

2018

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A record linkage study of individual fracture types

Chen Weiwen

Judy Simpson

Lynette March

Fiona Blyth

Dana Bliuc

See next page for additional authors

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This article was originally published as:

Weiwén, C., Simpson, J., March, L., Blyth, F., Bliuc, D., Tran, T., Nguyen, T., Eisman, J. A., & Center, J. (2018). Comorbidities only account for a small proportion of excess mortality after fracture: A record linkage study of individual fracture types. *Journal of Bone and Mineral Research*, 33 (5), 795-802.

<http://doi.org/10.1002/jbmr.3374>

This article is posted on ResearchOnline@ND at

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Authors

Chen Weiwen, Judy Simpson, Lynette March, Fiona Blyth, Dana Bliuc, Thach Tran, Tuan Nguyen, John A. Eisman, and Jacqueline Center

This is the peer reviewed version of the following article:

Chen, W., Simpson, J., March, L., Blyth, F., Bliuc, D., Tran, T., Nguyen, T. ... Center, J. (2018). Comorbidities only account for a small proportion of excess mortality after fracture: A record linkage study of individual fracture types. *Journal of Bone and Mineral Research*, 33(5), 795-802. doi: 10.1002/jbmr.3374

This article has been published in final form at: -

<https://onlinelibrary.wiley.com/doi/full/10.1002/jbmr.3374>

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Co-morbidities only account for a small proportion of excess mortality after fracture: a record linkage study of individual fracture types

Fracture Risk Analysis Collaboration Taking Advantage of Linkage

Authors

Weiwen Chen¹, Judy M. Simpson², Lyn M. March^{3,4,5}, Fiona M. Blyth^{3,6}, Dana Bliuc¹, Thach Tran¹, Tuan V. Nguyen^{1,7,8}, John A. Eisman^{1,9,10}, Jacqueline R. Center^{1,9,11}

Institutions

¹ Osteoporosis and Bone Biology, Garvan Institute of Medical Research, Sydney, NSW, Australia

² Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia

³ Sydney Medical School, University of Sydney, Sydney, NSW, Australia

⁴ Institute of Bone and Joint Research, Kolling Institute, Sydney, NSW, Australia

⁵ Clinical school, Royal North Shore Hospital, St Leonards, NSW, Australia

⁶ Clinical school, Concord Repatriation General Hospital, Sydney, NSW, Australia

⁷ Centre for Health Technology, University of Technology Sydney, Sydney, NSW, Australia

⁸ School of Biomedical Engineering, UNSW Sydney, Sydney, NSW, Australia

⁹ Clinical School, St Vincent's Hospital Sydney, Sydney, NSW, Australia

¹⁰ School of Medicine Sydney, University of Notre Dame, Sydney, NSW, Australia

¹¹ Faculty of Medicine, UNSW Sydney, Sydney, NSW, Australia

Word count: 3,542

Corresponding author:

Dr Weiwen Chen

Osteoporosis and Bone Biology

Garvan Institute of Medical Research

384 Victoria St, Darlinghurst NSW 2010 Australia

Ph: 9295-8240; **Fax:** 9295-8241

Email: w.chen@garvan.org.au

Abstract

Background: Non-hip non-vertebral fractures (NHNV) constitute the majority of osteoporotic fractures but few studies have examined the association between these fractures, co-morbidity and mortality.

Objective: To examine the relationship between individual non-hip non-vertebral fractures, co-morbidities and mortality.

Methods:

Prospective population-based cohort of 267,043 subjects (45 and Up Study, Australia) had baseline questionnaires linked to hospital administrative and all-cause mortality data from 2006 - 2013. Associations between fracture and mortality examined using multivariate, time dependent Cox models, adjusted for age, prior fracture, body mass index, smoking and co-morbidities (cardiovascular disease, diabetes, stroke, thrombosis and cancer) and survival function curves. Population attributable fraction calculated for each level of risk exposure.

Results:

During 1,490,651 person-years, women and men experienced 7,571 and 4,571 fractures and 7,064 deaths and 11,078 deaths, respectively. In addition to hip and vertebral fractures, pelvis, humerus, clavicle, rib, proximal tibia/fibula, elbow and distal forearm fractures in both sexes, and ankle fractures in men, were associated with increased multivariable adjusted mortality hazard ratios ranging from 1.3 to 3.4. Co-morbidity independently added to mortality such that a woman with a humeral fracture and one co-morbidity had a similarly reduced 5 year survival to that of a woman with a hip fracture and no co-morbidities.

Population mortality attributable to any fracture without co-morbidity was 9.2% in women and 5.3% in men.

Conclusion:

All proximal non-hip, non-vertebral fractures in women and men were associated with increased mortality risk. Co-existent co-morbidities independently further increased mortality. Population attributable risk for mortality for fracture was similar to cardiovascular disease and diabetes, highlighting their importance and potential benefit for early intervention and treatment.

Keywords: Epidemiology, Aging, Practice/ Policy-related issues

Introduction

Premature mortality post-fracture is well established for hip and vertebral fractures (1-3). There is increasing evidence that a range of other, non-hip non-vertebral (NHNV), osteoporotic fractures are also associated with increased mortality (4-6). However, published data are inconsistent, particularly for distal forearm fractures (7, 8), or lacking for many other fractures.

This potential association is important because NHNV fractures account for over 50% of fractures. Compared to hip and vertebral fractures, they receive less attention (9), possibly due to clinicians' perception they are not associated with adverse consequences, or to difficulties accessing accurate data as they often do not require hospital admission. However, there is increasing evidence that NHNV fractures contribute significantly to the burden of subsequent fractures (10, 11) and increased premature mortality (5, 12, 13).

Previous studies of NHNV fractures and mortality have a number of limitations (8, 12, 14-17). In particular, apart from sites such as the humerus (17, 18) and distal forearm (8, 19), NHNV fractures are commonly grouped (20, 21), due to limited fracture numbers for specific sites. In addition, data on co-morbidities, and other potential confounders for mortality, are often lacking.

To overcome some of these limitations, we used a large population cohort with baseline co-morbidity data and linkage capabilities to examine the relationship of hip, vertebral and multiple NHNV fracture sites with mortality. The study aims were to examine: (1) the

relationship between mortality and individual NHNV fracture sites, and (2) the independent contribution of fracture and co-morbidity to mortality.

Subjects and Methods

The Sax Institute's 45 and Up study is a prospective cohort study of over 260,000 residents of New South Wales (NSW), Australia. NSW's population accounts for one-third of Australia's population. The study, described previously (22), included subjects 45 and older who were invited to participate via random sampling of the Department of Human Services (formerly Medicare Australia) enrolment database, which provides near complete coverage of the Australian population. To allow for deaths and loss to follow-up, the study over-sampled by a factor of two, individuals 80+ years and individuals in rural areas. Recruitment occurred between 2005 and 2009. The response rate was 18% and the study cohort was healthier and better educated than the general NSW population (23). Participants completed a baseline questionnaire and consented to data linkage to a number of administrative health datasets. For this analysis participants were followed until 31 December 2013. To ensure a minimum 12-month follow-up post-fracture, participants who fractured in the last follow-up year were excluded.

Questionnaire Variables

Demographic data (age, date of recruitment, sex), lifestyle (smoking status, body mass index (BMI)) and co-morbidities were obtained from the baseline questionnaire. Co-morbidities included cardiovascular disease, cerebrovascular disease, thrombotic disorders, diabetes, melanoma, breast cancer, prostate cancer, and all other cancers including non-melanoma skin cancer and prior fracture within the last five years. For co-morbidities, participants were asked whether "a doctor ever told you that you have" the condition (Yes/No). BMI was

derived from self-reported height and weight. Smoking status was classified as never, previous or current. Alcohol intake was classified in three categories as none; within the Australian National Health and Medical Research Council guideline recommendations (≤ 2 standard drinks/day for women and ≤ 4 standard drinks/day for men, with 2 alcohol free days per week for both sexes); and exceeding guidelines.

Linked databases

1. NSW Ministry of Health: Emergency Department Data Collection (EDDC): The EDDC collates presentations to all NSW public hospitals Emergency Departments. All Emergency Department presentations for diagnoses of fractures were used. International Classification of Diseases (ICD-10) (24) and Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) (25) codes were used to identify fractures.
2. NSW Ministry of Health: Admitted Patient Data Collection (APDC): The APDC collates inpatient separations (discharges, transfers and deaths) from all NSW public, private, and repatriation hospitals and private day procedure centres. These data include demographic characteristics, diagnoses and length of stay for individual episodes of hospital care. Diagnoses are coded according to the Australian modification
3. NSW Registry of Births, Deaths and Marriages (RBDM): All-cause mortality data were identified using death registrations.

Baseline questionnaire data from the 45 and Up Study were linked to the EDDC data, APDC data, and RBDM data. Probabilistic record linkage was performed by the Centre for Health Record Linkage. The 45 and Up Study was approved by the University of NSW Human Research Ethics Committee. Ethics approval for the current study was obtained from the

NSW Population Health Services Research Ethics Committee. Informed consent was not required for the current study as only de-identified data was used.

Fracture identification

Fractures were identified through a combination of SNOMED-CT and ICD-10 diagnosis codes from the APDC and EDDC as outlined above, and also using the Australian Classification of Health Interventions (ACHI) (26) procedure codes to capture fractures presenting as a day procedure. All SNOMED-CT and ICD-10 diagnosis codes suggesting fractures resulting from high trauma and pathological fractures were excluded. In participants with 2 or more fractures during one admission, only the more axial fracture, deemed the most severe, was counted.

Outcome measures

The primary outcome was all-cause mortality following each fracture type adjusted for age, lifestyle factors and co-morbidities.

Statistical analysis

Participants who died were compared to those alive at the study end for women and men separately. Student's t-test was used to compare baseline characteristics for continuous variables and Pearson's χ^2 test for categorical variables. Fracture incidence and mortality were calculated as fractures and deaths per 1000 person-years of follow-up. Fracture incidence was calculated for age groups: 45-59, 60-74 and 75+. Individual covariates were examined for their relationship with mortality using Cox's proportional hazard models. Significance and 95% confidence intervals were calculated assuming a Poisson distribution.

Mortality rates were age standardised to the 2001 Australian population as recommended by the Australian Bureau of Statistics. As overall mortality rate of the study cohort was lower than the general Australian population, particularly in the 85+ age cohort, standardised mortality ratios, comparing the cohort and NSW population, are not presented. Mortality differences were compared within the cohort between fracture and non-fracture participants in several analyses.

Cox's proportional hazards regression was used to examine the association between fracture type and mortality with adjustment for covariates. Fracture was included as a time-dependent variable. Survival time was measured from recruitment until death or censor date. The proportional hazards assumption was checked for each variable by examining the residual plots. Thus age- and sex-specific adjusted hazard ratios (HR) were derived. Body mass index were missing in 11000 women (8.5%) and 7650 men (6.3%). These participants were excluded from the final modelling. Sensitivity analysis with imputation using the median BMI did not change the analysis meaningfully.

To examine the effect of co-morbidities on survival for different fracture types, estimated survival function curves with covariates were plotted using the baseline function in SAS. We chose humeral fracture as representative of a NHNV fracture to compare with the known increased mortality of hip fracture. Curves were plotted for women and men aged 60 or 80 for none, one or two co-morbidities, in addition to fracture.

To calculate population attributable fraction, the heuristic approach was taken (17) using combinations of six key risks (fracture during the study; baseline cardiovascular disease,

diabetes, stroke, cancer and thrombosis) resulting in 64 possible exposure levels. Participants who did not fracture, with no co-morbidities were the reference.

Analyses were performed using SAS 9.3 (SAS Institute, Inc. Cary, NC, USA).

Results

The study included data from 141,342 women and 122,877 men. Mean age (SD) was 61.8 (11.1) years in women and 63.8 (11.1) years in men. Mean follow-up was 5.67 (1.07) years for women and 5.60 (1.21) years for men, yielding 802,081 and 688,570 person-years of follow-up in women and men, respectively. The median time from fracture to death or study end was 2.6 years. In general, participants who died were older ($P<0.001$), more likely to have fractured ($P<0.001$), have had a prior fracture ($P<0.001$), have more co-morbidities ($P<0.001$) and, in men, have higher smoking rates ($P<0.001$) than participants who did not die during the follow-up period (Table 1).

Fracture incidence

During follow-up, women had 7,571 and men had 4,571 incident fractures, yielding fracture incidence rates of 9.71/1000 person-years (95% CI: 9.50-9.94) in women and 7.09/1000 person-years (95% CI: 6.89-7.30) in men. Pattern of fractures were similar between women and men (Figure 1). NHNV accounted for over 70% of fractures in both women and men.

There was an exponential increase in hip fractures, particularly after 75 years, and increased incidence of vertebral, pelvic, rib and humeral fractures with increasing age. Distal forearm fractures increased with age in women but not in men. By contrast, NHNV fracture at other sites, e.g. elbow and proximal tibia/fibula, remained relatively stable with increasing age.

Women had more distal site (distal forearm and ankle) fractures than men ($P<0.001$).

Mortality

Mortality rates were lower in the cohort than in the general Australian population (age adjusted rates: 17.3 vs 25.1 /1000 in women and 21.5 vs 27.7/1000 person-years in men. For the non-fracture study cohort, there were 5,981 deaths in 133,771 women and 10,068 deaths in 118,306 men yielding age-standardised mortality rates of 16.9/1000 person-years (95% CI: 16.3-17.3) in women and 21.9/1000 person-years (95% CI: 20.5-23.2) in men. Among participants who had fractured, there were 1,083 and 1092 deaths in women and men, respectively with higher age-standardised mortality rates of 21.9/1000 person-years (95% CI: 20.5-23.2) in women and 31.4/1000 person-years (95% CI: 29.4-33.4) in men.

Specific co-morbidities associated with increased mortality included cardiovascular disease, diabetes, stroke, and thrombotic disorders with age-adjusted mortality HRs ranging from 1.2-1.9 (Supplementary Table S1). Cancers other than breast or prostate were associated with the highest mortality risk (HR: 2.1-2.2). Low and high BMI and prior and current smoking were associated with increased mortality (HR: 1.4-2.7). Skin cancers other than melanoma were associated with a lower age-adjusted mortality risk. Alcohol intake in the cohort was low with 88% of women and 87% of men drinking within the recommended Australian alcohol guidelines or not drinking at all (non-drinkers: 41% and 23% in women and men, respectively). There was no clinically significant association between alcohol intake and mortality for either women or men.

Fracture and mortality risk

Increased mortality was observed for many different fracture sites in both women and men. This remained significant after multivariable adjustment (Figure 2, Supplementary Table S2). In general, mortality risk post fracture was greater in men than women ($P<0.001$). As

expected, the mortality risk post fracture was highest for the hip (women: 2.76 (95% CI: 2.46, 3.09) and men: 3.40 (95% CI: 3.05, 3.78). Fractures of the vertebrae and pelvis were associated with increased mortality of similar magnitude. Interestingly, rib, humeral, elbow, proximal tibia/fibula and clavicular fractures all had similar associations with mortality risk with HRs between 2.00 and 2.50. Amongst distal fracture sites, distal forearm fractures were associated with increased mortality risk in both women and men. Ankle fractures, however, were only associated with an increased mortality risk in men. Mortality risk was not increased following fracture of the hands, feet, fingers and toes and did not differ from the non-fracture population.

The estimated survival function curves highlight the relationship between fracture event, number of co-morbidities and survival (Figures 3a & 3b for women and men aged 60 and 80, respectively). For these analyses, co-morbidities selected were those most common in the cohort, namely cardiovascular disease and diabetes. These survival curves demonstrate fracture as a risk factor for mortality, and the additional independent contribution of co-morbidities. Indeed a woman with a humerus fracture and one co-morbidity had the same estimated 5-year survival as a woman with a hip fracture and no co-morbidities. A man with a humeral fracture and one co-morbidity had a somewhat better survival than a man with a hip fracture and no co-morbidities but having 2 co-morbidities together with a humeral fracture resulted in a greater 5 year mortality than a hip fracture alone.

Population attributable fraction

The proportion of deaths in the population that could be attributed to fracture in individuals without co-morbidity was 9.2% in women and 5.3% in men. In women, the PAF was less than cancer but of a similar magnitude to cardiovascular disease and diabetes. Fracture

incidence was lower and cardiovascular disease higher in men than women; as a result the PAF of any fracture in men was less than cardiovascular disease but similar to diabetes and cancer. However, the contribution of fracture with or without any single co-morbidity resulted in a PAF for mortality that was similar to cancer in women and cardiovascular disease in men (Tables 2a & 2b).

Discussion

In this large population-based cohort study of subjects aged 45 and older, a large range of NHNV fractures, in addition to hip and vertebral fractures, were associated with increased mortality risk, after adjusting for age, prior fracture, smoking, BMI, cancer and other major co-morbidities. Virtually all NHNV fractures, including ribs, pelvis, femur, elbow, proximal tibia/fibula, distal forearm in both sexes, as well as ankle in men, were associated with increased mortality post fracture with hazard ratios ranging from 1.3 to 3.4. Notably the mortality reported represents an early post fracture mortality with median time of 2.6 years from fracture to death or study end. Peripheral fractures of hands and feet were not associated with increased mortality. Moreover, this study demonstrated that co-morbidity contributed to mortality independently and additively from the fracture itself. The proportion of deaths that could be attributable to subjects with fracture alone or with fracture and one co-morbidity was of a similar magnitude to other major illnesses including cancer and heart disease, highlighting the magnitude of the problem.

We found that hip and vertebral fractures were associated with 3.0-fold and 2.7-fold increase in mortality, respectively, similar to previous reports (3). In relation to NHNV post-fracture mortality, humeral fractures have been the most frequently studied, with consistent findings of increased mortality (2, 15, 17, 18). Our study supports these findings, demonstrating

humeral fractures were associated with a two-fold increase in mortality in women (HR: 2.0) and men (HR: 1.95) after multivariable adjustment. Prior studies which have demonstrated increased mortality have not always discriminated by sex (2) and none has adjusted for co-morbidities (2, 15, 17, 18). Adjustment for co-morbidities in the current study had minimal effect on the fracture-mortality association itself but added an additional independent contribution to mortality.

The relationship between distal forearm fractures and mortality is controversial with conflicting data. Studies have variously reported increased (8, 27), similar (2, 7, 20, 28) or decreased mortality (16, 19). We found significant mortality increases of 30% and 50% (HR 1.30 and 1.50) in women and men, respectively and of a similar magnitude to the large Norwegian and Korean studies (8, 27). Previously published studies that did not find an association between mortality and distal forearm fractures may have been hindered by low fracture numbers (often below 200). Studies reporting increased mortality post distal forearm fractures generally had larger fracture numbers (27). Bliuc et al (5) found a group of minor fractures, including distal forearm, were associated with increased mortality but only in subjects >75 years, with insufficient forearm fractures for separate analysis. In a Medicaid US dataset where decreased mortality post distal forearm fractures was demonstrated (19), the authors postulated increased contact with the healthcare system as the cause. Unlike the USA, Australia has universal healthcare at all ages, perhaps explaining differences in findings between the USA and the current study.

Few studies have examined mortality after rib fractures. Of these, only three examined rib fractures as a distinct group. The Study of Osteoporotic Fractures reported a three-fold increased mortality following rib fractures in women (29). Of the remaining two studies, one

found no difference in mortality risk but with only 16 and 11 rib fractures in men and women, respectively (25). In the other study (21) increased mortality risk post rib fractures was observed for women but not men. By contrast, in the current study, rib fractures were associated with an increased mortality risk of similar magnitude (two-fold) to vertebral fractures in both women and men.

There is particularly limited evidence about other NHNV fracture sites. Previous studies generally did not find any association between mortality and other NHNV fractures but were limited by small numbers, leading to grouping of fractures and inability to adjust for co-morbidities. Piirtola et al. did not find any association between “other miscellaneous” fractures (fractures other than hip, vertebra, ribs, proximal humerus and ankle) and mortality, but there were only 47 fractures over 12 years (12). Melton et al. reported “other arm” fractures (excluding proximal humerus and distal forearm) being associated with increased one-year mortality (13). In the same study, the “other leg group” of fractures (all lower limb fractures other than hip, feet and toes), did not show increased mortality. We found two- to three-fold increased mortality following proximal tibia/fibula, elbow and distal femur fractures in both sexes.

The specific causes of excess mortality following fracture are poorly understood. The duration of increased mortality attributable to fractures is also questionable, so pre-fracture co-morbidities have been hypothesised to contribute significantly to excess mortality with the fracture being a signal of underlying frailty. Several studies have examined the role of co-morbidities, mainly following hip fracture (30-32). A large Danish hip fracture study did not demonstrate any association between mortality and pre-fracture co-morbidities (31). The major identified causes of mortality were post fracture complications. In the Fracture

Intervention Trial, adjustment for co-morbidities also did not affect mortality hazard ratios (28). Similarly, adjustment for co-morbidities in our study had minimal effect on the fracture-specific hazard ratios although the presence of co-morbidities contributed additively and independently to mortality. Apart from the post fracture mortality, it has been demonstrated that low bone density (33), sarcopenia (34, 35), low body weight (21) and weight loss are independent predictors of both fracture and mortality and thus may play a role in any post fracture associated mortality. However, these variables are generally not available in large registry studies.

One criticism of studies in this area is that control groups are often healthier with fewer co-morbidities. The current study addressed this using both estimated survival curves and the heuristic approach to calculating population attributable fraction. The estimated survival curves demonstrate visually the difference in mortality risks between an individual with none, one or two co-morbidities following a fracture. In an individual with co-morbidities, fracture and co-morbidity were each independent risk factors for mortality, while the combination of both increased mortality risk. Indeed, a woman with a humeral fracture and one co-morbidity had a similarly reduced 5 year survival to that of a woman with a hip fracture and no co-morbidities. Moreover, a fracture with either no or one co-morbidity, accounted for 19% of the deaths in women and 11% in men, which was similar to that for any other individual co-morbidity including both cancer and cardiovascular disease. Both approaches support fracture as an independent risk factor for mortality and the latter analysis demonstrates the significant contribution of fracture to overall population mortality.

The strengths of the current study include the large sample size of women and men giving statistical power to study individual fracture sites. Unlike previous studies, this dataset

captures both community and inpatient data, allowing adjustment for lifestyle factors and medical co-morbidities. Furthermore, the study is the first to estimate population attributable fraction for each level of exposure and delineate the independent and additive effects of co-morbidity to fracture-associated mortality.

The limitations of the study include potential underestimation of mortality risk associated with fracture, as 45 and Up Study cohort mortality rates were significantly lower than the general NSW population. However, as increased mortality risk was still observed in this healthy group with fracture, it is likely that this risk would still be evident, and possibly higher, in the general population with a greater number of co-morbidities. Fractures were identified from administrative hospital data so it is possible that not all high trauma fractures were excluded or that only more severe distal fractures were included, potentially overestimating mortality risk in this group. Moreover, the specifics of the fracture event itself was not able to be determined given the nature of the study. While validity of deaths and fracture data is high, validity of self-reported co-morbidities has not been well studied. However, administrative datasets are likely to under report co-morbid conditions compared with self-report (36). Medication use was not available in the current study so any effect of medication on survival could not be evaluated.

Conclusion

In this large cohort of healthy community-dwelling people, a wide range of non-hip non-vertebral fractures were associated with increased mortality after multivariable adjustment. Importantly these NHNV fractures accounted for approximately 75% of fractures in this study. Compared to the non-fracture group, women and men with any fracture had a 19% and 25% higher mortality rate, respectively. The population attributable fraction of mortality for

any fracture was 9.2% in women and 5.3% in men, similar in magnitude to other well described causes of mortality including cardiovascular disease, diabetes and cancer. Moreover, using estimated survival curves, this study demonstrated for the first time that individuals with co-morbidities had worse survival after a fracture than those who fractured but were co-morbidity free. This study highlights the potential benefit of early intervention after fracture to reduce risk of further fractures and possibly decrease mortality.

Acknowledgements

This research was completed using data collected through the 45 and Up study (www.saxinstitute.org.au). The 45 and Up study is managed by the Sax Institute in collaboration with major partner Cancer Council NSW; and partners: the National Heart Foundation of Australia (NSW Division); NSW Ministry of Health; NSW Government Family & Community Services – Ageing, Carers and the Disability Council NSW and the Australian Red Cross Blood Service. We thank the many thousands of people participating in the 45 and Up Study. We pay tribute to our colleague and collaborator, the late Dr Jian Sheng “Charles” Chen, who died before his work in developing the research questions, establishing the ethics approvals and setting up the data linkages to answer these important questions about osteoporotic fractures could be realised.

Contributors: Weiwen Chen wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper. Judy Simpson wrote the statistical analysis plan, drafted and revised the paper. Lyn March and Fiona Blyth initiated the collaboration, drafted and revised the paper. Dana Bliuc and Thach Tran analysed the data and revised the paper. Tuan Nguyen wrote the statistical plan and revised paper. John Eisman drafted and revised paper. Jacqueline Center initiated the collaboration, analysed data, drafted and revised the paper.

Table 1: Participant characteristics by sex and mortality outcome

Variable	Women (N = 141,342)		Men (N = 122,877)	
	Alive (n = 134,278)	Died (n = 7,064)	Alive (n = 111,799)	Died (n=11,078)
Age, mean (SD), yrs	61.0 (10.5)	76.7 (11.7)*	62.5 (10.4)	76.2 (10.2)*
BMI, mean (SD), kg/m ²	26.7 (5.3)*	25.8 (5.7)	27.3 (4.2)*	26.2 (4.7)
Fracture (%)	6,488 (4.8)	1,083 (15.3)*	3,561 (3.2)	1,010 (9.1)*
Prior fracture within last 5 yrs (%)	16,071 (12.0)	1,509 (21.4)*	9,129 (8.2)	1,134 (10.2)*
Ever smoked (%)	47,178 (35.3)	2,506 (35.6)	55,834 (50.1)	6,920 (62.8)*
Diseases				
Cardiovascular disease (%)	9,775 (7.3)	1,693 (24.0)*	16,279(14.6)	3,603 (32.5)*
Hypertension (%)	44,004 (32.8)	3,230 (45.7)*	41,611 (37.2)	5,002 (45.2)*
Diabetes (%)	9,154 (6.8)	1,073 (15.2)*	11,267 (10.1)	2,167 (19.6)*
Stroke (%)	2,964 (2.2)	718 (10.2)*	3,421 (3.1)	1,187 (10.7)*
Thrombosis (%)	7,058 (5.3)	711 (10.1)*	3,606 (3.2)	757 (6.8)*

Cancer (%)	14,075 (10.5)	1,829 (25.9)*	11,052 (9.9)	3,158 (28.5)*
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*P<0.001 for died vs alive

Table 2a: Population attributable fraction (Women)

Population	Number	Deaths	Person- years	Mortality rate (/1000 Person- years)	PAF (%)
No fracture/co- morbidity	97,672	2,488	560,591	4.4	
Fracture only	4,684	455	26,837	17.0	9.2
Cardiovascular	6,118	616	33,700	18.3	13.3
Diabetes	6,016	368	33,745	10.9	6.1
Cancer	10,965	922	60,678	15.2	18.5
Stroke	1,434	188	7,795	24.1	4.4
Thrombosis	4,272	176	24,364	7.2	1.9
Fracture & 1 co- morbidity	2,074	394	11,333	34.8	10.0

Table 2b: Population attributable fraction (Men)

Population	Number	Deaths	Person- years	Mortality rate (/1000 Person-years)	PAF (%)
No fracture/co- morbidity	81,300	4,252	463,458	9.2	
Fracture only	2,746	411	15,517	26.5	5.3
Cardiovascular	12,201	1,659	66,776	24.8	21.3
Diabetes	7,914	839	41,920	19.1	8.7
Cancer	4,391	698	23,576	29.6	10.0
Stroke	1,769	336	9,505	35.3	5.2
Thrombosis	2,059	212	11,547	18.4	2.1
Fracture & 1 co-morbidity	1,237	355	6,596	53.8	6.2

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