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ORIGINAL ARTICLE

Predictors of imminent non-vertebral fracture in elderly women with osteoporosis, low bone mass, or a history of fracture, based on data from the population-based Canadian Multicentre Osteoporosis Study (CaMos)

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Abstract

Summary Using data from the Canadian Multicentre Osteoporosis Study, several risk factors predictive of imminent (2-year) risk of low-trauma non-vertebral fracture among high-risk women were identified, including history of falls, history of low-trauma fracture, poorer physical function, and lower *T* score. Careful consideration should be given to targeting this population for therapy.

Purpose Fracture risk assessment has focused on a long-term horizon and populations with a broad risk range. For elderly women with osteoporosis or low bone mass, or a history of fragility fractures ("high-risk women"), risk prediction over a shorter horizon may have greater clinical relevance.

Methods A repeated-observations design and data from the Canadian Multicentre Osteoporosis Study were employed. Study population comprised women aged ≥ 65 years with *T* score (total hip, femoral neck, spine) ≤ − 1.0 or prior fracture. Hazard ratios (HR) for predictors of low-trauma non-vertebral fracture during 2-year follow-up were estimated using multivariable shared frailty model.

Results The study population included 3228 women who contributed 5004 observations; 4.8% experienced low-trauma non-vertebral fracture during the 2-year follow-up. In bivariate analyses, important risk factors included age, back pain, history of falls, history of low-trauma fracture, physical function, health status, and total hip *T* score. In multivariable analyses, only four independent predictors were identified: falls in past 12 months (≥ 2 falls: HR = 1.9; 1 fall: HR = 1.5), low-trauma fracture in past 12 months (≥ 1 fracture: HR = 1.7), SF-36 physical component summary score (≤ 42.0: HR = 1.6), and total hip *T* score (≤ − 3.5: HR = 3.7; > − 3.5 to ≤ − 2.5: HR = 2.5; > − 2.5 to ≤ − 1: HR = 1.3).

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Conclusions Imminent risk of low-trauma non-vertebral fracture is elevated among high-risk women with a history of falls or low-trauma fracture, poorer physical function, and lower *T* score. Careful consideration should be given to identifying and targeting this population for therapy.

Keywords Osteoporosis · Fractures · Bone · Risk factors

Introduction

Fractures among the elderly are a major cause of morbidity, mortality, and healthcare costs, especially those involving the hip [1, 2]. Loss of cortical and trabecular bone mass—and resulting osteoporosis—with advancing age and enhanced bone fragility is widely considered to be the major cause of fragility fractures occurring after minimal trauma in older persons. A number of other risk factors (e.g., fracture history, falls history, risk factors for falls) have been identified via risk assessment equations such as the Fracture Risk Assessment tool, the QFracture algorithm, and Garvan's fracture risk calculator, as well as other published models [3–11]. With two exceptions [7, 10], however, evaluation of fracture risk has focused on a longer-term horizon (e.g., 10 years), populations with a broad age and risk range, or populations that are institutionalized.

For populations comprising women of advanced age with established osteoporosis or low bone mass, or a history of fragility fractures (collectively, "high-risk women"), risk prediction over a shorter horizon (e.g., 1 year or 2 years) may have greater clinical relevance and thus may be more pertinent to patients, physicians, and payers. Moreover, the relative importance of age, bone mineral density (BMD), and other time-dependent risk factors (e.g., fracture history or falls history) may be different in the prediction of imminent fracture among this high-risk population of women versus the prediction of long-term fracture among a general population of women.

To date, only one published study has evaluated risk factors for imminent fracture in elderly high-risk women [7]. In this evaluation, data from the Study of Osteoporotic Fractures (SOF) were used to identify factors contributing to the 1-year risk of hip fracture and non-vertebral fracture, respectively, among osteoporotic women aged ≥ 65 years. Because results based on data from the SOF may not be generalizable to other populations, additional evidence from other data sources is needed to improve our understanding of the relationship between risk factors and fracture risk among high-risk women. We therefore evaluated important determinants of imminent low-trauma non-vertebral fracture among elderly women with osteoporosis, low bone mass, or a fracture history using data from the Canadian Multicentre Osteoporosis Study (CaM*os*).

Methods

Study design and data source A retrospective repeated-measures design and data from the CaM*os*, an ongoing population-based prospective cohort study, were employed. The original cohort, recruited from 1995 to 1997, included 9423 men (31%) and women (69%) aged ≥ 25 years who were non-institutionalized and lived within 50 km of a CaM*os* research center in Vancouver, Calgary, Saskatoon, Toronto, Hamilton, Kingston, Quebec, Halifax, or St. John's. The sampling framework consisted of randomly generated lists of non-institutionalized residential telephone subscribers in the nine study sites, who collectively represented 42% of all Canadian residents. CaM*os* has served as the basis of a number of studies on risk factors for fractures and bone loss in women, as well as many other studies concerning osteoporosis and aging, and is described in detail elsewhere [12–25].

CaM*os* participants underwent detailed assessments at the time of recruitment (i.e., baseline) and every 5 years thereafter to collect information—via interviewer-administered questionnaires and examinations—on various measures including socio-demographics, medical conditions, fracture history, falls history, family history, medication use, dietary intake, lifestyle data, quality of life, height and weight, and BMD (from cross-calibrated dual x-ray absorptiometry scanners). For participants aged ≥ 50 years, radiographs of the lateral lumbar and thoracic spine were also collected. In each of the intervening years, participants completed a mailed questionnaire regarding fractures, hospitalizations, and the use of medications for bone health. Data from three completed exams—spanning approximately 14 years—were available at initiation of this study.

The current study employed data from the Year 5 and the Year 10 Exams. Observations from the Baseline Exam were not considered since in that questionnaire, data on falls history were limited to the prior 1-month period, unlike the Year 5 and Year 10 Exams, which captured falls during the prior 1-year period. A schematic of the study design is set forth in the supplementary material (Online Supplement, Figure 1).

Study population The study population comprised women, who at the Year 5 Exam or Year 10 Exam, were aged ≥ 65 years and had osteoporosis (*T* score ≤ − 2.5 at the total

hip, femoral neck, or spine), low bone mass (*T* score > − 2.5 to ≤ − 1.0 at the total hip, femoral neck, or spine), or a history of fracture. For each woman in the study population, each exam with a qualifying *T* score or fracture history was considered as a separate observation in analyses. Participants thus could contribute up to two observations in total, one per qualifying exam, and all observations were pooled for analyses. A detailed description of CaM*os* methodology used to measure BMD and derive *T* scores has been published previously [17].

Study outcome The study outcome was incident low-trauma non-vertebral fracture of selected skeletal sites and was ascertained beginning on the day after the date of each qualifying exam and ending 730 days later, on the date of loss to follow-up, or on the date of death, whichever occurred earlier. Selected non-vertebral sites included the ankle, arm (forearm/wrist, upper), clavicle, elbow, foot, hand, hip, leg (upper/lower), knee, pelvis, and rib as well as other miscellaneous sites (e.g., shoulder blade). An alternative definition for low-trauma non-vertebral fracture that excluded fractures of the hand and foot was considered in sensitivity analyses.

Fractures were identified in the CaM*os* via yearly postal questionnaires and/or questionnaires administered at scheduled interviews. Structured interview confirmation of postal questionnaires determined the fracture-specific date, site, circumstances, trauma, and management. Independent medical records were obtained for 78% of all incident fractures, and all available x-ray reports were used to classify/confirm fractures by body site. Only fractures that were confirmed were employed in analyses described herein.

Risk factors Potential predictors of fracture were evaluated at each qualifying exam, and included variables classified within the following categories: demographics (age), BMD, anthropometric measures (e.g., weight, height), history of falls (i.e., within 12 months of exam), history of low-trauma non-vertebral/vertebral fracture (i.e., within 12 months of exam), lifestyle measures (e.g., smoking, alcohol use), medical history (e.g., selected comorbidities), medication use and duration of medication use (e.g., bisphosphonates, corticosteroids, hormone therapy), cognitive function (e.g., MMSE score), physical activity (e.g., ADLs), and health-related quality of life (HRQL) (e.g., the 36-Item Short Form Survey [SF-36], self-rated health). The SF-36 measures HRQL across eight domains (physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, general health), and includes summary measures for physical HRQL (physical component summary) and emotional HRQL (mental component summary) [26]. Scores for each domain range from 0 (lowest/worst possible level of functioning) to 100 (highest/best possible level of functioning).

Age, BMD, anthropometric measures, history of falls during the prior 12 months (self-reported), history of fractures during the prior 12 months (self-reported), cognitive function, and HRQL were ascertained on the date of the exam. Medical history was based on questions asked at the exam: "Have you ever been told by a doctor that you have any of the following conditions?" Medication use was based on questions asked at the exam: "Since your last interview, have you taken any of the following medications regularly or daily?" Duration of medication use was based on the follow-up question: "If yes, for approximately how many months total have you taken it?" A list of candidate predictors, and corresponding definitions, is set forth in the supplementary material (Online Supplement, Table).

Statistical analyses Crude (unadjusted) risks of 2-year low-trauma non-vertebral fracture were estimated for participants stratified by each potential predictor separately, as were corresponding (unadjusted) hazard ratios using a shared frailty/mixed-effects model (an extension of the Cox proportional hazards model that accounts for intra-cluster [i.e., intra-subject dependencies]). Potential predictors that were continuous in nature were also evaluated in a multi-level context; thresholds separating categories for a given predictor were defined initially based on the quintiles of their distributions, and some thresholds were subsequently modified based on distributional properties of the empirical data and thresholds previously employed in published clinical research.

A multivariable shared frailty/mixed-effects model was employed to identify independent predictors of low-trauma non-vertebral fracture. All factors with a *P* value < 0.10 in unadjusted analyses were initially included in the multivariable model, except for those that were redundant (i.e., measured the same attribute, such as physical function); grouped multi-level factors were included if any level had a *P* value < 0.10. Variables that were no longer important predictors in a multivariable context were excluded from the final model. The presence of multicollinearity, hazards assumptions, and model overfitting were evaluated using published methods [27, 28]. SAS v9.4 for Windows was used for all statistical analyses.

Results

The study population included 3228 women aged ≥ 65 years with osteoporosis, low bone mass, or a history of fracture who contributed 5004 observations; participants selected for analyses described herein represented approximately 83% of the total population of women aged ≥ 65 years in the CaM*os* (Table 1). Among study participants (i.e., at the time of the exams), 46% were aged 65–74 years, 44% were aged 75–84 years, and 10% were aged ≥ 85 years;

Table 1 Baseline characteristics of women aged ≥ 65 years with osteoporosis, low bone mass, or history of fracture in CaM*os*

Variable	Study population[a] (*N* = 5004)
Age, %	
65–74	46.3
75–84	43.7
≥85	10.0
Falls in past 12 months, %	
0	70.3
1	19.2
≥2	10.5
Missing	0.1
Fractures (low-trauma) in past 12 months, %	
Yes	3.8
No	96.2
Physical activity, %	
Time spent walking in typical week in last 6 months	
None/less than 1 h	18.4
Between 1 and 5 h/between 6 and 10 h	72.1
Between 11 and 20 h/more than 20 h	9.5
Missing	0.1
Moderate activity	
Never/0.5–1 h	7.2
2–3 h/4–6 h	32.7
7–10 h/11–20 h	38.1
21–30 h/31 h +	21.9
Missing	0.1
MMSE questionnaire, %	
Severe (< 10)	0.1
Moderate (10–18)	0.6
Mild (19–23)	3.1
Normal (≥ 24)	73.2
Missing	23.0
SF-36, %	
In general, rate health	
Excellent	8.8
Very Good	39.6
Good	37.9
Fair/poor	13.5
Missing	0.2
Compared to 1 yr ago, rate health	
Much better than one year ago/Somewhat better now than one year ago	14.5
About the same/Somewhat worse now than one year ago	84.1
Much worse now than one year ago	1.2
Missing	0.1
Physical	
Quintile 1 (7.138 to 32.889)	19.9
Quintile 2 (32.903 to 42.012)	19.9
Quintile 3 (42.013 to 48.289)	19.9
Quintile 4 (48.300 to 53.087)	19.9
Quintile 5 (53.096 to 68.585)	19.9
Missing	0.6
Mental	
Quintile 1 (13.241 to 49.434)	19.9
Quintile 2 (49.457 to 55.178)	19.9
Quintile 3 (55.179 to 58.207)	19.9
Quintile 4 (58.210 to 60.885)	19.9
Quintile 5 (60.890 to 73.853)	19.9
Missing	0.6
Total hip *T* score, %	
≤ − 3.5	2.3
≤ − 2.5 to > − 3.5	12.3
≤ − 1 to > − 2.5	49.3
> − 1	19.9
Missing	16.2

MMSE, Mini–Mental State Examination

[a] Each exam was considered as a separate observation in analyses; 3228 women contributed 5004 observations by meeting selection criteria at exams: osteoporosis, *n* = 2335; low bone mass, *n* = 2627; fracture history (no osteoporosis/low bone mass), *n* = 42

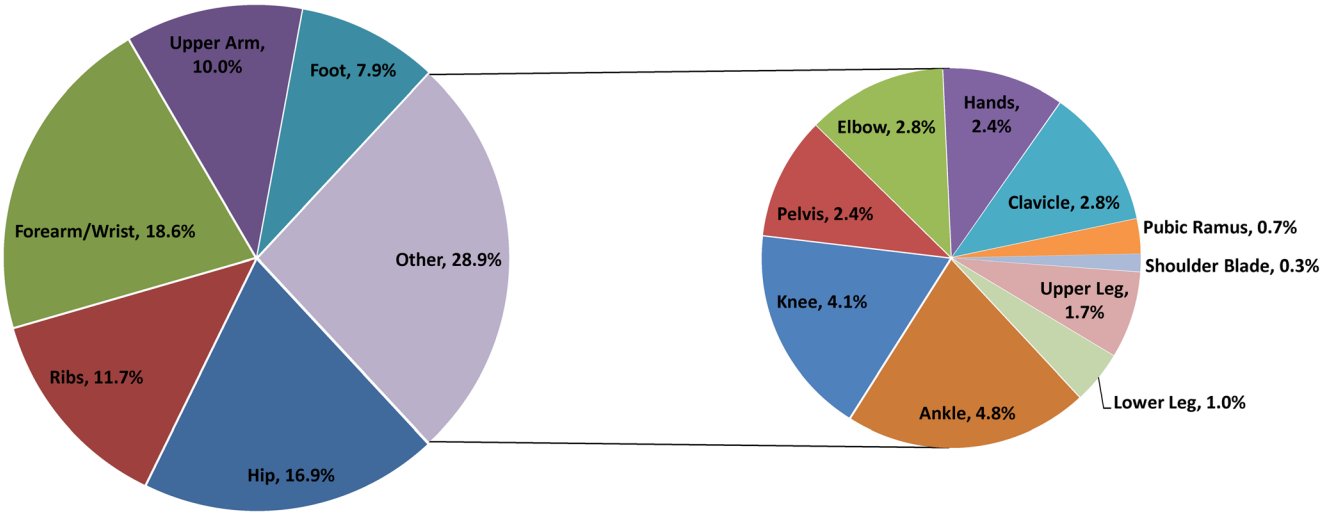


Fig. 1 Distribution of low-trauma non-vertebral fractures during 2-year follow-up period among women aged ≥ 65 years with osteoporosis, low bone mass, or history of fracture in CaMos, by site of fracture

30% had experienced ≥ 1 fall and 5% had experienced ≥ 1 low-trauma fracture during the prior 12-month period; and 47% had osteoporosis based on *T* score ≤ − 2.5 at the total hip, femoral neck, or spine. Participants were generally involved in moderate activity, and most had a normal cognitive status and were in good/excellent self-reported health.

During the 2-year follow-up period, 4.8% of study participants experienced a low-trauma non-vertebral fracture; the forearm/wrist (19%), hip (17%), ribs (12%), and upper arm (10%) were the most common sites of fracture (Fig. 1). In bivariate analyses, many risk factors were found to be important in predicting 2-year risk of low-trauma non-vertebral fracture, including (but not limited to) age, back pain, history of falls, history of low-trauma fracture, physical function/performance, health status, and total hip *T* score (Online Supplement, Table).

In multivariable analyses, only four risk factors were found to be independent predictors of 2-year low-trauma non-vertebral fracture: number of falls in the past 12 months (≥ 2 falls: HR = 1.9, $P = 0.001$; 1 fall: HR = 1.5, $P = 0.014$), low-trauma fracture in the past 12 months (≥ 1 fracture: HR = 1.7, $P = 0.055$), SF-36 physical component summary score (≤ 42.0: HR = 1.6, $P < 0.001$), and total hip *T* score (≤ − 3.5: HR = 3.7, $P < 0.001$; > − 3.5 to ≤ − 2.5: HR = 2.5, $P < 0.001$; > − 2.5 to ≤ − 1: HR = 1.3, $P = 0.187$). Model discrimination based on the *c*-statistic was 0.65 (0.61–0.69) (Table 2). Multicollinearity between independent variables, non-proportional hazards, and overfitting were determined not to be significant. Results were largely the same when considering the alternative definition of low-trauma non-vertebral fracture (i.e., when excluding fractures of the hand and foot).

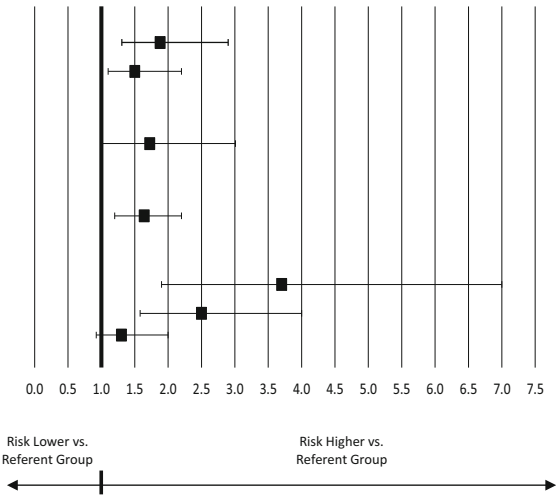
Discussion

using data from women aged ≥ 65 years with osteoporosis, low bone mass, or history of fracture in the population-based CaM*os*, we identified several clinical characteristics predictive of low-trauma non-vertebral fracture within a 2-year follow-up period. In bivariate analyses, risk factors that were found to be important in predicting 2-year risk of low-trauma non-vertebral fracture included (but were not limited to) age, back pain, history of falls, history of low-trauma fracture, physical function/performance, health status, and total hip *T* score. In multivariable analyses, however, only falls history, fracture (low-trauma) history, poorer physical function/performance, and lower BMD (i.e., indicating osteoporosis) were found to be important independent predictors of imminent fracture in this population. We note that although three of the four predictors (falls history, fracture history, and BMD) may be easily employed in clinical practice to assess imminent fracture risk for an individual, the use of the SF-36 physical component summary score is more challenging. Although not formally evaluated, we would anticipate that other measures of physical function/performance (e.g., timed up and go test, chair stand, walking speed) would be highly correlated with the SF-36 physical component summary score and might serve as a reasonable replacement for use in clinical practice.

In the aforementioned SOF-based evaluation, which focused on 1-year non-vertebral fracture in women aged ≥ 65 years with osteoporosis, risk factors found to be independent predictors and their relative importance (i.e., their hazard ratios) in predicting risk were largely comparable with those found in the current study [7]. History of falls, history of fracture, poorer physical function/performance, and low total

Table 2 Multivariate analyses of 2-year low-trauma non-vertebral fracture risk among women aged ≥ 65 years with osteoporosis, low bone mass, or history of fracture in CaM*os* *c*-statistic (95% CI): 0.65 (0.61–0.69)

Risk Factors	No. of Obs.	No. of Fx	% Fx	HR	95% CI LL	95% CI UL	*P*-value
Falls in Past 12 Months							
≥2	524	41	7.8	1.9	1.3	2.9	0.001
1	959	59	6.2	1.5	1.1	2.2	0.014
0	3,518	139	4.0	REF			
Fractures (low-trauma) in Past 12 Months							
≥1	190	22	11.6	1.7	1.0	3.0	0.055
0	4,814	218	4.5	REF			
SF-36 Physical Component Summary							
Quintile 1 - Quintile 2 (7.138 to 42.012)	1,989	131	6.6	1.6	1.2	2.2	<0.001
Quintile 3 - Quintile 5 (42.013 to 68.585)	2,984	106	3.6	REF			
Total Hip T-Score							
≤ -3.5	116	14	12.1	3.7	1.9	7.0	<0.001
≤ -2.5 to > -3.5	616	51	8.3	2.5	1.6	4.0	<0.001
≤ -1 to > -2.5	2,467	100	4.1	1.3	0.9	2.0	0.187
> -1	996	31	3.1	REF			



CI, confidence interval; *Fx*, fracture; *HR*, hazard ratio; *LL*, lower limit; *REF*, referent group; *UL*, upper limit

Candidate risk factors (Online Supplement - Table) with a p-value <0.10 in unadjusted analyses, except for those that were redundant (i.e., measured the same attribute), were considered initially for inclusion in the multivariable model. Variables that were no longer important predictors in a multivariable context were excluded from the final model

hip *T* score (i.e., ≤ − 2.5 and ≤ − 3.0 in the current study and SOF study, respectively) were associated with higher future fracture risk in both studies. Predictors common to both analytic files that were found to be important in the SOF study but not the current CaM*os* study were age, smoking status, and a composite for Parkinson's/stroke. However, in the SOF study, fracture risk was elevated only among those aged ≥ 85 years (HR = 1.4 [vs. 65–74 years], $P = 0.095$), and the hazard ratio for smoking status (per 10 pack-years) was relatively small (HR = 1.1). Moreover, when forcing neuromuscular disease/stroke into the CaM*os* model, the corresponding hazard ratio (HR = 1.4, $P = 0.150$) was similar to that in the SOF model (HR = 1.3, $P = 0.033$). We suspect the lack of statistical significance in the CaM*os* study is due to the relatively small numbers of participants with a history of neuromuscular disease/stroke and the importance of physical function/performance as a predictor of low-trauma non-vertebral fracture. We note that the results of the present evaluation are also largely comparable with those based on analyses of data from the Framingham Osteoporosis Study (FOS)—poster presentation at American Society for Bone and Mineral Research—which included 2778 women aged ≥ 65 years with osteoporosis, low bone mass, or a fracture history [29]. In analyses of data from the FOS, history of fracture (HR = 1.4, $P = 0.05$) and *T* score (≤ − 2.5 [vs. > − 1.0]: HR = 2.0, $P < 0.001$) were reported to be significant predictors of non-vertebral fracture over the 2-year follow-up period.

As in the prior evaluation using SOF data, the *c*-statistic in the current study was low (0.65 [0.61–0.69] vs. 0.62 [0.59–0.65] in the SOF-based study) and thus model discrimination was poor, although model discrimination is not the only indicator of the clinical utility of a model [30–34]. It is likely that the low *c*-statistic is due to the heterogeneous definition of non-vertebral fractures and the fact that risk factors for various types of osteoporotic fractures may differ [35–38]. For example, more active women appear to be at higher risk of wrist fracture, as compared with frail, inactive women, who are at higher risk of hip fracture [37]. Thus, combining the various types of low-trauma non-vertebral fracture into a single outcome measure for a predictive model would be expected to lower its discriminatory power.

This study has numerous strengths. The CaM*os* participants were selected at random from the population and represent an age-, sex-, and region-specific sample of the Canadian population. For the majority of the CaM*os* participants, data on important risk factors for fracture were available at multiple exams, thereby increasing the size of the denominator population and the number of events that could be considered in analyses. The CaM*os* participants were followed prospectively for fractures after each exam, and quality control was routinely performed to confirm/classify fractures and to ensure longitudinal reliability of risk factors (including BMD measurements). This study also has a few limitations. While the CaM*os* participants are representative of their respective regions, caution should be exercised in generalizing study results to other populations and settings. Although the CaM*os* participants underwent exams every 3–5 years to collect information on various measures, not all risk factors were ascertained at each exam. Moreover, it is not

possible to capture potentially important changes in time-dependent risk factors that occurred between exams or prior to the occurrence of fracture during a given interval. Practice patterns (e.g., use of menopausal hormone therapy and bisphosphonates), technology, and other largely unobservable/unquantifiable factors may have changed over the period of observation in the CaM*os*, which could impact measurements of risk factors over time and estimated relationships with fracture. Although the 2-year timeframe gives our model several advantages over those with longer timeframes, it does have the disadvantage of permitting a greater role for chance in determining the occurrence of fractures, which may have detracted somewhat from the discriminatory power of our models. For those who died while participating in CaM*os*, specific dates of death were not available; thus, death was not treated as a competing risk in base-case analyses [39]. However, in a sensitivity analysis in which year of death was employed to define a competing risk, results were largely the same.

In conclusion, imminent fracture risk among elderly women with osteoporosis, low bone mass, or a history of fracture is higher among those with a history of falls, history of low-trauma fracture, poorer physical function/performance by SF-36, and/or lower total hip BMD. Careful consideration should be given to this population and frequently evaluating their fracture risk, and targeting those at elevated risk for appropriate therapy based on the benefits and risks associated with such therapy.

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Authors' contributions Authorship was designated based on the guidelines promulgated by the International Committee of Medical Journal Editors (2004). All persons who meet criteria for authorship are listed as authors on the title page. The contribution of each of these persons to this study is as follows: (1) conception and design (all authors), acquisition of data (all authors except Barron, Shyta, Silvia, Weycker), and analysis or interpretation of data (all authors) and (2) preparation of manuscript (Barron, Shyta, Silvia, Weycker) and critical review of manuscript (all authors). The study sponsor reviewed the study protocol and study manuscript; data management, processing, and analyses were conducted by PAI, and all final analytic decisions were made by study investigators. All authors have read and approved the final version of the manuscript.

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Compliance with ethical standards

Conflicts of interest Rich Barron was employed by Amgen Inc. during the conduct of this study and owns stock in Amgen Inc. Derek Weycker and Amanda Silvia are employed by PAI; Erinda Shyta was employed by PAI during the conduct of this study. Jonathan D. Adachi has grants and personal fees with Amgen Inc. and personal fees with Eli Lilly. K. Shawn Davison has speaker honoraria with Amgen Inc. David A. Hanley has a research grant and speaker honoraria with Amgen Inc. Robert G. Josse has consultancy fees and a speaking honoraria with Amgen Inc. and Merck. Stephanie M. Kaiser has consultancy fees and speaking honoraria with Amgen Inc. Christopher S. Kovacs has an honorarium with Amgen Inc. Suzanne N. Morin has research grants with Amgen Inc. and Merck. Tanveer Towheed has an honorarium and speaker fees with Amgen Inc. Tassos P. Anastassiades, Claudie Berger, David Goltzman, George Ioannidis, Stuart A. Jackson, William D. Leslie, Alexandra Papaioannou, and Jerilynn C. Prior have no conflicts of interest for this work.

References

1. Cooper C (1996) Epidemiology and definition of osteoporosis. In: Compston JE (ed) Osteoporosis. New perspectives on causes, prevention, and treatment. Royal College of Physicians of London, London, pp 1–10
2. Weycker D, Li X, Barron R, Bornheimer R, Chandler D (2016) Hospitalizations for osteoporosis-related fractures: economic costs and clinical outcomes. Bone Rep 5:186–191
3. Ensrud KE, Lui LY, Taylor BC, Schousboe JT, Donaldson MG, Fink HA, Cauley JA, Hillier TA, Browner WS, Cummings SR, Study of Osteoporotic Fractures Research Group (2009) A comparison of prediction models for fractures in older women: is more better? Arch Intern Med 169(22):2087–2094
4. Kanis JA, Oden A, Johnell O, Johansson H, de Laet C, Brown J, Burckhardt P, Cooper C, Christiansen C, Cummings S, Eisman JA, Fujiwara S, Glüer C, Goltzman D, Hans D, Krieg MA, la Croix A, McCloskey E, Mellstrom D, Melton LJ, Pols H, Reeve J, Sanders K, Schott AM, Silman A, Torgerson D, van Staa T, Watts NB, Yoshimura N (2007) The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. Osteoporos Int 18(8):1033–1046
5. Langsetmo L, Nguyen TV, Nguyen ND, Kovacs CS, Prior JC, Center JR, Morin S, Josse RG, Adachi JD, Hanley DA, Eisman JA, the Canadian Multicentre Osteoporosis Study Research Group (2011) Independent external validation of nomograms for predicting risk of low-trauma fracture and hip fracture. CMAJ 183(2):E107–E114
6. Hippisley-Cox J, Coupland C (2012) Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. BMJ 344:e3427
7. Weycker D, Edelsberg J, Barron R, Atwood M, Oster G, Crittenden DB, Grauer A (2017) Predictors of near-term fracture in osteoporotic women aged ≥65 years, based on data from the study of osteoporotic fractures. Osteoporos Int 28(9):2565–2571
8. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV (2008) Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks. Osteoporos Int 19(10):1431–1444
9. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV (2007) Development of a nomogram for individualizing hip fracture risk in men and women. Osteoporos Int 18(8):1109–1117
10. Bonafede M, Shi N, Barron R, Li X, Crittenden DB, Chandler D (2016) Predicting imminent risk of fracture in patients aged 50 or older with osteoporosis using US claims data. Arch Osteoporos 11(1):26
11. Ioannidis G, Jantzi M, Bucek J, Adachi JD, Giangregorio L, Hirdes J, Pickard L, Papaioannou A (2017) Development and validation of the Fracture Risk Scale (FRS) that predicts fracture over a 1-year time period in institutionalised frail older people living in Canada: an electronic record-linked longitudinal cohort study. BMJ Open 7: e016477. https://doi.org/10.1136/bmjopen-2017-016477

12. Berger C, Langsetmo L, Joseph L, Hanley DA, Davison KS, Josse R, Kreiger N, Tenenhouse A, Goltzman D, and the Canadian Multicentre Osteoporosis Study Research Group (2008) Bone mineral change as a function of age in women and men and association with the use of antiresorptive agents. CMAJ 178(13):1660–1668
13. Langsetmo LA, Morin S, Richards JB, Davison KS, Olszynski WP, Prior JC, Josse R, Goltzman D, the CaMos Research Group (2009) Effectiveness of antiresorptives for the prevention of nonvertebral low-trauma fractures in a population-based cohort of women. Osteoporos Int 20(2):283–290
14. Berger C, Langsetmo L, Joseph L, Hanley DA, Davison KS, Josse RG, Prior JC, Kreiger N, Tenenhouse A, Goltzman D, the CaMos Research Group (2009) Association between change in BMD and fragility fracture in women and men. J Bone Miner Res 24(2):361–370
15. Ioannidis G, Papaioannou A, Hopman WM, Akhtar-Danesh N, Anastassiades T, Pickard L, Kennedy CC, Prior JC, Olszynski WP, Davison KS, Goltzman D, Thabane L, Gafni A, Papadimitropoulos EA, Brown JP, Josse RG, Hanley DA, Adachi JD (2009) Relation between fractures and mortality: results from the Canadian Multicentre Osteoporosis Study. CMAJ 181(5): 265–271
16. Langsetmo L, Goltzman D, Kovacs CS, Adachi JD, Hanley DA, Kreiger N, Josse R, Papaioannou A, Olszynski WP, Jamal SA, the CaMos Research Group (2009) Repeat low-trauma fractures occur frequently among men and women who have osteopenic BMD. J Bone Miner Res 24(9):1515–1522
17. Berger C, Goltzman D, Langsetmo L, Joseph L, Jackson S, Kreiger N, Tenenhouse A, Davison KS, Josse RG, Prior JC, Hanley DA, CaMos Research Group (2010) Peak bone mass from longitudinal data: implications for the prevalence, pathophysiology, and diagnosis of osteoporosis. J Bone Miner Res 25(9):1948–1957
18. Langsetmo L, Morin S, Kovacs CS, Kreiger N, Josse R, Adachi JD, Papaioannou A, Goltzman D, Hanley DA, Olszynski WP, Prior J, Jamal SA (2010) Determining whether women with osteopenic bone mineral density have low, moderate, or high clinical fracture risk. Menopause 17(5):1010–1016
19. Langsetmo L, Hanley DA, Prior JC, Barr SI, Anastassiades T, Towheed T, Goltzman D, Morin S, Poliquin S, Kreiger N, for the CaMos Research Group (2011) Dietary patterns and incident low-trauma fractures in postmenopausal women and men aged ≥ 50 y: a population-based cohort study. Am J Clin Nutr 93(1): 192–199
20. Fraser LA, Ioannidis G, Adachi JD, Pickard L, Kaiser SM, Prior J, Brown JP, Hanley DA, Olszynski WP, Anastassiades T, Jamal S, Josse R, Goltzman D, Papaioannou A, CaMos Research Group (2011) Fragility fractures and the osteoporosis care gap in women: the Canadian Multicentre Osteoporosis Study. Osteoporos Int 22(3):789–796
21. Fraser LA, Langsetmo L, Berger C, Ioannidis G, Goltzman D, Adachi JD, Papaioannou A, Josse R, Kovacs CS, Olszynski WP, Towheed T, Hanley DA, Kaiser SM, Prior J, Jamal S, Kreiger N, Brown JP, Johansson H, Oden A, McCloskey E, Kanis JA, Leslie WD, CaMos Research Group (2011) Construction of a FRAX® model for the assessment of fracture probability in Canada and implications for treatment. Osteoporos Int 22(3): 817–827
22. Fraser LA, Langsetmo L, Berger C, Ioannidis G, Goltzman D, Adachi JD, Papaioannou A, Josse R, Kovacs CS, Olszynski WP, Towheed T, Hanley DA, Kaiser SM, Prior J, Jamal S, Kreiger N, Brown JP, Johansson H, Oden A, McCloskey E, Kanis JA, Leslie WD, CaMos Research Group (2011) Fracture prediction and calibration of a Canadian FRAX® tool: a population-based report from CaM*os*. Osteoporos Int 22(3):829–837
23. Langsetmo L, Berger C, Kreiger N, Kovacs CS, Hanley DA, Jamal SA, Whiting SJ, Genest J, Morin SN, Hodsman A, Prior JC, Lentle B, Patel MS, Brown JP, Anastasiades T, Towheed T, Josse RG, Papaioannou A, Adachi JD, Leslie WD, Davison KS, Goltzman D, and the CaMos Group (2013) Calcium and vitamin D intake and mortality: results from the Canadian Multicentre Osteoporosis Study (CaM*os*). J Clin Endocrinol Metab 98(7): 3010–3018
24. McCloskey EV, Odén A, Harvey NC, Leslie WD, Hans D, Johansson H, Barkmann R, Boutroy S, Brown J, Chapurlat R, Elders PJM, Fujita Y, Glüer CC, Goltzman D, Iki M, Karlsson M, Kindmark A, Kotowicz M, Kurumatani N, Kwok T, Lamy O, Leung J, Lippuner K, Ljunggren Ö, Lorentzon M, Mellström D, Merlijn T, Oei L, Ohlsson C, Pasco JA, Rivadeneira F, Rosengren B, Sornay-Rendu E, Szulc P, Tamaki J, Kanis JA (2015) A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. J Bone Miner Res 31(5):940–948
25. Prior JC, Langsetmo L, Lentle BC, Berger C, Goltzman D, Kovacs CS, Kaiser SM, Adachi JD, Papaioannou A, Anastassiades T, Towheed T, Josse RG, Brown JP, Leslie WD, Kreiger N, CaMoS Research Group.(2015) 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 71C:237–243
26. RAND Health (2018) RAND Medical Outcomes Study, 36-Item Short Form Survey (SF-36). Available at: https://www.rand.org/health/surveys_tools/mos/36-item-short-form.html. Accessed on: 26 April 2018
27. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS (2008) Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 27(2):157–172
28. Allison PD (1995) Survival analysis using the SAS system: a practical guide. SAS Institute Inc., Cary, p 292
29. Hannan MT, Weycker D, McLean RR, Sahni S, Travison TG, Bornheimer R, Dufour AB, Barron R, Kiel DP (2016) Predictors of imminent risk of non-vertebral fracture in older women: The Framingham Osteoporosis Study. Presented at the ASBMR 2016 Annual Meeting, Atlanta, GA, September 16–19, 2016. Poster #MO0232. Available at: http://www.asbmr.org/education/AbstractDetail?aid=d660a55e-0dba-4847-83cc-03849411de19
30. Cook NR, Buring JE, Ridker PM (2006) The effect of including C-reactive protein in cardiovascular risk prediction models for women. Ann Intern Med 145(1):21–29
31. Cook NR (2007) Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation 115(7): 928–935
32. Cook NR (2008) Comments on evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 27(2):191–195
33. Cook NR (2008) Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. Clin Chem 54(1):17–23
34. Ridker PM, Buring JE, Rifai N, Cook NR (2007) Development and validation of improved algorithms for the assessment of global cardiovascular risk in women. JAMA 297(6):611–619
35. Nguyen TV, Center JR, Sambrook PN, Eisman JA (2001) Risk factors for proximal humerus, forearm, and wrist fractures in elderly men and women: the Dubbo Osteoporosis Epidemiology Study. Am J Epidemiol 153(6):587–595
36. Oyen J, Brudvik C, Gjesdal CG, Tell GS, Lie SA, Hove LM. (2011) Osteoporosis as a risk factor for distal radial fractures: a case-control study. J Bone Joint Surg Am 93(4):348–356

37. Silman AJ (2003) Risk factors for Colles' fracture in men and women: results from the European Prospective Osteoporosis Study. Osteoporos Int 14(3):213–218
38. Hasselman CT, Vogt MT, Stone KL, Cauley JA, Conti SF (2003) Foot and ankle fractures in elderly white women. Incidence and risk factors. J Bone Joint Surg Am 85-A(5):820–824
39. Pencina MJ, D'Agostino RB Sr, Larson MG, Massaro JM, Vasan RS (2009) Predicting the 30-year risk of cardiovascular disease: the Framingham Heart Study. Circulation 119(24):3078–3084