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# Population-Wide Impact of Non-Hip Non-Vertebral Fractures on Mortality

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## ABSTRACT

Data on long-term consequences of non-hip non-vertebral (NHNV) fractures, accounting for approximately two-thirds of all fragility fractures, are scanty. Our study aimed to quantify the population-wide impact of NHNV fractures on mortality. The national population-based prospective cohort study (Canadian Multicentre Osteoporosis Study) included 5526 community dwelling women and 2163 men aged 50 years or older followed from July 1995 to September 2013. Population impact number was used to quantify the average number of people for whom one death would be attributable to fracture and case impact number to quantify the number of deaths out of which one would be attributable to a fracture. There were 1370 fragility fractures followed by 296 deaths in women (mortality rate: 3.49; 95% CI, 3.11 to 3.91), and 302 fractures with 92 deaths in men (5.05; 95% CI, 4.12 to 6.20). NHNV fractures accounted for three-quarters of fractures. In women, the population-wide impact of NHNV fractures on mortality was greater than that of hip and vertebral fractures because of the greater number of NHNV fractures. Out of 800 women, one death was estimated to be attributable to a NHNV fracture, compared with one death in 2000 women attributable to hip or vertebral fracture. Similarly, out of 15 deaths in women, one was estimated to be attributable to a NHNV fracture, compared with one in over 40 deaths for hip or vertebral fracture. The impact of forearm fractures (ie, one death in 2400 women and one out of 42 deaths in women attributable to forearm fracture) was similar to that of hip, vertebral, or rib fractures. Similar, albeit not significant, results were noted for men. The study highlights the important contribution of NHNV fractures on mortality because many NHNV fracture types, except for the most distal fractures, have serious adverse consequences that affect a significant proportion of the population. © 2017 American Society for Bone and Mineral Research.

**KEY WORDS:** EPIDEMIOLOGY; AGING; PRACTICE/POLICY-RELATED ISSUES

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## Introduction

Fragility fracture is a significant public health problem globally. The residual lifetime risk of fracture from 60 years old has been estimated to be 44% for women and 25% for men.[1] Among individuals with osteoporosis by a DXA *T*-score $< -2.5$, 65% of women and 42% of men will sustain a fragility fracture after the age of 60 years.[1] Importantly, estimated medical and hospitalization costs for the year after fragility fractures were sixfold higher than prefracture costs, and almost 3.5 times higher than those for matched nonfracture controls.[2] Given the ongoing aging of the population, the burden of fracture is expected to increase, especially in developing countries.

Fracture, often related to frailty and falling as well as bone-specific characteristics, also imposes a significant burden to an individual's health. Indeed, several studies have reported that a preexisting fracture increases the risk of premature mortality by twofold[3,4] and the excess mortality is highest in the first 12 months after a fracture.[5] Hip and vertebral fractures are associated with an increased risk of mortality, independent of age, comorbidities, and other confounding effects.[3–10] Nevertheless, it is not clear to what extent fractures other than hip and vertebrae (non-hip non-vertebral [NHNV]) are associated with an increased risk of mortality.[3,4,6–9,11–14] Previous studies examining the contribution of NHNV fractures on mortality had either short duration of follow-up[4,7,11,12] or recruited participants from a single setting.[3,6,8,9,11,13,14]

Because NHNV fractures account for more than two-thirds of all fragility fractures,[14] it is important to study their impact on mortality. Moreover, these fractures tend to occur in younger individuals, which would result in greater years of life lost than from other fractures that typically occur later in life. We hypothesize that at the population level, the impact of NHNV fracture on mortality is as pronounced as that of hip and vertebral fracture.

In order to quantify the impact of fracture on mortality, we need a new and practical measure. Traditionally, the association between a risk factor and an outcome is assessed in terms of relative risk (RR) or its related metric of hazard ratio (HR). However, RR or HR cannot quantify the importance of a risk factor at a population level. From a practical point of view, the unanswered public health question of interest among individuals in an entire population is how many deaths could be attributable to fracture. This question is analogous to the number needed to treat in clinical trials,[15] and is able to be qualified using the newly proposed population impact metrics in observational studies.[16] This impact metric[16] is a function of the prevalence of the risk factor (ie, fracture) and its magnitude of association with the event (ie, mortality). Although the effect of fracture on mortality has been documented, its population-wide impact has not been ascertained. Therefore, in the present study we sought to determine the population-wide impact of NHNV fractures on mortality. We also aimed to compare the impact of fracture by age and gender so that a full spectrum of burden of fractures could be elucidated.

## Subjects and Methods

### Study cohort

This study was part of the Canadian Multicentre Osteoporosis Study (CaMos), for which the protocol and procedures have been described.[17] Briefly, CaMos is a national population-based prospective cohort study with an age-, sex-, and region-specific sampling of the Canadian population. In 1995 to 1997, community-dwelling participants were invited to participate in the study if they lived within a 50-km radius of one of the following nine Canadian cities: St John's, Halifax, Québec City, Kingston, Toronto, Hamilton, Saskatoon, Calgary, and Vancouver. Each participant provided written informed consent. The study was approved by the IRB at each study center. Households were randomly selected from residential phone numbers. An age- and sex-stratified protocol, weighted to older women, was used to randomly select eligible participants within households. This sample framework represented 40% of the Canadian population in 1995. Approximately 9423 people (6538 women, 2885 men), or 42% of all invited people, fully participated in the study. For the current analysis, we excluded participants aged less than 50 years at recruitment ($n = 1670$), as well as those who had pathological fractures ($n = 8$) or had no follow-up data ($n = 78$).

Data collection was conducted from interviewer-administered questionnaires at scheduled visits at baseline, 5 and 10 years of follow-up, and from annual posted questionnaires. Data on anthropometric and demographic characteristics, medications, comorbidities, health-related habits, and quality of life were collected by a questionnaire via face-to-face interviews. BMD, weight, and height were also measured at the interviews. Self-reported comorbidities at the time of interview included, among others, rheumatoid arthritis, osteoarthritis, thyroid, liver or kidney disease, cancer (breast, uterine, prostate), Paget's disease of bone, hypertension, heart attack, stroke or transient ischemic attack, neuromuscular diseases, diabetes mellitus, phlebitis, and chronic obstructive pulmonary diseases. Health-related habits including caffeine intake, use of calcium and vitamin D supplementation, alcohol intake, regular physical activity, and smoking status were also ascertained by questionnaire. The Medical Outcomes Trust SF-36 Health Survey questionnaire was used to assess quality of life in terms of the standardized physical and mental health component scores.

### Fracture assessment

The incidence of fracture was ascertained by annual posted self-reported questionnaire and verified from medical records or from telephone interview. Approximately 78% of fractures were confirmed from X-ray reports.[18] The date, site, and circumstances of the fracture were recorded. We included only minimal trauma fractures involving trauma less than or equivalent to fall from standing height. Fractures of the skull, face, finger, and toe were excluded from the analysis, as well as fractures classified as potentially pathological; ie, Paget's or metastatic cancer. The initial incident fracture was defined as the first fracture reported after recruitment. If an individual had sustained more than one fracture during one event, only the more serious fracture was considered. Fractures were broadly classified into 11 skeletal sites as follows: hip, clinical vertebral, clavicle, rib, humerus, forearm (including wrist), elbow, pelvis, upper leg (ie, femur but not hip), lower leg (ie, knee, lower leg, and ankle), and hand/foot.

### Mortality ascertainment

The incidence of mortality of study participants was ascertained through contact with a member of the participant's family or a contact person (if the annual questionnaire was not returned) or obituary review. Although mortality data were not formally

validated using national figures or other external data sources, given the individual nature of the follow-up it was highly unlikely that these deaths were misclassified.

### Statistical methods

Statistical analyses were performed separately for women and men to address three specific issues: the age- and sex-specific incidence of fracture; the fracture-mortality association; and the population impact of fracture on mortality. We estimated the incidence rate of specific fracture type per 1000 person-years, assuming a Poisson distribution.

We assessed the association between fracture and mortality where fracture was analyzed as a time-dependent variable. Specifically, the analysis examined time from fracture (for individuals who sustained a fracture), and time from study entry (for nonfracture participants) to death or censor. Two analysis approaches were conducted. First, sex- and age-specific cumulative survival probability was estimated for each fracture type by using the Kaplan-Meier method. The log-rank test statistic was used to test for the hypothesis of differential survival probabilities between fracture types. Second, we used the Cox proportional hazards model to assess the magnitude of association between fracture and mortality with adjustment for joint effects of potential covariates. The covariates considered in the Cox model were age, BMI, BMD, educational attainment, lifestyle factors, and comorbidities. We did not find any interaction between lifestyle factors, such as smoking or alcohol and prior fracture on mortality risk. Because there were many potential covariates, the number of possible models would be very large. Moreover, because the covariates were interrelated, the challenge was to identify relevant covariates that might modify the relationship between fracture and mortality. We used the Bayesian Average Modeling method to search for relevant covariates.[19] Therefore, the association between fracture and mortality was examined in three different multivariable analysis models that made adjustment for age, potential confounding effects from relevant and all reported covariates, respectively. The assumptions of proportional hazards were checked using Schoenfeld residuals.[20] There were no missing data for the primary outcome (ie, death) and the risk factor of interest (ie, types of fracture). However, missing data were present in several covariates that were used for adjustment in the analysis, such as comorbidities, weight, BMI, SF-36 scores (<3%), and BMD (~13.9%). The plausible values of missing data in the covariates were imputed using multivariate imputation by a chained equations algorithm,[21] which created five completed imputed datasets. Each variable has its own imputation equation.

Next, population impact number (PIN) and case impact number (CIN)[16] were computed to quantify the impact of fracture on mortality on an entire population. PIN is the number of individuals in the population among whom one death is attributable to fracture. CIN is the number of deceased individuals among whom one case is attributable to fracture. All impact metrics were calculated as a function of the hazards ratio, prevalence of fracture, and incidence rate of mortality (Supporting Methods). Their 95% confidence intervals (CIs) were computed using the confidence limits of the adjusted HRs accounting for uncertainty of the magnitude of association between specific types of fracture and mortality.[16] Population impact measures were not computed for a statistically nonsignificant association between fracture and mortality.[16] All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA), and R statistical environment (R Foundation, Vienna, Austria; https://www.r-project.org) on a Windows platform (Microsoft Corp., Redmond, WA, USA).

## Results

The study included 7689 participants (5526 women and 2163 men), whose average age at study entry was 66 years (interquartile range, 59 to 73). The individuals were followed for a median of 14 years (range, 7 to 15). During the follow-up period, 1102 women (20%) and 596 men (28%) died (Fig. 1). The baseline characteristics of participants stratified by survival status are shown in Table 1. As expected, deceased individuals were older, had lower body weight, lower BMD, more comorbidities, more previous surgeries, and poorer physical health status at recruitment than survivors.

### Incidence of fractures

There were 1370 incident fractures over 54,031 person-years of follow-up in women, yielding a fracture incidence rate of 25 per 1000 person-years (95% CI, 24 to 27). In men the incident fracture rate was 14 per 1000 person-years, approximately 1.8 times lower than that in women (Table 2). Overall, in absolute numbers, NHNV fractures accounted for three-quarters of the total number of fractures in women (77%) and men (75%). The incidence of NHNV fractures in women was 20 per 1000 person-years (95% CI, 19 to 22), which was higher than men (11 per 1000 person-years; 95% CI, 10 to 13). The incidence of NHNV fractures increased with advancing age but not as steeply as that for hip and vertebral fracture. For instance, among those aged 75 years and above, the risk of NHNV fractures was 1.5-fold higher than those aged between 50 and 74 years old. The risks of hip and vertebral fractures in elderly individuals aged 75 years or older were fivefold and threefold higher than the younger population, respectively.

Among individuals aged between 50 and 59 years, minor/distal fractures, such as lower leg, hand/foot, forearm, and elbow fractures, accounted for 65% of total fractures. On the other hand, these fractures accounted for only 30% of total fractures among individuals aged 75 years and older ($p$ value of test for trend <0.0001).

### Mortality after fractures

There were 1698 deaths over 85,437 person-years of follow up (absolute mortality rate: 1.99/100 person-years; 95% CI, 1.89 to 2.08), including 1102 women (1.76/100 person-years; 95% CI, 1.66 to 1.87) and 596 men (2.60/100 person-years; 95% CI, 2.39 to 2.82). For both genders, individuals with any fragility fracture had a greater risk of mortality compared with those without a fracture (Table 3, Supporting Tables 1 and 2).

The age-adjusted hazards ratio of mortality associated with a NHNV fracture was 1.27 (95% CI, 1.08 to 1.48) in women and 1.22 (95% CI, 0.93 to 1.62) in men. The reduced survival probability was more pronounced during the first 5 years after a fracture, although the trend was not clear for individuals aged 60 to 74 years at fracture (Fig. 2). Survival probabilities after hip, rib, and humerus fractures were lower than nonfractures at all ages, and the differences became even wider with advancing age (Supporting Fig. 1). Individuals with clinical vertebral fracture

**Table 1.** Baseline Characteristics

| Baseline characteristics | Women | | | Men | | |
|---|---|---|---|---|---|---|
| | Alive ($n = 4424$) | Deceased ($n = 1102$) | $p$ | Alive ($n = 1567$) | Deceased ($n = 596$) | $p$ |
| Age (years), mean ± SD | 65.2 ± 8.7 | 73.1 ± 8.8 | 0.001 | 64.1 ± 8.8 | 72.0 ± 8.7 | 0.001 |
| Weight (kg), mean ± SD | 68.9 ± 13.4 | 67.2 ± 14.4 | 0.001 | 82.1 ± 13.6 | 78.9 ± 14.0 | 0.001 |
| Body mass index (kg/m$^2$), mean ± SD | 27.1 ± 5.0 | 26.9 ± 5.5 | 0.29 | 27.3 ± 3.8 | 26.7 ± 4.2 | 0.005 |
| Education lower than university, *n* (%) | 3419 ± 77.3 | 948 ± 86.0 | 0.001 | 1010 ± 64.5 | 428 ± 71.8 | 0.001 |
| Prior minimal trauma fracture, *n* (%) | 1191 ± 26.9 | 397 ± 36.0 | 0.001 | 382 ± 24.4 | 142 ± 23.8 | 0.79 |
| Number of prior surgeries, *n* (%) | | | 0.001 | | | 0.001 |
| None | 3230 ± 73.0 | 692 ± 62.8 | | 1332 ± 85.0 | 459 ± 77.0 | |
| One | 1050 ± 23.7 | 327 ± 29.7 | | 209 ± 13.3 | 115 ± 19.3 | |
| Two or more | 144 ± 3.3 | 83 ± 7.5 | | 26 ± 1.7 | 22 ± 3.7 | |
| Number of comorbidities, *n* (%) | | | 0.001 | | | 0.001 |
| None | 2163 ± 48.9 | 303 ± 27.5 | | 816 ± 52.1 | 199 ± 33.4 | |
| One | 1507 ± 34.1 | 422 ± 38.3 | | 519 ± 33.1 | 197 ± 33.1 | |
| Two | 558 ± 12.6 | 210 ± 19.1 | | 170 ± 10.8 | 127 ± 21.3 | |
| At least three | 196 ± 4.5 | 167 ± 15.1 | | 62 ± 4.0 | 73 ± 12.2 | |
| Specific comorbidity, *n* (%) | | | | | | |
| Hypertension | 1342 ± 30.5 | 511 ± 46.6 | 0.001 | 415 ± 26.6 | 230 ± 38.7 | 0.001 |
| Gallbladder | 915 ± 20.7 | 300 ± 27.3 | 0.001 | 121 ± 7.7 | 78 ± 13.1 | 0.001 |
| Thyroid | 835 ± 18.9 | 233 ± 21.2 | 0.08 | 42 ± 2.7 | 35 ± 5.9 | 0.001 |
| Chronic pulmonary diseases | 337 ± 7.6 | 176 ± 16.0 | 0.001 | 97 ± 6.2 | 65 ± 10.9 | 0.001 |
| Phlebitis | 317 ± 7.2 | 98 ± 8.9 | 0.05 | 39 ± 2.5 | 35 ± 5.9 | 0.001 |
| Diabetes mellitus | 240 ± 5.4 | 153 ± 13.9 | 0.001 | 127 ± 8.1 | 81 ± 13.6 | 0.001 |
| Rheumatoid arthritis | 273 ± 6.3 | 106 ± 10.1 | 0.001 | 71 ± 4.6 | 33 ± 5.7 | 0.29 |
| Cancer | 276 ± 6.2 | 106 ± 9.6 | 0.001 | 44 ± 2.8 | 47 ± 7.9 | 0.001 |
| Gastrointestinal | 270 ± 6.1 | 131 ± 11.9 | 0.001 | 123 ± 7.8 | 70 ± 11.7 | 0.005 |
| Heart disease | 184 ± 4.2 | 126 ± 11.5 | 0.001 | 141 ± 9.0 | 116 ± 19.9 | 0.001 |
| Stroke | 138 ± 3.1 | 94 ± 8.6 | 0.001 | 62 ± 4.0 | 55 ± 9.3 | 0.001 |
| Neuromuscular | 132 ± 3.0 | 47 ± 4.3 | 0.03 | 28 ± 1.8 | 20 ± 3.4 | 0.03 |
| Kidney disease | 57 ± 1.3 | 32 ± 2.9 | 0.001 | 21 ± 1.3 | 14 ± 2.3 | 0.10 |
| Vitamin D use, *n* (%) | 1525 ± 34.5 | 350 ± 31.8 | 0.09 | 344 ± 22.0 | 121 ± 20.3 | 0.40 |
| Hormone therapy use, *n* (%) | 1199 ± 27.1 | 172 ± 15.6 | 0.001 | | | |
| Corticosteroid use, *n* (%) | 54 ± 1.2 | 37 ± 3.4 | 0.001 | 18 ± 1.1 | 16 ± 2.7 | 0.01 |
| Lack of physical activity, *n* (%) | 1847 ± 41.7 | 618 ± 56.1 | 0.001 | 679 ± 43.3 | 282 ± 47.3 | 0.10 |
| History of fall in the last month, *n* (%) | 273 ± 6.2 | 90 ± 8.2 | 0.02 | 95 ± 6.1 | 38 ± 6.4 | 0.79 |
| Current smoker, *n* (%) | 539 ± 12.2 | 209 ± 19.0 | 0.001 | 266 ± 17.0 | 122 ± 20.5 | 0.06 |
| Alcohol consumption (drinks/year), mean ± SD | 187.2 ± 234 | 226.9 ± 358 | 0.002 | 368.2 ± 434 | 445.3 ± 582 | 0.006 |
| Total hip BMD (g/cm$^2$), mean ± SD | 0.85 ± 0.14 | 0.79 ± 0.15 | 0.001 | 1.01 ± 0.14 | 0.96 ± 0.17 | 0.001 |
| Physical score (SF-36), mean ± SD | 46.9 ± 10.1 | 40.8 ± 11.1 | 0.001 | 48.8 ± 9.2 | 44.4 ± 10.0 | 0.001 |
| Mental score (SF-36), mean ± SD | 53.4 ± 8.7 | 53.7 ± 9.5 | 0.26 | 54.7 ± 7.7 | 54.8 ± 7.8 | 0.97 |

SF-36 = Medical Outcomes Trust SF-36 Health Survey questionnaire.

also had a lower associated survival at all ages except in a group of seven men who sustained a vertebral fracture between 60 and 74 years. On the other hand, higher mortality risk after forearm fractures was only evident in elderly women aged 75 years or older.

The occurrence of fragility fracture was associated with 50% increased risk of mortality after adjustment for potential confounding effects (Table 3). In comparison, osteoporosis, defined as total hip BMD *T*-score < –2.5 at study entry, was associated with 30% increased mortality risk for women (HR 1.32; 95% CI, 1.09 to 1.60), and a similar but not significant increase in men (HR 1.35; 95% CI, 0.79 to 2.31). Further adjustment for covariates other than age did not substantially change the magnitude of the postfracture mortality risk. These analyses also demonstrated an increased risk of mortality after hip, vertebral, and NHNV fractures as a group, though the association between NHNV fracture and mortality did not achieve statistical significance in men (HR 1.15; 95% CI, 0.85 to 1.56). Fractures of hip, vertebrae, and humerus increased the mortality risk by two to three times for both sexes. The risk of mortality after forearm, rib, and pelvic fracture was 1.5-fold to 2.0-fold higher than nonfracture in women; with similar, albeit not significant, estimates of the relative mortality risk for men who sustained rib and pelvic fracture.

## Population-wide impact of fragility fracture on mortality

Point estimates and 95% CIs of PINs and CINs are shown in Table 4. Overall, one death would be attributable to fragility fracture for every 447 women and 722 men in the entire

**Table 2.** Incidence of Fracture Types by Gender

| Fracture types | Women | | Men | | |
|---|---|---|---|---|---|
| | Number | Incidence[a] | Number | Incidence[a] | Difference[b] |
| Any fractures | 1370 | 25.4 (24 to 26.7) | 302 | 14.3 (12.7 to 16) | 11 (9 to 13.1) |
| Hip | 163 | 3.5 (3 to 4.1) | 51 | 2.6 (1.9 to 3.4) | 0.9 (0.01 to 1.8) |
| Vertebrae | 150 | 3.2 (2.7 to 3.8) | 23 | 1.2 (0.7 to 1.8) | 2.1 (1.3 to 2.8) |
| NHNV | 1057 | 20.4 (19.1 to 21.6) | 228 | 11.1 (9.7 to 12.6) | 9.3 (7.4 to 11.1) |
| Clavicle | 18 | 0.4 (0.2 to 0.6) | 4 | 0.2 (0.1 to 0.5) | 0.2 (–0.1 to 0.5) |
| Rib | 160 | 3.4 (2.9 to 4.0) | 87 | 4.4 (3.5 to 5.4) | –0.9 (–2. 0.1) |
| Humerus | 123 | 2.7 (2.2 to 3.2) | 17 | 0.9 (0.5 to 1.4) | 1.8 (1.2 to 2.4) |
| Elbow | 33 | 0.7 (0.5 to 1.0) | 3 | 0.2 (0.1 to 0.5) | 0.6 (0.3 to 0.9) |
| Forearm | 311 | 6.6 (5.9 to 7.3) | 40 | 2.0 (1.5 to 2.9) | 4.5 (3.6 to 5.5) |
| Hand/foot | 108 | 2.3 (1.9 to 2.8) | 21 | 1.1 (0.7 to 1.7) | 1.3 (0.6 to 1.9) |
| Other | 7 | 0.2 (0.1 to 0.3) | | | |
| Pelvis | 50 | 1.1 (0.8 to 1.4) | 6 | 0.3 (0.1 to 0.7) | 0.8 (0.4 to 1.2) |
| Upper leg | 19 | 0.4 (0.3 to 0.7) | 7 | 0.4 (0.1 to 0.7) | 0.05 (–0.3 to 0.4) |
| Lower leg | 228 | 4.9 (4.3 to 5.5) | 43 | 2.2 (1.6 to 3.0) | 2.7 (1.9 to 3.6) |

[a]Data are presented as number of fractures/1000 person-years (95% CI).
[b]Difference = incidence of fracture in women – incidence of fracture in men; number of fractures/1000 person-years (95% CI).

population, suggesting that the impact of fracture on mortality was more pronounced in women than men. However, in either sex, the impact of fracture on mortality appeared to increase with advancing age. For example, the population impact number was one death attributable to fracture for every 1021 women aged 60 to 74 years in the population, and this number was increased to one fracture-related death for every 70 women among those aged 75 years or older. Focusing specifically on deaths, one in nine deaths in women (CIN = 9) and one in 20 deaths in men (CIN = 20) were attributable to fragility fracture in the population, and these risks increased to one in five and one in 11 in elderly women and men aged 75 or older at fracture, respectively. In comparison, one death was attributable to osteoporosis at study entry for every 2700 women, whereas for 46 deaths in women, one was attributable to osteoporosis.

We also found that all NHNV fractures together had a greater overall impact on mortality than hip and vertebral fracture in women. A similar trend was noted in men, though the association between NHNV fracture and mortality did not reach statistical significance. For every 800 women, one death would be attributable to NHNV fractures, compared with one death for every 2000 women for hip or vertebral fracture. Similarly, on average, one in every 15 and one in every 40 deaths in the community would be related to NHNV and hip or vertebral fracture, respectively.

Analysis by individual types of fracture revealed that the impact of forearm fracture on mortality in women (PIN ≅ 2400) was close to that of hip or clinical vertebral (PIN ≅ 2000), and rib fracture (PIN ≅ 3000). Similarly, on average one in 40 deaths in women would be attributable to forearm (CIN = 42), hip (CIN = 34), vertebral (CIN = 42), and rib fracture (CIN = 53).

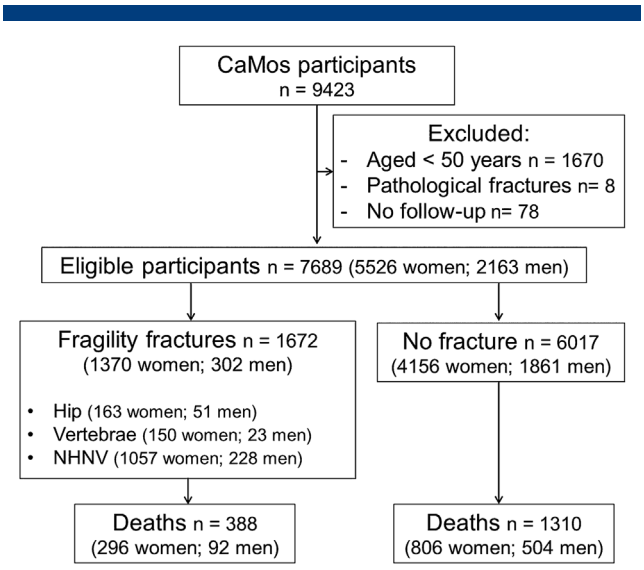


**Fig. 1.** Flowchart of follow-up.

## Discussion

The association between NHNV fracture and mortality is controversial. The underlying hypothesis of this study was that NHNV fracture imposes a greater impact on mortality in the general population than either hip or clinical vertebral fractures because of the large proportion of all incident fragility fractures at NHNV sites. The present results are consistent with this hypothesis. Our analyses suggested NHNV fractures were associated with an increased risk of mortality even after adjustment for potential confounding effects, although the association did not achieve statistical significance in men, possibly related to smaller numbers of men and of fractures in men and their higher general mortality. Importantly, on average there would be one death attributable to NHNV fracture for every 800 women, which is twofold higher than the impact of hip or vertebral fracture. For individual types of fracture, hip, vertebral, and humerus fractures were associated with 1.5-fold to 3.0-fold increased risk of mortality in both genders. Increased risk of mortality was also documented after forearm, rib, and pelvic fractures in women, but not in men. Interestingly, the population impact of forearm fracture on mortality was close to that of more severe fractures.

The deleterious impact of fracture on mortality in the entire population (ie, PIN ≅ 450 for women and 700 for men) was greater than that of smoking on coronary heart disease–related deaths (PIN ≅ 1300) and lung cancer–related deaths (PIN

**Table 3.** Incidence of Mortality and Adjusted HRs of Mortality by Types of Fragility Fracture

| | Mortality incidence (per 100 person-years) (95% CI) | HR adjusted for age (95% CI) | HR adjusted for relevant confounders (95% CI)[a] | HR adjusted for all confounders (95% CI)[b] |
|---|---|---|---|---|
| Women | | | | |
| Nonfracture | 1.77 (1.65–1.90) | 1 | 1 | 1 |
| Any fracture | 3.49 (3.11–3.91) | **1.43 (1.24–1.64)** | **1.50 (1.30–1.73)** | **1.51 (1.31–1.75)** |
| Hip | 8.47 (6.45–11.1) | **2.14 (1.62–2.84)** | **2.06 (1.55–2.73)** | **2.13 (1.58–2.87)** |
| Vertebrae | 5.41 (4.05–7.22) | **1.93 (1.42–2.64)** | **1.87 (1.30–2.69)** | **1.82 (1.28–2.57)** |
| NHNV | 2.82 (2.45–3.24) | **1.27 (1.08–1.48)** | **1.36 (1.16–1.60)** | **1.38 (1.18–1.62)** |
| Clavicle | 3.87 (1.45–10.3) | 1.64 (0.60–4.46) | 1.33 (0.48–3.69) | 1.33 (0.47–3.81) |
| Rib | 4.33 (3.21–5.84) | **1.84 (1.34–2.52)** | **1.69 (1.25–2.29)** | **1.67 (1.22–2.28)** |
| Humerus | 4.50 (3.18–6.36) | **1.54 (1.10–2.14)** | **1.49 (1.06–2.10)** | **1.62 (1.15–2.29)** |
| Elbow | 1.74 (0.65–4.64) | 0.83 (0.29–2.38) | 0.88 (0.33–2.35) | 0.96 (0.38–2.39) |
| Forearm | 2.59 (1.99–3.37) | 1.15 (0.88–1.51) | **1.40 (1.04–1.87)** | **1.43 (1.07–1.92)** |
| Hand/foot | 1.57 (0.89–2.77) | 0.84 (0.48–1.48) | 0.99 (0.55–1.80) | 1.08 (0.60–1.94) |
| Pelvis | 6.01 (3.49–10.4) | 1.64 (0.97–2.77) | **1.97 (1.21–3.20)** | **1.80 (1.08–3.01)** |
| Upper leg | 4.90 (2.2–10.9) | 1.61 (0.74–3.51) | 1.69 (0.86–3.31) | 1.49 (0.73–3.02) |
| Lower leg | 1.64 (0.53–5.09) | 0.99 (0.69–1.40) | 1.03 (0.73–1.46) | 1.03 (0.73–1.45) |
| Men | | | | |
| Nonfracture | 2.61 (2.39–2.85) | 1 | 1 | 1 |
| Any fracture | 5.05 (4.12–6.20) | **1.42 (1.12–1.79)** | **1.34 (1.05–1.71)** | **1.38 (1.07–1.78)** |
| Hip | 11.41 (7.73–16.90) | **1.91 (1.18–3.08)** | **2.00 (1.27–3.13)** | **2.08 (1.36–3.18)** |
| Vertebrae | 8.14 (4.23–15.60) | **2.29 (1.38–3.79)** | **2.31 (1.36–3.93)** | **2.65 (1.57–4.49)** |
| NHNV | 3.89 (3.01–5.03) | 1.22 (0.93–1.62) | 1.12 (0.83–1.50) | 1.15 (0.85–1.56) |
| Clavicle | 3.02 (0.42–21.4) | 1.39 (0.41–4.72) | 1.88 (0.34–10.32) | 1.46 (0.29–7.24) |
| Rib | 4.37 (2.87–6.63) | 1.21 (0.79–1.88) | 1.31 (0.71–1.82) | 1.37 (0.74–1.95) |
| Humerus | 7.51 (3.38–16.70) | **2.57 (1.03–6.41)** | **2.85 (1.35–6.02)** | **2.64 (1.14–6.13)** |
| Forearm | 2.99 (1.49–5.97) | 1.02 (0.51–2.01) | 0.89 (0.43–1.84) | 0.86 (0.38–1.93) |
| Hand/foot | 4.06 (1.93–8.51) | 1.55 (0.64–3.79) | 1.20 (0.38–2.87) | 1.19 (0.48–2.95) |
| Pelvis | 10.90 (3.52–33.90) | 1.54 (0.61–3.86) | 1.61 (0.59–4.41) | 1.71 (0.62–4.48) |
| Upper leg | 3.58 (0.89–14.30) | 0.83 (0.17–4.12) | 0.77 (0.09–3.79) | 0.83 (0.12–3.99) |
| Lower leg | 2.75 (1.43–5.28) | 1.01 (0.54–1.90) | 1.11 (0.59–2.11) | 1.13 (0.59–2.16) |

Bold indicates statistically significant association with mortality.

[a]Relevant confounders from the Bayesian model averaging approach included age, smoking status, diabetes mellitus, chronic obstructive pulmonary diseases, hypertension, and physical health status (for both genders), and physical activity, education level, BMD (for women only), heart diseases, mental health status (for men only).

[b]Age, BMI, education level, smoking status, physical activity, number of comorbidities, all reported comorbidities, number of prior surgeries, prior fractures, falling history, BMD, use of vitamin D, calcium or corticosteroid (and hormone therapy for women), physical and mental health status (SF-36), and study centers.

≅2600) in British male physicians.[16] It was also higher than osteoporosis per se (PIN ≅ 2700) in the CaMos population. The finding that NHNV fractures had a greater impact on mortality (PIN ≅ 800) than hip or vertebral fracture (PIN ≅ 2000) can be explained by the interaction of two parameters: prevalence and strength of association. In terms of prevalence, NHNV fractures accounted for three-quarters of total fractures in this population, which is consistent with previous findings.[14] More important, the effect size of NHNV fractures on mortality is substantial and statistically comparable to that of hip and vertebral fractures. Because the population impact is determined by both prevalence and effect size of a risk factor,[16] it is perhaps not surprising that NHNV fractures impose a substantial burden to the population at large.

The 95% CIs of the population impact metrics for some subgroups of fracture, especially in men, are indeed wide, largely because of the small number of fractures observed. However, formal statistical tests to access the significance of the difference in the population impact estimates between groups have not yet been developed, thus it is not possible to make a direct inference on this significance based solely on the CIs. In fact, it is not necessarily true that two statistics with overlapping CIs are not significantly different.[22] However, these metrics are useful to provide a guide to the overall population impact of osteoporotic fractures in relation to other common diseases.

Our findings are in line with other studies which found that hip, vertebral,[3,6,8–13] and NHNV fractures[14] were associated

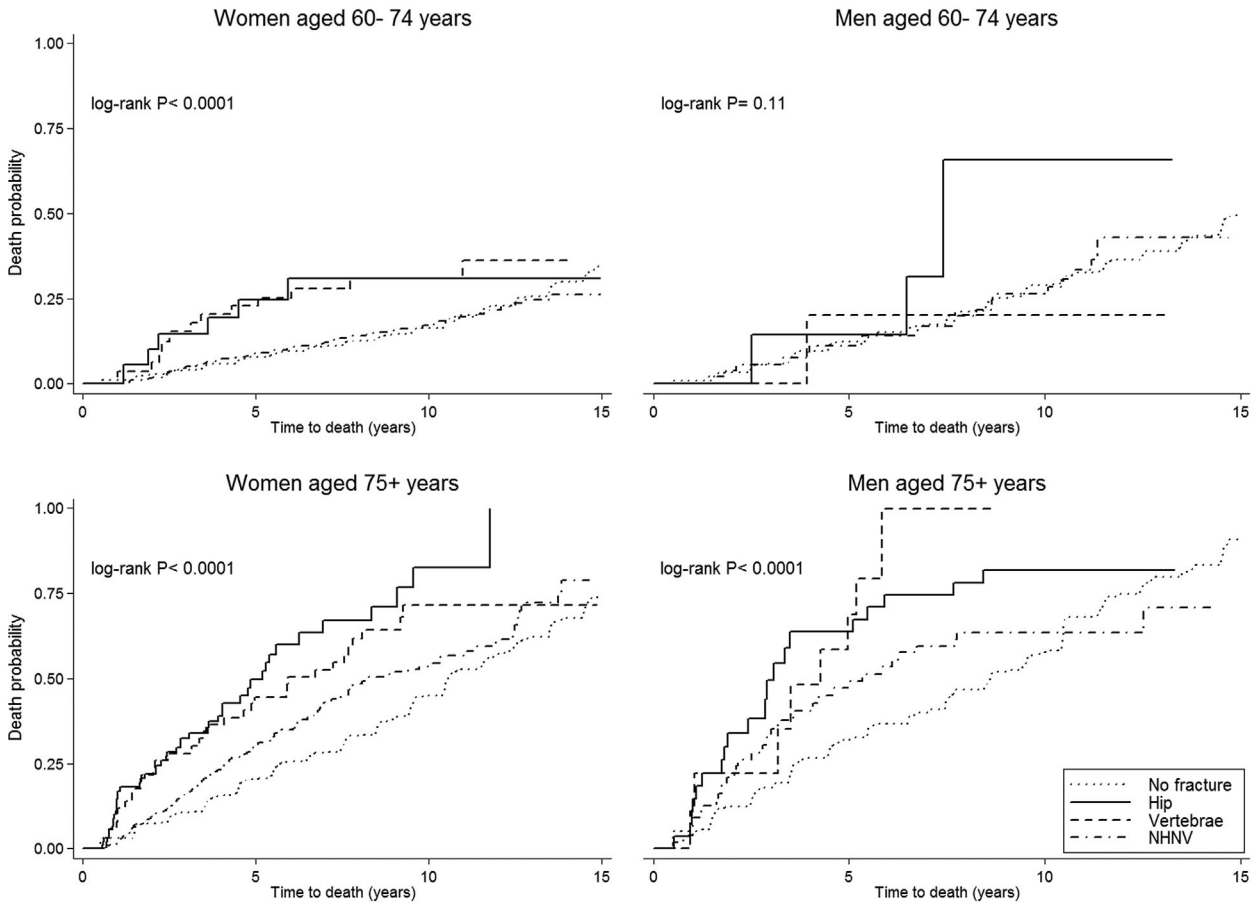


**Fig. 2.** Kaplan-Meier curves for mortality probability after different types of fragility fracture according to gender and age at fracture.

with an increased mortality risk after controlling for confounding effects. For individual types of NHNV fractures, our results support the findings that humerus,[8,9,11–13] rib,[8,11] pelvic,[8,11] or forearm fractures[9,12,23,24] are related to excess mortality risk. Like the current study, forearm fractures have been more consistently documented to be associated with an increased mortality in elderly populations,[9,12,23,24] but not in younger populations.[8] A study in Finland of men and women aged 65 years or older[13] reported a statistically nonsignificant increase in mortality risk by 50% in men and 30% in women after adjustment for confounding effects. The cause for the increased mortality associated with forearm fractures in the elderly is not

**Table 4.** Population-Wide Impact of Fragility Fracture on Mortality by Gender and Fracture Types

| | Women | | Men | |
|---|---|---|---|---|
| | PIN | CIN | PIN | CIN |
| Any fracture | 447 (304–735) | 9 (6–14) | 722 (352–3920) | 20 (10–103) |
| 60–74 years | 1021 (455–29,598) | 17 (8–471)) | NA | NA |
| 75+ years | 70 (45–130) | 5 (3–8) | 125 (52–4360) | 11 (5–363) |
| Hip | 1841 (1112–3586) | 34 (21–65) | 3336 (1653–10,007) | 88 (44–262) |
| Vertebrae | 2334 (1219–6836) | 42 (23–122) | 985 (466–2850) | 27 (13–75) |
| NHNV | 777 (476–1640)) | 15 (9–30) | NA | NA |
| Humerus | 4091 (1966–16,909) | 73 (36–301) | 2972 (950–34,815) | 79 (26–910) |
| Pelvis | 7799 (3104–77,995) | 139 (56–1383) | NA | NA |
| Rib | 2910 (1523–8863) | 53 (28–158) | NA | NA |
| Forearm | 2333 (1090–14,331) | 42 (20–255) | NA | NA |

Data are number of individuals in an entire population (PIN) or among those who died (CIN) for whom one death would be attributable to fracture and their corresponding 95% CIs.

PIN = population impact number; CIN = case impact number; NA = nonapplicable because population impact numbers were not computed for nonsignificant association with mortality; NHNV = non-hip non-vertebrae.

clear. Distal fractures, including forearm fractures, were associated with increased mortality risk only in the group who suffered a subsequent fracture in an Australian study.[14] In addition, several factors, such as loss of independence and mobility, limited activities of daily living,[25] or reduced muscle strength,[26] that are associated with forearm fracture are likely to have a detrimental impact on an elderly person's health status. Older women with wrist fracture in the Study of Osteoporotic Fractures were 50% more likely than those without fracture to experience a clinically important functional decline, such as decreased ability to prepare meals, perform heavy housekeeping, climb 10 stairs, go shopping, or get out of a car.[27]

The findings from this study have important implications for public health as well as for clinical decisions. From a public health point of view, it has been commonly stated that hip fracture is consistently associated with increased risk of mortality.[3–10] In addition to its related consequences, such as infections, thromboembolism,[28,29] and myocardial infarction,[30] hip fracture per se has been found to account for postfracture excess mortality over and above other known risk factors.[10,31,32] However, in this study, we show that the population-wide impact on mortality of hip fracture is lower than the impact of NHNV fracture in women, with a similar albeit nonsignificant trend in men. This was the case because hip fracture accounted for only 13% of all fractures, and primarily occurred in the very elderly population (average age at hip fracture was 81 years in women, 79 years in men). The impact of NHNV fractures on mortality underlines a new concept that these fractures represent a significant burden, perhaps an even greater burden than hip fracture in the entire population, because of their greater numbers and occurrence across all ages. At the individual level, our finding implies that individuals with NHNV fractures should be considered for timely treatment.

The strengths of our study include a large representative age-, sex-, and region-specific sample of the Canadian population and rigorous statistical analysis methods. The occurrence of fragility fracture was examined as one of several factors related to mortality and considered in a time-dependent manner, so that the specific contribution of fracture on mortality was able to be estimated. This is, to our knowledge, the first study reporting the impact of fragility fracture on mortality at a population level, which is expected to assist health professionals to make rational and evidence-based public health decisions.[33,34] Different measures of population impact have been used to examine fracture risk,[35] as a tool to help prioritize therapeutic interventions[36,37] or to implement guidelines in primary care.[38] We calculated the population impact metrics using HRs estimated from a Cox proportional regression model that took into account time from fracture to death. These calculated metrics did not address variations in probability of death over time following a fracture. However, because the proportional hazards assumption was met in our model, we did not consider that variation in probability of death over time to be a significant issues. In addition, the findings were more prominent in women because the association between several types of fractures and an increased mortality risk did not achieve statistical significance in men. Given the observational nature of the study, we can only report an association, rather than a causal relationship between fragility fractures and premature mortality. Nevertheless, even if a clear causal relationship could not be established, our data should at least highlight the importance of recognizing an NHNV fracture as an indicator of possible mortality because its population-wide impact on mortality appeared to be greater than that of smoking on coronary heart disease–related mortality and cancer,[16] and therefore should prompt further assessment of a fracture patient for early intervention. Finally, our analysis was not able to address the difference in mortality following a fracture between rural and urban areas because the CaMos participants were mainly from urban and suburban areas, although the mortality risk was not significantly different between the study centers.

In conclusion, fragility fracture was associated with an increase in mortality risk over and above other known mortality risk factors. Compared with those without fracture, elderly people who sustained hip, vertebral, and NHNV fractures had a 1.5-fold to 2.0-fold increased risk of premature mortality, although the association between NHNV fracture and mortality was not statistically significant in men, possibly due to small numbers. Importantly, the deleterious population-wide impact of the more frequent NHNV fractures on mortality was greater than that of hip and clinical vertebral fractures. The impact of forearm fracture on mortality in women was very close to that of other more severe fractures. This study adds to the growing body of evidence that it is not just hip and vertebral fractures that are associated with an increased mortality risk but that many fracture types except for the most distal fractures have serious consequences and thus deserve early attention and treatment.

### Disclosures

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## References


1. Nguyen ND, Ahlborg HG, Center JR, Eisman JA, Nguyen TV. Residual lifetime risk of fractures in women and men. J Bone Miner Res. 2007;22(6):781–8.
2. Budhia S, Mikyas Y, Tang M, Badamgarav E. Osteoporotic fractures: a systematic review of U.S. healthcare costs and resource utilization. Pharmacoeconomics. 2012;30(2):147–70.
3. 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.
4. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D. Risk of mortality following clinical fractures. Osteoporos Int. 2000;11(7): 556–61.
5. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int. 2009;20(10):1633–50.
6. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet. 1999;353(9156):878–82.
7. Ioannidis G, Papaioannou A, Hopman WM, et al. Relation between fractures and mortality: results from the Canadian Multicentre Osteoporosis Study. CMAJ. 2009;181(5):265–71.
8. 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.
9. 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.
10. 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.
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. Johnell O, Kanis JA, Oden A, et al. Mortality after osteoporotic fractures. Osteoporos Int. 2004;15(1):38–42.
13. 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.
14. 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.
15. Laupacis A, Sackett DL, Roberts RS. Therapeutic priorities of Canadian internists. CMAJ. 1990;142(4):329–33.
16. Heller RF, Dobson AJ, Attia J, Page J. Impact numbers: measures of risk factor impact on the whole population from case-control and cohort studies. J Epidemiol Community Health. 2002;56(8):606–10.
17. Kreiger N, Tenenhouse A, Joseph L, et al. Research notes: the Canadian Multicentre Osteoporosis Study (CaMos): background, rationale, methods. Can J Aging. 1999;18(3):376–87. DOI: 10.1017/S0714980800009934.
18. Prior JC, Langsetmo L, Lentle BC, et al. Ten-year incident osteoporosis-related fractures in the population-based Canadian Multicentre Osteoporosis Study—comparing site and age-specific risks in women and men. Bone. 2015;71:237–43.
19. Hoeting JA, Madigan D, Raftery AE, Volinsky CT. Bayesian model averaging: a tutorial. Stat Sci. 1999;14(4):382–401.
20. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996;15(4):361–87.
21. van Buuren S, Groothuis-Oudshoorn K. MICE: multivariate imputation by chained equations in R. J Stat Softw. 2011;45(3):1–67.
22. Cumming G. Inference by eye: reading the overlap of independent confidence intervals. Stat Med. 2009;28(2):205–20.
23. 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.
24. Rozental TD, Branas CC, Bozentka DJ, Beredjiklian PK. Survival among elderly patients after fractures of the distal radius. J Hand Surg Br. 2002;27(6):948–52.
25. Sabesan VJ, Valikodath T, Childs A, Sharma VK. Economic and social impact of upper extremity fragility fractures in elderly patients. Aging Clin Exp Res. 2015;27(4):539–46.
26. Crockett K, Arnold CM, Farthing JP, et al. Bone strength and muscle properties in postmenopausal women with and without a recent distal radius fracture. Osteoporos Int. 2015;26(10):2461–9.
27. Edwards BJ, Song J, Dunlop DD, Fink HA, Cauley JA. Functional decline after incident wrist fractures—Study of Osteoporotic Fractures: prospective cohort study. BMJ. 2010;341:c3324.
28. Lawrence VA, Hilsenbeck SG, Noveck H, Poses RM, Carson JL. Medical complications and outcomes after hip fracture repair. Arch Int Med. 2002;162(18):2053–7.
29. Rosencher N, Vielpeau C, Emmerich J, Fagnani F, Samama CM; Escorte group. Venous thromboembolism and mortality after hip fracture surgery: the ESCORTE study. J Thromb Haemost. 2005;3(9):2006–14.
30. Huddleston JM, Gullerud RE, Smither F, et al. Myocardial infarction after hip fracture repair: a population-based study. J Am Geriatr Soc. 2012;60(11):2020–6.
31. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK. The components of excess mortality after hip fracture. Bone. 2003;32(5): 468–73.
32. 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.
33. Attia J, Page J, Heller RF, Dobson AJ. Impact numbers in health policy decisions. J Epidemiol Community Health. 2002;56(8):600–5.
34. Heller RF, Buchan I, Edwards R, Lyratzopoulos G, McElduff P, St Leger S. Communicating risks at the population level: application of population impact numbers. BMJ. 2003;327(7424):1162–5.
35. Abrahamsen B, Nielsen MF, Eskildsen P, Andersen JT, Walter S, Brixen K. Fracture risk in Danish men with prostate cancer: a nationwide register study. BJU Int. 2007;100(4):749–54.
36. Fischer U, Mono ML, Zwahlen M, et al. Impact of thrombolysis on stroke outcome at 12 months in a population: the Bern stroke project. Stroke. 2012;43(4):1039–45.
37. Gemmell I, Heller RF, Payne K, Edwards R, Roland M, Durrington P. Potential population impact of the UK government strategy for reducing the burden of coronary heart disease in England: comparing primary and secondary prevention strategies. Qual Saf Health Care. 2006;15(5):339–43.
38. Heller RF, Edwards R, McElduff P. Implementing guidelines in primary care: can population impact measures help? BMC Public Health. 2003;3:7.