSENS, Piet; Vestergaard, Peter; Nguyen, Tuan V. & Center, Jacqueline R. (2018) Persistence of Excess Mortality Following Individual Nonhip Fractures: A Relative Survival Analysis. In: JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, 103(9), p. 3205-3214.

DOI: 10.1210/jc.2017-02656
Handle: http://hdl.handle.net/1942/27634

Persistence of excess mortality following individual non-hip fractures: A relative survival analysis

Thach Tran, Dana Bliuc, Louise Hansen, Bo Abrahamsen, Joop van den Bergh, John A Eisman, Tineke van Geel, Piet Geusens, Peter Vestergaard, Tuan V Nguyen, and Jacqueline R Center

The Journal of Clinical Endocrinology & Metabolism
Endocrine Society

Submitted: December 06, 2017
Accepted: May 11, 2018
First Online: July 19, 2018

The Journal of Clinical Endocrinology & Metabolism; Copyright 2018 DOI: 10.1210/jc.2017-02656

Persistence of excess mortality following individual non-hip fractures: A relative survival analysis

Thach Tran,[1] Dana Bliuc,[1] Louise Hansen,[2] Bo Abrahamsen,[3,4] Joop van den Bergh,[5,6] John A Eisman,[1,7,8,9,10] Tineke van Geel,[11] Piet Geusens,[12,13] Peter Vestergaard,[14,15] Tuan V Nguyen,[1,8] and Jacqueline R Center[1,7,8] *

[1]*Osteoporosis and Bone Biology, Garvan Institute of Medical Research, Sydney Australia*

[2]*Danish Center for Healthcare Improvements, Department of Business and Management, Aalborg University, Aalborg East, Denmark*

[3]*Department of Medicine, Holbæk Hospital, Holbæk, Denmark*

[4]*Department of Clinical Research, Odense Patient Data Explorative Network, University of Southern Denmark, 5000, Odense, Denmark*

[5]*Maastricht University Medical Center, Research school Nutrim, Department of Internal Medicine, Subdivision of Rheumatology, Maastricht, The Netherlands*

[6]*VieCuri Medical Centre of Noord-Limburg, Department of Internal Medicine, Venlo, The Netherlands*

[7]*Clinical School, St Vincent's Hospital, Sydney, Australia*

[8]*Faculty of Medicine, University of New South Wales, Sydney Australia*

[9]*Clinical Translation and Advanced Education, Garvan Institute of Medical Research, Sydney Australia*

[10]*School of Medicine Sydney, University of Notre Dame Australia, Sydney, Australia*

[11]*Maastricht University, Research School CAPHRI, Department of Family Medicine, Maastricht, The Netherlands*

[12]*Maastricht University Medical Center, Research School CAPHRI, Department of Internal Medicine, Subdivision of Rheumatology, The Netherlands*

[13]*University Hasselt, Biomedical Research Institute, Hasselt, Belgium*

[14]*Department of Clinical Medicine, Aalborg University, Aalborg, Denmark*

[15]*Department of Endocrinology, Aalborg University Hospital, Aalborg, Denmark*

Received 06 December 2017. Accepted 11 May 2018.

Context: Little is known about long-term excess mortality following fragility non-hip fractures.
Objective: The study aimed to determine which fracture was associated with excess mortality, and for how long the post-fracture excess mortality persisted.
Design, Setting, and Patients: This nationwide, registry-based follow-up study included all individuals in Denmark aged 50+ years who first experienced fragility fractures in 2001 and were followed up to 10 years for their mortality risk.
Main outcome measure: The contribution of fracture to mortality at precise time intervals post-fracture was examined using relative survival analysis, accounting for time-related mortality changes in the background population.
Results: There were 21123 women (aged 72± 13 years) and 9481 men (67±12) with an incident fragility fracture in 2001 followed by 10668 and 4745 deaths, respectively. Excess mortality was observed following all proximal and lower leg fractures. The majority of deaths occurred within the first year post-fracture and thereafter excess mortality gradually declined. Hip fractures were associated with the highest excess mortality (33% and 20% at one year post-fracture in men and women, respectively). One-year excess mortality was 20-25% after femur or pelvis, 10% following vertebral, 5-10% following humerus, rib or clavicle, and 3%

following lower leg fractures. A significant- although smaller- excess mortality was still observed until 10 years for hip, and approximately 5 years after femur, other proximal and lower leg fractures.
Conclusion: This study highlights the important contribution of a wide variety of fragility fractures to long-term excess mortality, and thus the potential for benefit from early intervention.

Excess mortality was found for 10 years after hip fractures and approximately 5 years after virtually all proximal and lower leg fractures in this nationwide, registry-based follow-up study.

INTRODUCTION

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

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

In order to examine the potential impact of a specific fracture on mortality risk needs to be conducted in a population-based study both large enough and with the ability to capture and follow all the fracture subjects long enough to obtain their long-term mortality risk. The analysis should be robust to differentiate the risk of mortality attributable to a fracture from the risk due to other causes. The Danish national register is a unique population-based data source where information on healthcare utilisation and diagnoses are systematically obtained for the entire country, providing an excellent representative study population with minimal risk of selection bias and loss to follow-up as well as being of sufficient size for this type of analysis(17).

We thus conducted relative survival analysis to determine (i) which fragility fracture is associated with excess mortality, and (ii) for how long the post-fracture excess mortality persists.

METHODS AND MATERIALS

Study design

This nationwide, registry-based follow-up study included all individuals aged 50+ years who experienced an incident fragility fracture in Denmark between 1/1/2001 and 31/12/2001. This was not a clinical trial. The Danish National Hospital Discharge Register (NHDR) was used to identify the participants with a diagnosis of an index fracture at one of the following sites:

hip (ICD-10 codes: S72.0-2), femur (non-hip) (S72.3-9), vertebrae (S22.0–S22.1, S32.0–S32.2, S32.7, S32.8, T08.x), clavicle (S42.0), rib (S22.3-4), humerus (S42.x), forearm (S52.x), hand (S62.0-4, S62.8), finger (S62.5-7), pelvis (S32.3-5), knee (S82.0), lower leg (S82.2-8), ankle (S82.5-6), foot (S92.0-3, S92.7, S92.9) and toe (S92.4-5). The NHDR has a national coverage of both inpatient and outpatient contacts since 1995 with an excellent completeness of medical records and precision of diagnoses(18,19). The concordance between fracture reports in NHDR and patient files was documented to be 97%(19).The study (Statistics Denmark project number 703381 and 706667) was subject to approval and monitoring by the National Board of Health, the Danish Data Protection Agency and Statistics Denmark.

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

Death of the study participants was ascertained from the Danish Register on Causes of Death until 31/12/2011. The follow-up time was calculated from time of the first diagnosis of an incident fracture to either date of death or 31/12/2011. The first primary cause of death was also documented for our fracture patients and for all individuals aged 50 or older in 2001 in Denmark, using ICD-10 classification system.

Statistical analysis

Statistical analyses were carried out separately for women and men to address: (i) age-standardized mortality incidence following a specific fracture, (ii) excess mortality associated with a fracture, and (iii) length of time during which post-fracture excess mortality persisted.

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

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

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

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

RESULTS

The study included 21123 women and 9481 men who experienced an incident fragility fracture in the year 2001 at an average age (mean± SD) of 72 (±13) and 67 (±12) years, respectively (Figure 1). None of these subjects experienced any fragility fracture between 1996 and 2000 or fractures related solely to traffic accidents in 2001. A third of women and a half of men in the study population sustained a first fragility fracture between 50 to 64 years of age. Forearm, hip and humerus fractures together contributed 63% and 42% of total fractures found in women and men, respectively (Table 1). Hip fracture occurred late (81± 9 years in women versus 78± 11years in men; P<0.001), while the peripheral fractures, such as hand, fingers, foot and toes were diagnosed at a mean age of 60 years. Fracture patients who eventually died during the study period were more likely to have higher Charlson comorbidity index and more comorbidities reported at fracture time, especially congestive heart failure, dementia and chronic pulmonary disease, than those alive until the end of the year 2011 (Table 1).

Absolute mortality rates according to fracture type

During an average follow-up period of 7.2 (± 4.0) years (7.1± 4.1 years in women versus 7.3± 3.9 years in men), 10668 women (51%) and 4745 men (50%) died (Figure 1). Overall, fracture patients had higher mortality incidence than the Danish general population aged 50 years or older in 2001 (Table 2). There were four more deaths following a fragility fracture in men than women for every 100 person-years of follow up (95% CI: 3.7, 4.4), after difference in age at fracture was taken into consideration. Moreover, post-fracture mortality rates were higher in men than women for all fracture types, though the differences following a clavicle, rib, lower leg, foot or toe fracture did not achieve statistical significance.

As expected, hip, femur, and pelvis fractures were associated with the highest mortality incidence, even after accounting for difference in age at fracture (Table 2). The age-standardized mortality incidences following specific fracture types varied greatly, from 20 deaths/100 person-years (95% CI: 19, 21) following a hip fracture to 7 deaths/100 person-years (6, 8) after a lower leg fracture in men. Comparable rates in women were 13 deaths/100 person-years (95% CI: 12, 13) and 6 deaths/100 person-years (5, 7) following hip and lower leg fracture, respectively. The lowest mortality rate was found for hand, finger, foot and toe fractures. Over the 10 years follow-up there were overall increased age-standardized mortality incidence for every fracture type. However, for the majority of distal fractures there was no excess mortality when mortality rates in the general population were considered for each individual calendar year (Figure 2 and relative survival analysis below).

Approximately 65% of deaths occurred within 5 years post-fracture, ranging from about 75%-80% after hip, femur or pelvis fracture to 40%-50% after a peripheral fracture

(Supplemental table 1). The most common causes of death included cardiac (30% in fracture patients and 24% in general population), malignant (16% and 14%) and respiratory diseases (10% and 18%) (Table 3). Compared with the general population aged 50 years or older in 2001 who died between 1/1/2001 and 31/12/2011, fracture subjects were more likely to have cardiovascular disorders or external causes of morbidity and mortality (including falls) reported as the first primary cause of death. More deaths in fracture patients, especially hip fracture were documented to have the first primary cause of death as "Diseases of musculoskeletal system" (1.6% and 0.5% of the first primary cause of death in women and men, respectively who sustained a hip fracture versus 0.2% and 0.1% in the general population).

Excess mortality following a fragility fracture

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

Significant excess mortality was observed following essentially all proximal and lower leg fractures for both genders with the magnitude gradually declining after the first year post-fracture. By contrast, the observed mortality following other distal fractures, such as forearm, hand, finger, knee, ankle, foot or toe did not differ from the expected survival in the background comparative population, suggesting that these distal fractures were not associated with an increased risk of mortality. As expected, hip fractures were associated with the highest excess mortality with a one-year excess mortality of 33% in men and 20% in women. For non-hip fractures, excess mortality at one year post-fracture was 20-25% following femur or pelvic fractures, 10% following vertebral fractures, 5-10% following humerus, rib or clavicle fractures, and 3% following lower leg fractures. There was also a non-significant 2% excess mortality one year after a forearm or knee fracture in men. These percentages equated to an approximate 33 extra deaths one year post-fracture for an average 100 men with hip fracture, compared with 100 equivalently aged non-fracture men. The comparable number of excess deaths in 100 women with hip fracture was 20. By contrast, there were only 2 and 3 additional deaths observed at one year post-fracture in 100 men and 100 women, respectively, with a lower leg fracture.

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

Persistence of excess mortality post-fracture

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

Besides cardiovascular diseases reported in almost a third of all deaths, the causes of early mortality, defined as deaths within one year post-fracture differed from those of late

mortality ≥ five years after a fracture (Supplemental table 3). Malignancy (~20-25% of early mortality, versus 10-15% of late mortality) and external causes of morbidity and mortality (~25-30% and 10% of early mortality following a hip and non-hip fracture, respectively versus 2-3% of late mortality) were much more commonly reported as the cause of death that occurred within 1 year post fracture. By contrast, diseases of respiratory system were more likely to be reported for late mortality (~10-15% of late versus 7% of early mortality).

DISCUSSION

There is still controversy over whether a non-hip non-vertebral fracture is associated with excess mortality, and more importantly for how long any excess mortality persists following a specific fracture. This is the first study capable of determining excess mortality following specific fracture types in a nationwide representative cohort using a robust analysis method accounting for time-related mortality changes in the matched reference population. The whole-nation cohort included all individuals in Denmark with a fragility fracture during 2001 who had not had a prior fracture in the preceding 5 years and who were followed for up to 10 years for their risk of mortality. We hypothesized that the more severe fractures were associated with excess mortality, with the length of the excess mortality being fracture type specific. The study findings are consistent with the hypothesis, suggesting excess mortality was associated with virtually all proximal and lower leg fractures. Excess mortality remained evident for more than 10 years after a hip fracture and for approximately 5 years following a proximal non-hip or lower leg fracture, ranging from 3 years following a rib fracture to about 6-7 years following a vertebral or humerus fracture.

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

The novelty of our study is the ability to quantify not only the magnitude but also the length of excess mortality following individual non-hip fractures where the data are scarce. Our findings confirm other studies that vertebral(2,3,9-12), humerus(2-4,11,27,28), rib(2,11), or pelvis fracture(2,11,29) are associated with an increased mortality risk. Mortality risk has not been examined separately for a clavicle fracture, though the group of clavicle, scapula and sternum fractures was reported to be associated with an increased mortality risk in a large population-based study in Olmsted county, USA(2). Elderly patients with a fracture of the tibia or fibula above the ankle also had an associated 4-fold increased mortality risk within the first 90 days and 10% increased risk after one year greater than their matched non-fracture controls(30). The impact of forearm fracture on mortality nevertheless remains controversial. We found that a forearm fracture was not associated with excess mortality, though a non-significant excess mortality of 2% was noted in men within one year post fracture. A follow-up study using healthcare database of 14,000 Canadians with a forearm fracture(3) also reported an increased mortality risk within one year after a wrist fracture for men (RR 1.5; 95% CI: 1.2, 1.9) but not women (0.8; 0.7, 1.0). Forearm fractures have been documented not to be associated with an increased mortality in other studies(2,4,11,28), although increased risk of mortality has been noted in special subgroups, such as those aged 70+ at fracture(3,30,31) or those who then suffered a subsequent fracture(10).

This is the first study addressing the length of excess mortality following a non-hip fracture accounting for time-related mortality risk in the comparative background population. Other studies have found long-term increased mortality risk up to 5(2) to 10 years(12) after a

new clinical vertebral fracture, 3(32) to 5 years(33) after a pelvis fracture, or 5 years after a humerus fracture(2,27,28) but all these analyses assumed that mortality risk was proportional over time. By contrast a few studies have shown excess mortality was no longer evident after two(29), eight(34) or 12 months(2) post-pelvis fracture. Some of reasons for these discrepancies include difference in analysis approach(2) and study participants(29,34). The standardized mortality ratio approach averages mortality rates over long time intervals (such as 5-year and more-than-5-year intervals) to compute average excess mortality after one year post-fracture(2). As a result, these analyses are not able to account for time-related changes, making it far less robust than the relative survival analysis to examine excess mortality at precise intervals following a low-frequency fracture(16). The other studies demonstrating only short-term increased mortality either included different types of pelvis fracture (such as minor fracture of coccyx, ischium, unspecified fracture of pelvis)(34) or recruited patients who had fractured at much older ages (88 years in women, and 87 years in men) than our patients (81 years in women, 73 years in men)(29).

Few studies have examined potential causes of long-term excess mortality following non-hip fractures. The most common primary causes of death for our fracture subjects, including diseases of circulatory system, neoplasm or respiratory system, were similar to those reported in an Australian fracture population, even though respiratory disorders were more likely to be reported as cause of death in Australian fracture subjects (26% versus 10%)(9). Interestingly, there appeared to be a difference in the current study between early (mortality within one year post fracture) and late (≥5 years post fracture) mortality. Malignancy and "external cause" were more commonly recorded for early mortality while respiratory disease was more commonly recorded for mortality that occurred ≥ 5 years post fracture. Cardiac causes remained the most common recorded cause for both early and late mortality. These findings deserve further exploration. The postulated pathways for excess mortality following a non-hip fracture include rapid bone loss(35) and reduced muscular strength(36), which have been documented to be independent predictors for long-term mortality risk following both clinical vertebral and non-hip non-vertebral fractures as a group. Vertebral fracture was also found to be associated with 25% increased risk of incident cardiovascular events(24) and deteriorating functional capacity(12), which itself may contribute to an elevated risk of mortality.

The results of the current study should be viewed in the context of its strengths and limitations. Our data were collected from a nationwide register which captures virtually all fracture-related diagnoses in the whole country with very high precision of diagnoses(18,19) and low likelihood of selection bias or misclassification(19). Our large study sample of more than 30000 individuals with an initial fracture followed up for 10 years was robust in size to determine the long-term excess mortality following specific fracture types in yearly intervals. No patient with a previous fracture within 5 years before the study entry point was included, making the clean sample powerful to examine excess mortality following an incident fracture. The relative survival analysis is well recognized as a rigorous method to identify the length of persistence of the excess mortality as it is able to estimate excess mortality at specific time points after a fracture(16). The fact that cause-specific mortality data are not needed in relative survival analysis makes it especially relevant for the examination of the fracture-mortality association since a fracture is rarely mentioned as a contributing cause of death(14,37). However, the study was not able to completely distinguish the impact of a fragility fracture on mortality from that of chronic diseases. Post-fracture excess mortality was estimated using the expected survival from the age, gender and calendar year-matched Danish general population life table data obtained from the Human Mortality Database(22). No comorbidity-specific life table data have been created in Human Mortality Database(22), precluding complete adjustment for potential confounding effects of presence of comorbidities. The potential aging and gender-related confounding effects of chronic diseases

have been, at least partly, accounted for in relative survival analysis which estimates excess mortality (attributable to a fracture) under the assumption that the expected mortality from the comparative general population with the same age, gender and calendar year reflects mortality due to reasons other than fracture(16). Our analyses were not able to exclude patients with bone metastases. Nevertheless, patients with any site metastasis comprised only 2-3% of total deaths during the study follow-up period, only a quarter of which would have been bone metastases(38) and even fewer responsible for the fracture itself. Excluding these few patients with bone metastases would thus not change the overall findings. Finally, the length of persistent excess mortality following pelvis fractures in men with limited numbers of subjects and deaths over ongoing follow-up might have been underestimated due to limited statistical power(39). Thus the length of persistent mortality in this study should be considered a minimum.

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

ACKNOWLEDGEMENT

This work was supported by the National Health Medical Research Council Australia Project Grants 1070187 (to T.T, D.A., J.A.E, T.V.N, and J.R.C), 1008219 (to J.R.C), and 1073430 (to D.B.). Other funding bodies were an Osteoporosis Australia-Amgen grant; the Bupa Health Foundation (formerly MBF Foundation); the Mrs Gibson and Ernst Heine Family Foundation; and untied grants from Amgen, Merck Sharp & Dohme, Sanofi-Aventis, Servier, and Novartis.

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; of preparation, review, or approval of the manuscript.

National Health Medical Research Council Australia, 1070187, Thach S Tran; National Health Medical Research Council Australia, 1070187, Dana Bliuc; National Health Medical Research Council Australia, 1070187, John A Eisman; National Health Medical Research Council Australia, 1070187, Tuan V Nguyen; National Health Medical Research Council Australia, 1070187, Jacqueline R Center; National Health Medical Research Council Australia, 1008219, Jacqueline R Center; National Health Medical Research Council Australia, 1073430, Dana Bliuc

Contributors:

T.T., D.B., B.A., P.V., J.A.E., T.V.N., and J.R.C. contributed to study conceptualization and design. T.T., D.B., L.H., J.A.E., T.V.N., and J.R.C. contributed to data analysis. T.T., D.B., T.V.N., and J.R.C. contributed to drafting the manuscript. All authors contributed to revising the manuscript contents and approving the final version of the manuscript.

Address all correspondence and requests for reprints to: Professor Jacqueline R Center, Clinical Studies and Epidemiology, Osteoporosis and Bone Biology, Garvan Institute of Medical Research, 384 Victoria St, Darlinghurst NSW 2010 Australia, **Phone**: 9295-8271; **Fax**: 9295-8241, **Email**: j.center@garvan.org.au

Disclosure Summary:

T.T., D.B., T.v.G. and P.V. have no competing interests to declare. L.H. has received speaker fee from Eli Lilly. B.A. has had institutional research contracts with UCB and Novartis.

J.v.d.B has received grants and/or personal fees from Amgen and Eli Lilly. J.A.E has consulted for and/or received research funding from Amgen, deCode, Merck Sharp and Dohme, and Sanofi-Aventis. P.G. was advisory member for Amgen, has received speaker fee and/or research grants from Abbott, Amgen, BMS, Celgene, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, UCB, Will-Pharma. T.V.N. has received honoraria for consulting and symposia from Merck Sharp and Dohme, Roche, Servier, Sanofi-Aventis, and Novartis. J.R.C has consulted for and/or given educational talks for Merck Sharp and Dohme, Amgen, Actavis and Sanofi-Aventis.

REFERENCE

1. **LeBlanc ES, Hillier TA, Pedula KLet al**. Hip fracture and increased short-term but not long-term mortality in healthy older women. *Arch Intern Med.* 2011;171(20):1831-7.
2. **Melton LJ, 3rd, Achenbach SJ, Atkinson EJ, Therneau TM, Amin S**. Long-term mortality following fractures at different skeletal sites: a population-based cohort study. *Osteoporos Int.* 2013;24(5):1689-96.
3. **Morin S, Lix LM, Azimaee M, Metge C, Caetano P, Leslie WD**. Mortality rates after incident non-traumatic fractures in older men and women. *Osteoporos Int.* 2011;22(9):2439-48.
4. **Piirtola M, Vahlberg T, Lopponen M, Raiha I, Isoaho R, Kivela SL**. Fractures as predictors of excess mortality in the aged-A population-based study with a 12-year follow-up. *Eur J Epidemiol.* 2008;23(11):747-55.
5. **Tosteson AN, Gottlieb DJ, Radley DC, Fisher ES, Melton LJ, 3rd**. Excess mortality following hip fracture: the role of underlying health status. *Osteoporos Int.* 2007;18(11):1463-72.
6. **Cameron ID, Chen JS, March LM, et al**. Hip fracture causes excess mortality owing to cardiovascular and infectious disease in institutionalized older people: a prospective 5-year study. *J Bone Miner Res.* 2010;25(4):866-72.
7. **Vestergaard P, Rejnmark L, Mosekilde L**. Increased mortality in patients with a hip fracture-effect of pre-morbid conditions and post-fracture complications. *Osteoporos Int.* 2007;18(12):1583-93.
8. **von Friesendorff M, McGuigan FE, Wizert Aet al**. Hip fracture, mortality risk, and cause of death over two decades. *Osteoporos Int.* 2016;27(10):2945-53.
9. **Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR**. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA.* 2009;301(5):513-21.
10. **Bliuc D, Nguyen TV, Eisman JA, Center JR**. The impact of nonhip nonvertebral fractures in elderly women and men. *J Clin Endocrinol Metab.* 2014;99(2):415-23.
11. **Browner WS, Pressman AR, Nevitt MC, Cummings SR**. Mortality following fractures in older women - The study of osteoporotic fractures. *Arch Intern Med.* 1996;156(14):1521-5.
12. **Hasserius R, Karlsson MK, Jonsson B, Redlund-Johnell I, Johnell O**. Long-term morbidity and mortality after a clinically diagnosed vertebral fracture in the elderly--a 12- and 22-year follow-up of 257 patients. *Calcif Tissue Int.* 2005;76(4):235-42.
13. **Frost SA, Nguyen ND, Center JR, Eisman JA, Nguyen TV**. Excess mortality attributable to hip-fracture: a relative survival analysis. *Bone.* 2013;56(1):23-9.
14. **Hindmarsh DM, Hayen A, Finch CF, Close JC**. Relative survival after hospitalisation for hip fracture in older people in New South Wales, Australia. *Osteoporos Int.* 2009;20(2):221-9.
15. **Lee YK, Lee YJ, Ha YC, Koo KH**. Five-year relative survival of patients with osteoporotic hip fracture. *J Clin Endocrinol Metab.* 2014;99(1):97-100.

16. **Dickman PW, Sloggett A, Hills M, Hakulinen T**. Regression models for relative survival. *Stat Med.* 2004;23(1):51-64.
17. **Frank L**. Epidemiology. When an entire country is a cohort. *Science.* 2000;287(5462):2398-9.
18. **Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH**. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull.* 1999;46(3):263-8.
19. **Vestergaard P, Mosekilde L.** Fracture risk in patients with celiac Disease, Crohn's disease, and ulcerative colitis: a nationwide follow-up study of 16,416 patients in Denmark. *Am J Epidemiol* 2002;156(1):1-10.
20. **Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V.** Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011; 173:676-682
21. **Breslow N, Day N**. Statistical methods in cancer research. VolumeII- The design and analysis of cohort studies: IARC Scientific Publication No 82. Lyon, France; 1987.
22. **Human Mortality Database**. In: University of California Berkely (USA), Max Planck Institute of Demographic Research (Germany): 2008.
23. **Ederer F, Axtell LM, Cutler SJ**. The relative survival rate: a statistical methodology. *National Cancer Institute monograph.* 1961;6:101-21.
24. **Veronese N, Stubbs B, Crepaldi G et al**. Relationship Between Low Bone Mineral Density and Fractures With Incident Cardiovascular Disease: A Systematic Review and Meta-Analysis. *J Bone Miner Res.* 2017;32(5):1126-35.
25. **Miller RR, Cappola AR, Shardell MD et al**. Persistent changes in interleukin-6 and lower extremity function following hip fracture. *J Gerontol A Biol Sci Med Sci.* 2006;61(10):1053-8.
26. **Gulin T, Kruljac I, Kirigin Bilos LS, Gulin M, Grgurevic M, Borojevic M.** The role of adipokines as prognostic factors of one-year mortality in hip fracture patients. *Osteoporos Int*. 2017;28(8):2475-2483.
27. **Johnell O, Kanis JA, Oden A et al**. Mortality after osteoporotic fractures. *Osteoporos Int.* 2004; 15(1):38-42.
28. **Shortt NL, Robinson CM.** Mortality after low-energy fractures in patients aged at least 45 years old. *J Orthop Trauma.* 2005;19(6):396-400.
29. **Rapp K, Cameron ID, Kurrle S et al**. Excess mortality after pelvic fractures in institutionalized older people. *Osteoporos Int.* 2010;21(11):1835-9.
30. **Barrett JA, Baron JA, Beach ML**. Mortality and pulmonary embolism after fracture in the elderly. *Osteoporos Int.* 2003;14(11):889-94.
31. **Oyen J, Diamantopoulos AP, Haugeberg G**. Mortality after distal radius fracture in men and women aged 50 years and older in southern Norway. *PloS ONE.* 2014;9(11):e112098.
32. **Prieto-Alhambra D, Aviles FF, Judge A et al**. Burden of pelvis fracture: a population-based study of incidence, hospitalisation and mortality. *Osteoporos Int.* 2012;23(12):2797-803.
33. **Hill RM, Robinson CM, Keating JF**. Fractures of the pubic rami. Epidemiology and five-year survival. *J Bone Joint Surg Br.* 2001;83(8):1141-4.
34. **Andrich S, Haastert B, Neuhaus E et al**. Excess Mortality After Pelvic Fractures Among Older People. *J Bone Min Res*. 2017;32(9):1789-1801.
35. **Bliuc D, Nguyen ND, Alarkawi D, Nguyen TV, Eisman JA, Center JR**. Accelerated bone loss and increased post-fracture mortality in elderly women and men. *Osteoporos Int.* 2015; 26(4):1331-9.

36. **Pham HM, Nguyen SC, Ho-Le TP, Center JR, Eisman JA, Nguyen TV**. Association of Muscle Weakness With Post-Fracture Mortality in Older Men and Women: A 25-Year Prospective Study. *J Bone Min Res.* 2017;32(4):698-707.
37. **Calder SJ, Anderson GH, Gregg PJ**. Certification of cause of death in patients dying soon after proximal femoral fracture. *BMJ.* 1996;312(7045):1515.
38. **Abrams HL, Spiro R, Goldstein N**. Metastases in carcinoma; analysis of 1000 autopsied cases. *Cancer* 1950; 3:74-85.
39. **Katz MH**. Multivariable analysis: a primer for readers of medical research. *Ann Intern Med.* 2003;138(8):644-50.

Figure 1. Flow chart of follow up

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

Figure 3. Persistent excess mortality following individual types of fragility fracture: (A) proximal fractures, (B) distal fractures, *: the last year a post-fracture excess mortality was still evident. **: the first year a post-fracture excess mortality was no longer evident.

Table 1: Characteristics of the study population at time of fracture

	Women		Men	
	Alive	**Dead**	**Alive**	**Dead**
	(n= 10455)	(n=10668)	(n= 4736)	(n= 4745)
Comorbidities at fracture time:				
Charlson comorbidity index*	0 (0-0)	0 (0-2)	0 (0-0)	0 (0-2)
. 0	9233 (88.3)	6714 (62.9)	4310 (91.0)	2682 (56.5)
. 1- 2	1137 (10.9)	2936 (27.5)	378 (8.0)	1374 (29.0)
. 3- 4	70 (0.7)	691 (6.5)	39 (0.8)	434 (9.1)
. 5+	15 (0.1)	327 (3.1)	9 (0.2)	255 (5.4)
Specific comorbidities:				
. Congestive heart failure	90 (0.9)	1111 (10.4)	60 (1.3)	619 (13.1)
. Dementia	37 (0.4)	883 (8.3)	21 (0.4)	349 (7.4)
. Chronic pulmonary disease	362 (3.5)	991 (9.3)	130 (2.7)	614 (12.9)
. Rheumatologic disease	211 (2.0)	408 (3.8)	33 (0.7)	91 (1.9)
. Mild liver disease	56 (0.5)	103 (1.0)	36 (0.8)	142 (3.0)
. Diabetes with chronic complications	66 (0.6)	214 (2.0)	47 (1.0)	194 (4.1)
. Hemiplegia or paraplegia	13 (0.1)	35 (0.3)	11 (0.2)	30 (0.6)
. Renal disease	19 (0.2)	108 (1.0)	11 (0.2)	108 (2.3)
. Any malignancy, including leukemia and lymphoma	456 (4.4)	1123 (10.5)	118 (2.5)	605 (12.8)
. Moderate or severe liver disease	4 (0.04)	22 (0.2)	6 (0.1)	56 (1.2)
. Metastatic solid tumor	12 (0.1)	213 (2.0)	6 (0.1)	135 (2.9)
. AIDS/HIV	0 (0.0)	0 (0.0)	1 (0.02)	7 (0.2)
	Women		**Men**	
	Alive	**Dead**	**Alive**	**Dead**
	(n= 10455)	(n=10668)	(n= 4736)	(n= 4745)
Fracture types:				
Any fracture	10455	10668	4736	4745
Proximal fractures:				
. Hip	724 (6.9)	3885 (36.4)	235 (5.0)	1722 (36.3)
. Femur	75 (0.7)	248 (2.3)	33 (0.7)	102 (2.1)
. Pelvis	100 (1.0)	398 (3.7)	40 (0.8)	106 (2.2)
. Vertebrae	223 (2.1)	470 (4.4)	186 (3.9)	252 (5.3)
. Clavicle	138 (1.3)	181 (1.7)	184 (3.9)	147 (3.1)
. Rib	116 (1.1)	128 (1.2)	253 (5.3)	194 (4.1)
. Humerus	1106 (10.6)	1353 (12.6)	276 (5.8)	520 (10.9)
Distal fractures:				
. Forearm	3839 (36.7)	2409 (22.6)	733 (15.5)	538 (11.4)
. Knee	152 (1.5)	71 (0.7)	63 (1.3)	47 (1.0)
. Lower leg	626 (6.0)	384 (3.6)	383 (8.1)	201 (4.2)
. Ankle	872 (8.3)	302 (2.8)	416 (8.8)	226 (4.8)

. Hand	785 (7.5)	306 (2.9)	500 (10.6)	235 (5.0)
. Fingers	573 (5.5)	207 (1.9)	745 (15.7)	247 (5.2)
. Foot	655 (6.3)	246 (2.3)	363 (7.7)	133 (2.8)
. Toes	471 (4.5)	80 (0.7)	326 (6.9)	75 (1.6)

Data presented as number (%) unless otherwise indicated.*: data presented as median (IQR).

Table 2: Mortality incidence by genders

	Women					Men				
Fracture types	**Age at fracture (years)**	**Number of deaths**	**Follow-up (person-years)**	**Crude mortality incidence (95% CI)**	**Age-standardized mortality incidence (95% CI)**	**Age at fracture (years)**	**Number of deaths**	**Follow-up (person-years)**	**Crude mortality incidence (95% CI)**	**Age-standardized mortality incidence (95% CI)**
General population*		1045880	28760930	3.64(3.63, 3.64)			1010630	24458382	4.13 (4.12, 4.14)	
Any fracture	72 (13)	10668	153595	6.9 (6.8, 7.1)	6.7 (6.6, 6.8)	67 (12)	4745	66935	7.1 (6.9, 7.3)	10.7 (10.4, 11.0)
Proximal fractures:										
Hip	81 (9)	3885	20068	19.4 (18.8, 20.0)	12.7 (12.1, 13.3)	78 (11)	1722	6613	26.0 (24.8, 27.3)	20.3 (19.2, 21.4)
Femur	78 (12)	248	1540	16.1 (14.2, 18.2)	11.8 (10.2, 13.7)	71 (13)	102	660	15.5 (12.7, 18.8)	16.7 (13.6, 20.4)
Pelvis	81 (11)	398	2357	16.9 (15.3, 18.6)	11.0 (9.7, 12.4)	73 (12)	106	733	14.5 (12.0, 17.5)	16.0 (13.1, 19.4)
Vertebrae	75 (12)	470	4094	11.5 (10.5, 12.6)	9.4 (8.5, 10.3)	68 (12)	252	2853	8.8 (7.8, 10.0)	12.5 (10.9, 14.2)
Clavicle	70 (14)	181	2206	8.2 (7.1, 9.5)	9.0 (7.7, 10.4)	64 (12)	147	2496	5.9 (5.0, 6.9)	10.8 (8.9, 12.9)
Rib	70 (13)	128	1754	7.3 (6.1, 8.7)	8.3 (6.9, 9.8)	64 (11)	194	3514	5.5 (4.8, 6.4)	9.2 (7.8, 10.8)
Humerus	73 (11)	1353	17434	7.8 (7.4, 8.2)	6.6 (6.3, 7.0)	69 (12)	520	4714	11.0 (10.1, 12.0)	12.5 (11.4, 13.6)
Distal fractures:										
Forearm	70 (11)	2409	52741	4.6 (4.4, 4.8)	4.6 (4.5, 4.8)	65 (11)	538	10084	5.3 (4.9, 5.8)	7.6 (6.9, 8.3)
Knee	67 (11)	71	1977	3.6 (2.9, 4.5)	4.1 (3.2, 5.2)	66 (11)	47	890	5.3 (4.0, 7.0)	6.5 (4.8, 8.7)
Lower leg	67 (12)	384	8226	4.7 (4.2, 5.2)	6.0 (5.4, 6.7)	62 (10)	201	5000	4.0 (3.5, 4.6)	6.9 (5.7, 8.2)
Ankle	64 (11)	302	10730	2.8 (2.5, 3.2)	4.3 (3.8, 4.9)	63 (10)	226	5501	4.1 (3.6, 4.7)	6.4 (5.5, 7.5)
Hand	66 (11)	306	9899	3.1 (2.8, 3.5)	4.2 (3.7, 4.7)	62 (11)	235	6383	3.7 (3.2, 4.2)	6.9 (5.9, 7.9)
Fingers	65 (12)	207	7058	2.9 (2.6, 3.4)	4.4 (3.8, 5.0)	61 (10)	247	9103	2.7 (2.4, 3.1)	6.6 (5.6, 7.7)
Foot	64 (11)	246	8158	3.0 (2.7, 3.4)	4.8 (4.2, 5.5)	60 (8)	133	4526	2.9 (2.5, 3.5)	5.1 (4.0, 6.3)
Toes	60 (9)	80	5352	1.5 (1.2, 1.9)	3.6 (2.7, 4.7)	59 (8)	75	3865	1.9 (1.6, 2.4)	4.3 (3.1, 5.9)

Age-standardized mortality incidence was estimated by the direct standardization method using the Danish general population of same age, gender and calendar period. Rates and incidence are presented as numbers of deaths/100 person-years. Age at fracture are presented as mean (SD).*included all individuals aged 50+ in 2001 in Denmark with follow-up time calculated as a sum of person-years lived, obtained from Human Mortality Database (22).

Table 3: Primary causes of death

	Women						Men					
	General populatio	**Any fracture (n=**	**Hip (n=3885)**	**Vertebrae (n=470)**	**Proximal (n=2308)**	**Distal (n=4005)**	**General population* (n=262761)**	**Any fractu**	**Hip (n=1722)**	**Vertebrae (n=252)**	**Proximal (n=1069)**	**Distal (n=1702)**

	n* (n=291565)	**10668)**						**re (n=4745)**				
Diseases of the circulatory system	69853 (24.0)	3409 (32.0)	1296 (33.4)	134 (28.5)	721 (31.2)	1258 (31.4)	63047 (24.0)	1425 (30.0)	551 (32.0)	66 (26.2)	307 (28.7)	501 (29.4)
Diseases of the respiratory system	52135 (17.9)	1084 (10.2)	399 (10.3)	57 (12.1)	247 (10.7)	381 (9.5)	48382 (18.4)	536 (11.3)	217 (12.6)	44 (17.5)	135 (12.6)	140 (8.2)
Abnormal clinical and laboratory findings, not elsewhere classified	49286 (16.9)	719 (6.7)	265 (6.8)	32 (6.8)	173 (7.5)	249 (6.2)	38931 (14.8)	210 (4.4)	71 (4.1)	10 (4.0)	45 (4.2)	84 (4.9)
Neoplasm	39436 (13.5)	1707 (16.0)	453 (11.7)	73 (15.5)	391 (16.9)	790 (19.7)	39384 (15.0)	957 (20.2)	270 (15.7)	37 (14.7)	242 (22.6)	408 (24.0)
Infectious diseases	9696 (3.3)	147 (1.4)	50 (1.3)	9 (1.9)	30 (1.3)	58 (1.4)	9537 (3.6)	50 (1.1)	16 (0.9)	4 (1.6)	6 (0.6)	24 (1.4)
Diseases of the digestive system	8610 (3.0)	508 (4.8)	163 (4.2)	26 (5.5)	122 (5.3)	197 (4.9)	7562 (2.9)	277 (5.8)	74 (4.3)	20 (7.9)	64 (6.0)	119 (7.0)
Endocrine diseases	8255 (2.8)	407 (3.8)	155 (4.0)	27 (5.7)	94 (4.1)	131 (3.3)	4899 (1.9)	150 (3.2)	42 (2.4)	9 (3.6)	35 (3.3)	64 (3.8)
Diseases of the genitourinary system	4879 (1.7)	176 (1.6)	63 (1.6)	10 (2.1)	45 (1.9)	58 (1.4)	5267 (2.0)	94 (2.0)	38 (2.2)	8 (3.2)	20 (1.9)	28 (1.6)
Mental disorders	4584 (1.6)	672 (6.3)	277 (7.1)	32 (6.8)	138 (6.0)	225 (5.6)	2732 (1.0)	238 (5.0)	67 (3.9)	13 (15.2)	64 (6.0)	94 (5.5)
Diseases of the nervous system	4281 (1.5)	332 (3.1)	137 (3.5)	10 (2.1)	75 (3.2)	110 (2.7)	3311 (1.3)	125 (2.6)	56 (3.3)	3 (1.2)	27 (2.5)	39 (2.3)
External causes of morbidity and mortality	3937 (1.4)	664 (6.2)	396 (10.2)	23 (4.9)	116 (5.0)	129 (3.2)	5042 (1.9)	397 (8.4)	261 (15.2)	15 (6.0)	66 (6.2)	55 (3.2)
Diseases of the blood and	1417 (0.5)	61 (0.6)	26 (0.7)	4 (0.9)	8 (0.3)	23 (0.6)	1171 (0.4)	18 (0.4)	5 (0.3)	3 (1.2)	4 (0.4)	6 (0.4)

immune disorders												
Diseases of the musculoskeletal system	503 (0.2)	122 (1.1)	62 (1.6)	11 (2.3)	16 (0.7)	33 (0.8)	208 (0.1)	24 (0.5)	9 (0.5)	6 (2.4)	3 (0.3)	6 (0.4)
Not registered	34693 (11.9)	660 (6.2)	143 (3.7)	22 (4.7)	132 (5.7)	363 (9.1)	33288 (12.7)	244 (5.1)	45 (2.6)	14 (5.6)	51 (4.8)	134 (7.9)

Data presented as number of deaths (% of total death). Proximal fractures included clavicle, rib, humerus, femur, and pelvis fracture. Distal fractures included forearm, knee, lower leg, ankle, hand, foot, fingers, and toes.*included all individuals aged 50+ in 2001 in Denmark who died between 1/1/2001 and 31/12/2011.