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Effect of co-morbidities on fracture risk: Findings from the Global Longitudinal Study of Osteoporosis in Women (GLOW)

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Abstract

Introduction—Greater awareness of the relationship between co-morbidities and fracture risk may improve fracture-prediction algorithms such as FRAX.

Materials and methods—We used a large, multinational cohort study (GLOW) to investigate the effect of co-morbidities on fracture risk. Women completed a baseline questionnaire detailing past medical history, including co-morbidity history and fracture. They were re-contacted annually

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to determine incident clinical fractures. A co-morbidity index, defined as number of baseline co-morbidities, was derived. The effect of adding the co-morbidity index to FRAX risk factors on fracture prevention was examined using chi-squared tests, the May-Hosmer test, c index and comparison of predicted versus observed fracture rates.

Results—Of 52,960 women with follow-up data, enrolled between October 2006 and February 2008, 3224 (6.1%) sustained an incident fracture over 2 years. All recorded co-morbidities were significantly associated with fracture, except for high cholesterol, hypertension, celiac disease, and cancer. The strongest association was seen with Parkinson's disease (age-adjusted hazard ratio [HR]: 2.2; 95% CI: 1.6–3.1; $P<0.001$). Co-morbidities that contributed most to fracture prediction in a Cox regression model with FRAX risk factors as additional predictors were: Parkinson's disease, multiple sclerosis, chronic obstructive pulmonary disease, osteoarthritis, and heart disease.

Conclusion—Co-morbidities, as captured in a co-morbidity index, contributed significantly to fracture risk in this study population. Parkinson's disease carried a particularly high risk of fracture; and increasing co-morbidity index was associated with increasing fracture risk. Addition of co-morbidity index to FRAX risk factors improved fracture prediction.

Keywords

Fracture risk; Co-morbidities; Parkinson's disease; Multiple sclerosis; FRAX

1. Introduction

Since its launch, the fracture-prediction algorithm, FRAX, has been in constant evolution to improve its predictive capacity internationally [1]. It has been suggested that further collection of information regarding co-morbidities may be helpful in this process. At present, the investigator is asked to provide information on the presence of rheumatoid arthritis, and to consider whether a number of conditions associated with "secondary osteoporosis" are present. Examples given are inflammatory bowel disease, insulin-dependent diabetes, and diseases associated with reduced mobility, such as stroke and Parkinson's disease. However, a number of other co-morbidities have been shown to be associated with fracture. For example, some papers have reported an excess risk of cardiovascular disease among patients with low bone density [2,3]. The cause of this association is likely to be multifactorial, representing a combination of the disease process itself (ongoing inflammatory process and sex hormone deficiency) and lifestyle factors (poor mobility and tobacco use). Other studies suggest that there is an increased risk of fracture among patients with respiratory disease that cannot be explained by steroid use alone [4,5]; while other co-morbidities, such as Parkinson's disease, may be associated with a significantly increased risk of falling.

We used a large, multinational cohort study to investigate the size of the effect of single co-morbidities on fracture risk, and specifically to investigate whether the number of co-morbidities present might also be an important determinant of fracture risk. Finally, we also considered whether incorporation of further information on medical history by means of generation of a 'co-morbidity index' might improve fracture prediction by the FRAX algorithm.

2. Material and methods

2.1. Setting

GLOW is an observational cohort study that is being conducted in physician practices at 17 sites in 10 countries (Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Spain, U.K., and U.S.). These sites are located in major population centers. Clinical investigators at each of the 17 sites constitute the GLOW Scientific Advisory Board and are responsible for the management of the study. Details of the study design and methods have been previously described [6]. In brief, practices typical of each region were recruited through primary care networks organized for administrative, research, or educational purposes, or by identifying all physicians in a geographic area. Physician networks included regional health-system-owned or managed practices, health maintenance organizations, independent practice associations, and other primary care practice networks. Networks established for the purpose of general medical research were only used if they were not established exclusively for osteoporosis research and did not consist primarily of physicians whose primary focus was academic. Each study site obtained ethics committee approval to conduct the study in the specific location.

2.2. Definitions

Primary care physicians were defined as those who spent most of their time providing primary healthcare to patients, and included internists, family practitioners, and general practitioners. If the physician network or study area included more eligible physicians than were required to recruit a sufficient number of patients, a random sample of those physicians within the network or study was invited. Each practice provided a list of the names and addresses of women aged 55 years and older who had been attended by their physician in the past 24 months. Sampling was stratified by age to ensure that two thirds consisted of women 65 years of age and older. In each practice, we recruited from all eligible women aged ≥65 years and, from a random sample, half that number aged <65 years. Patients were excluded if they were unable to complete the study survey due to cognitive impairment, language barriers, institutionalization, or were too ill.

2.3. Questionnaires

All data were collected by patient self-report. While this approach is subject to limitations of recall and recall bias, it has the advantages of efficiency and methodological consistency. The efficiency of the mail and phone survey approach also made it feasible to obtain a substantial sample size and to provide adequate statistical power for the analysis of fracture outcomes, which are relatively rare events. The survey format also allows standardized administration that reduces the issues of noncomparability and variation in data quality that would arise if medical records and public health care databases from several different countries were used. Furthermore, self-report may be preferable to the abstraction from medical records of data on diagnosis and treatment, given inconsistencies in record keeping between physicians and between study regions and countries. Additionally, records from primary care physicians may not include evidence of treatment initiated by a specialist physician.

The process for entering, verifying, and managing survey data was uniform across all study sites. Completed questionnaires were sent to the central coordinating center; twice yearly meetings were held with study coordinators from each of the study sites to review survey administration and ensure uniformity of the process. For study sites using telephone follow-up in addition to mail, a standard telephone script was used and reviewed with each site to ensure consistency of telephone survey administration.

Questionnaires were designed to be self administered, and covered domains that included: patient characteristics and risk factors; perception about fracture risk and osteoporosis; medication use (currently taking or ever taken); medical diagnoses, healthcare use, and access; physical activity; and physical and emotional health status. Self reports of personal risk factors included: current weight and height; parental hip fracture; two or more falls in the past 12 months; current use of cortisone or prednisone; diagnosis of rheumatoid arthritis, personal history of fracture (clavicle, upper arm, wrist i.e. distal forearm, spine, rib, hip, pelvis, upper leg, lower leg, and ankle) since age 45 years; current cigarette smoking; and consumption of three or more units of alcohol daily. Subjects were deemed to have rheumatoid arthritis if they gave a self report of the diagnosis and were on disease-modifying therapy (methotrexate and/or adalimumab). Subjects were considered to be taking anti-osteoporosis medications if they reported current use of alendronate, calcitonin, estrogen, etidronate, ibandronate, pamidronate, PTH [1–84], raloxifene, risedronate, strontium ranelate, teriparatide, tibolone, or zoledronate.

The FRAX tool [7] is a risk-assessment survey that calculates the 10-year probabilities of hip fracture and major osteoporosis-related fracture (clinical spine, forearm, hip, or proximal humerus fracture). It is composed of 11 variables: age, sex, weight, height, previous fracture as an adult, parental hip fracture, current cigarette smoking, current (or 3 months in the past) use of glucocorticoids, diagnosis of rheumatoid arthritis, consumption of ≥3 units of alcohol daily, and secondary osteoporosis. It can be used with or without the addition of the bone mineral density derived T-score at the femoral neck. Bone density testing may have been obtained in some subjects by their primary physicians as part of routine care, but since it was not performed as a component of the GLOW protocol, bone density was not included in this analysis. Women were sent follow-up questionnaires at 1 and 2 years; these asked about any incident fractures, and requested information on the site of fracture, and any hospital treatment received.

2.4. Statistical analysis

Women who had completed a 1- and/or 2-year follow-up survey and reported any incident fracture that occurred between baseline and 2 years after baseline were classed as incident fracture positive. We calculated Kaplan-Meier estimates of 2-year incident fracture rates for each baseline lifestyle or demographic characteristic (age, body mass index [BMI], prior fracture, current smoking, ≥21 units/week of alcohol, fair/poor general health, fallen in the last year, and highest education level) and co-morbidity studied (hypertension, heart disease, high cholesterol, asthma, chronic obstructive pulmonary disease [COPD], arthritis [reported osteoarthritis or rheumatoid arthritis], stroke, inflammatory bowel disease, celiac disease, Parkinson's disease, multiple sclerosis, cancer, and type I diabetes). Unadjusted hazard

ratios (HRs) and 95% confidence intervals (CIs) are reported, in addition to age-adjusted HRs. We then fitted a Cox regression model assessing the outcome (incident fracture at 2 years of follow-up) to see what effect co-morbidities added to the FRAX risk factors had on fracture prediction. Only co-morbidities not already included in the FRAX risk factors were added to the model. Co-morbidities were removed from the model according to significance level alpha of 0.05. We then created a weighted value for each co-morbidity based on parameter estimates from the final Cox regression model. The co-morbidity index was the sum of index points for each woman who had complete data on the baseline survey.

The two models compared were one modeling fracture as a function of FRAX risk factors (including "conventional" co-morbidity data) and one with the FRAX risk factors and the co-morbidity index as predictors of fracture. These models were compared in four ways: a chi-square test for change in log-likelihood between the models with one degree of freedom; the May-Hosmer Goodness of Fit test was used to compare the models to themselves plus the grouping variable; a calibration table was created to compare the predicted fracture rate to the observed by groups of co-morbidity index scores; and the c index of the two Cox proportional hazards models was compared.

3. Results

A total of 60,393 patients from the practices of 723 physicians were enrolled in the study between October 2006 and February 2008. Approximately 25,000 women were recruited from 274 physician practices in Europe; 28,000 from 255 practices in the U.S.; and almost 7,000 from 86 practices in Canada and Australia. Of the 52,960 women with follow-up data, 3224 (6.1%) sustained an incident fracture over 2 years of follow-up. Co-morbidities were common: 26,215 women (49.5%) reported hypertension and 26,084 women (49.3%) had high cholesterol levels. There was a significant association between hypertension and high cholesterol ($p<0.001$, chi-square test).

Table 1 shows the unadjusted and age-adjusted HRs for incident fracture according to age, BMI, risk factors for fracture, and co-morbidity. All recorded co-morbidities were significantly associated with fracture, apart from hypertension, high cholesterol, celiac disease, and cancer. The strongest association was seen with Parkinson's disease (age-adjusted HR: 2.2; 95% CI: 1.6–3.1; $P<0.001$).

We then fitted a model assessing incident fracture at 2 years to see what effect co-morbidities had on fracture prediction when added to the FRAX risk factors. The first model included only the FRAX risk factors. The second model also included the co-morbidities recorded in GLOW. Variables were removed from the second model according to significance level, leaving heart disease, emphysema (COPD), osteoarthritis, Parkinson's disease, and multiple sclerosis as the relevant variables. We then created a weighted value for each co-morbidity based on parameter estimates from the Cox regression model. The HRs and 95% CIs, along with the points assigned to each co-morbidity, are given in Table 2. A co-morbidity index was then created for each participant; this was the sum of points for each woman who had complete data on the baseline survey. A test for interaction between age and co-morbidity index was not statistically significant.

The two models predicting fracture (FRAX risk factors alone vs FRAX risk factors + co-morbidity index) were then compared in four ways. The chi-square test showed a difference for the two models of 62.1 ($P<0.001$ [with one degree of freedom]). Using the May-Hosmer Goodness of Fit test, the model including conventional FRAX risk factors and the co-morbidity index had a good fit over the range of risk ($P=0.79$), while the FRAX risk factors only model demonstrated some lack of fit over the risk range ($P=0.01$). The calibration table (Table 3) shows a higher score was always associated with a higher observed fracture rate. In the model containing FRAX plus the co-morbidity index, if the co-morbidity index was not a useful supplement to the FRAX score, observed fracture rates would not increase with a higher co-morbidity index. By contrast, the fourth comparison of the Cox regression models demonstrated that the c index was similar using FRAX risk factors alone and using FRAX risk factors plus the co-morbidity index (FRAX risk factors only: c=0.632; FRAX risk factors and co-morbidity index: c=0.636). There were no significant interactions between any of the diseases included in the final model.

A test for proportional hazard assumption results revealed that the prior fracture by log(time) interaction was significant (p-value=0.0111) When we examined the relationship between time to fracture and prior fracture, we found that the effect of prior fracture on risk of fracture hanges over time (adjusted HR for incident fracture (95% CI) following prior fracture 1 year ago or less: 2.32 (2.06, 2.60); adjusted HR for incident fracture (95% CI) following prior fracture more than 1 year ago 1.75 (1.54, 1.99). There were no other significant interactions with time.

Finally, we calculated the attributable risk of each risk factor studied; as such of the medical conditions studied are very common, they could contribute to a higher fracture burden than a less common medical condition with a higher relative risk. Our results concluded that 2.6% of incident fractures would be prevented if no women had heart disease; 7.2% of incident fractures would be prevented if no women had osteoarthritis; 1.5% of incident fractures would be prevented if no women had COPD; 0.4 % of incident fractures would be prevented if no women had multiple sclerosis and 0.4% of incident fractures would be prevented if no women had Parkinson’s disease.

4. Discussion

In this study, all recorded co-morbidities were significantly associated with fracture, except for high cholesterol, hypertension, celiac disease, and cancer. The strongest association was seen with Parkinson’s disease. Further analyses suggested that addition of information on co-morbidities to the conventional FRAX risk factors was a valuable addition, although one comparison (the c index) suggested that this was not the case. Other studies, however, have suggested that this statistic may not be optimal in assessing models that predict fracture risk [8].

Many published studies have assessed the fracture risk in patients with rheumatoid arthritis or spondyloarthropathies. In one such study, rheumatoid arthritis was associated with an excess overall fracture risk, vertebral fracture, and hip fracture risk [9]. These risks were also increased among subjects who had never received glucocorticoids, suggesting that other

factors, including uncontrolled inflammation, reduced physical activity, increased falls [10], and cigarette smoking may all be relevant. In addition, investigators have suggested that osteoarthritis may be a risk factor for fracture, possibly through an increased fall rate, reduced levels of physical activity, or increased bone loss rates [11].

It has been reported that Parkinson's disease patients have a higher incidence of hip fractures than the general population [12,13]. The Study of Osteoporotic Fractures reported that women with self-reported Parkinson's disease had a 2.6 fold higher age-adjusted risk for incident hip fracture, although there were no associations between the condition and non-spine, non-hip fractures in this group [15]. Another study reported a crude odds ratio of any fracture of 2.2 for Parkinson's disease, with an adjusted odds ratio of 1.2 [16]. This group reported particularly strong associations in men, a finding supported by the Osteoporotic Fractures in Men study that reported age-adjusted hazards ratios of non-spine fracture of 3.5 for men with the condition [17]. The association between fracture and Parkinson's disease may be because falls are common among these patients [14]. Koller et al. [18] reported that 38% of Parkinson's disease patients reported falls and 13% fell more than once a week; these patients may have reduced sunlight exposure and a lower dietary intake of calcium and vitamin D. The use of dopaminergic drugs in many Parkinson's disease patients has also been shown to be a contributory factor to fracture risk [19].

Patients with multiple sclerosis may be at an increased risk of fracture due to a greater risk of falling and decreased bone mineral density, when compared with the general population [20]. COPD, bronchial asthma, and other chronic respiratory diseases (e.g. cystic fibrosis) are also associated with reduced bone mass, and were associated with an increased risk of fracture in this cohort [20]. The loss of bone mass in such patients has been reported in patients treated with and without oral or inhaled glucocorticoids [21]. However, the extent to which inhaled glucocorticoids affect bone metabolism and bone density is less clear [22]. Other factors that play a role in reduced bone density in this group of patients are systemic inflammation [23], acidosis [24], hypercapnia [25], low body weight, lack of physical activity, and cigarette smoking.

Two meta-analyses have shown an excess risk of fracture among subjects with type 1 diabetes [26,27]. By contrast, the data regarding type 2 diabetes and fracture risk are conflicting, probably because of the confounding effects of BMI and heart disease [28,29]. Cardiovascular disease has traditionally been associated with fracture risk [2]. However, when considering individual risk factors, we found no association between high cholesterol levels and fracture risk. Adipocytes and osteoblasts share a common progenitor from the stromal cells in the bone marrow; and the role of the low-density lipoprotein receptor related protein (LRP) 5 gene in the regulation of bone mass and fracture risk has recently been highlighted [30,31]. Also, a single mutation in LRP6, a closely related homolog of LRP5 that encodes a co-receptor in the Wnt signaling pathway, has been shown to be genetically linked with early coronary disease, features of the metabolic syndrome, osteoporosis, and fractures [32]. Finally, there are several drugs (e.g. hormone replacement therapy and statins) that exert effects on both bone and lipid metabolism [33]. Hence, the absence of an observed effect may reflect our inability to adjust for statin use and to assess the level of hypercholesterolemia.

Many medications used to control blood pressure have also been associated with bone metabolism [34]. Solomon et al. [34] have examined the relative risk of fracture among subjects with hypertension initiating single-drug therapy as antihypertension treatment. Rates varied significantly across the various types of antihypertensives, with thiazide diuretics having the lowest rate (28.5 per 1000 person-years; 95% CI: 25.4–31.9) and loop diuretics the highest rate (49.0 per 1000 person-years; 95% CI: 46.1–52.1) [34]. In models that adjusted for relevant co-morbidities and co-medications accessible in healthcare utilization data, the risk of fracture was reduced in users of angiotensin receptor blockers (HR: 0.76; 95% CI: 0.68–0.86) and thiazide diuretics (HR: 0.85; 95% CI: 0.76–0.97) compared with those taking calcium channel blockers [34]. The adjusted fracture risk was not significantly different from the reference for loop diuretics, beta blockers, or angiotensin-converting enzyme inhibitors.

den Uyl et al. [35] have recently performed a systematic literature search to identify all clinical studies that investigated the association between cardiovascular disease and osteoporosis. However, owing to large heterogeneity between study populations, designs, and outcome measures, a formal meta-analysis was not possible. Six of the highest ranked studies (mean n=2000) showed that individuals with prevalent subclinical cardiovascular disease had a higher risk of increased bone loss and fractures during follow-up compared to those without cardiovascular disease (range of reported risk: HR: 1.5; odds ratio [OR]: 2.3–3.0) [35].

Osteoporosis is common in patients with gastrointestinal diseases, particularly those associated with malabsorption [36,37]. At least one study has shown an increased rate of hip and vertebral fractures among patients with gastrointestinal disease [37]; and the evidence appears to be more robust for Crohn’s disease than for ulcerative colitis [37], although the role of glucocorticoids in this observation is ill defined [36]. Malabsorption of vitamin D and calcium is also likely to be important, as are low body weight, inflammation, and reduced levels of physical activity [38]. In our study, we found only borderline associations between celiac disease and fracture, possibly reflecting adequate treatment of the condition with adherence to a gluten-free diet (perhaps plausible in this self-selected group) or perhaps misclassification by participants. We note that a recent meta-analysis by Olmos et al [39] did report an association between celiac disease and fracture, although considerable heterogeneity in studies was reported, perhaps suggesting that the factors suggested above may be acting in other studies.

Finally, a self report of cancer was also associated with fracture risk, although the observed association was weaker than for other co-morbidities. Both breast and prostate cancer are well recognized as significant risk factors for accelerated bone loss, through the use of hormonal therapies to treat these conditions [37]. Other lifestyle factors may also be important, particularly levels of physical activity, inadequate vitamin D levels, and nutritional factors (with associated reduced body weight).

There are a number of limitations of this study. Specifically, this study did not collect data on ethnicity in locations other than the US and Canada, where 86% of the population was recorded as white, non-Hispanic. Practical considerations limited our sample selection to

women from 17 study locations in ten countries. An expanded sample that included a broader representation of racial and ethnic groups was not pursued because of the complexity of administering a recruitment methodology involving oversampling of particular racial and ethnic groups in ten different countries, where the definitions of these groups were likely to vary considerably. We relied on self-report of conditions in this study; this approach was adopted as while this approach is subject to limitations of recall and recall bias, it has the advantages of efficiency and methodological consistency, allowing us to obtain a substantial sample size and to provide adequate statistical power for the analysis of fracture outcomes, which are relatively rare events. The survey format also allows standardized administration. Other studies have suggested that this approach is valid for many conditions, including fracture [40]. However, this approach clearly does not us to take into account the severity of disease, or allow us to fully investigate interactions between the disease and medication used to treat it. As a non-randomized, observational, practice-based study, GLOW is subject to bias, both in the selection of physicians and the sampling and recruitment of patients. It is possible that participants would have a greater interest in bone health issues, and seek information, screening, and treatment more actively. Furthermore, physicians who agreed to participate may not be representative of all physicians in a given area with respect to osteoporosis recognition and management. We also considered only current use of the glucocorticoids, prednisone and cortisone, as a risk factor whereas FRAX considers “ever use” a risk. However, we took this decision following reports that have critically assessed increased susceptibility to fracture risk and the timing of glucocorticoid use, and suggest that current use is the most important predictor and that once use is discontinued, fracture susceptibility returns to baseline levels [41].

We also found classification of rheumatoid arthritis and osteoarthritis challenging. Ultimately, the decision was taken to restrict a diagnosis of rheumatoid arthritis to a woman who had reported the condition and listed methotrexate and adalimumab amongst her medication, an approach that was likely to have high specificity but low sensitivity. Finally, a diagnosis of heart disease or cancer was based on self report, and did not allow further sub-classification. By contrast, this large, multinational study has allowed us to study relationships between self-reported co-morbidity and incident fracture in a well-characterized population.

In conclusion, we have demonstrated that a number of co-morbidities are associated with fracture risk in this cohort of postmenopausal women. However, our results also suggest that if the “secondary osteoporosis” question in the fracture algorithm FRAX is used appropriately, further inclusion of co-morbidity history in the algorithm may not be useful. We would recommend appropriate education of physicians and other health care professionals in using this tool.

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Abbreviations

BMI	body mass index
CI	confidence interval
COPD	chronic obstructive pulmonary disease
HR	hazard ratio
LRP	lipoprotein receptor related protein
OR	odds ratio

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Table 1

Kaplan-Meier 2-year incident fracture rate estimates by baseline characteristics and co-morbidities (n=52,960), unadjusted and adjusted for age.

	2-year fracture rate (%)	Unadjusted HR (95% CI) for incident fracture	*P* value	Age-adjusted HR (95% CI) for incident fracture	*P* value
Age			<0.001		
55–64 years	5.2	Referent		-	-
65–74 years	6.2	1.2 (1.1–1.3)		-	-
75–84 years	8.8	1.8 (1.6–1.9)		-	-
≥85 years	11.6	2.3 (2.0–2.7)		-	-
BMI			0.26		0.59
<18.5 kg/m^2	7.5	Referent			
18.5–24.9 kg/m^2	6.7	0.9 (0.7–1.2)		1.0 (0.7–1.3)	
25–29.9 kg/m^2	6.5	0.9 (0.7–1.1)		0.9 (0.7–1.2)	
≥30 kg/m^2	6.1	0.8 (0.6–1.1)		0.9 (0.7–1.2)	
Prior fracture	11.6	2.4 (2.3–2.6)	<0.001	2.2 (2.1–2.4)	<0.001
Current smoking	7.1	1.1 (1.0–1.2)	0.11	1.2 (1.1–1.4)	<0.001
Alcohol intake ≥21 units/week	9.3	1.5 (1.0–2.3)	0.05	1.7 (1.1–2.5)	0.01
Fair/poor general health	9.3	1.7 (1.5–1.8)	<0.001	1.6 (1.5–1.7)	<0.001
Fallen in the last year	8.7	1.7 (1.6–1.9)	<0.001	1.7 (1.6–1.8)	<0.001
Highest education level	6.2	0.9 (0.8–1.0)	0.11	1.0 (0.9–1.1)	0.76
Self-reported osteoporosis	10.4	2.0 (1.8–2.1)	<0.001	1.8 (1.7–2.0)	<0.001
Hypertension	6.8	1.1 (1.0–1.2)	0.004	1.0 (0.9–1.1)	0.91
Heart disease	8.7	1.5 (1.3–1.6)	<0.001	1.3 (1.2–1.4)	<0.001
High cholesterol	6.7	1.1 (1.0–1.1)	0.16	1.0 (1.0–1.1)	0.43
Asthma	7.8	1.2 (1.1–1.4)	<0.001	1.3 (1.1–1.4)	<0.001
COPD	9.4	1.6 (1.4–1.7)	<0.001	1.5 (1.3–1.7)	<0.001
Osteoarthritis	7.7	1.4 (1.3–1.5)	<.001	1.3 (1.2–1.4)	<.001
Age			<0.001		
55–64 years	5.2	Referent		-	-
65–74 years	6.2	1.2 (1.1–1.3)		-	-
75–84 years	8.8	1.8 (1.6–1.9)		-	-

	2-year fracture rate (%)	Unadjusted HR (95% CI) for incident fracture	P value	Age-adjusted HR (95% CI) for incident fracture	P value
≥85 years	11.6	2.3 (2.0–2.7)		-	-
BMI			0.26		0.59
<18.5 kg/m^2	7.5	Referent			
18.5–24.9 kg/m^2	6.7	0.9 (0.7–1.2)		1.0 (0.7–1.3)	
25–29.9 kg/m^2	6.5	0.9 (0.7–1.1)		0.9 (0.7–1.2)	
≥30 kg/m^2	6.1	0.8 (0.6–1.1)		0.9 (0.7–1.2)	
Prior fracture	11.6	2.4 (2.3–2.6)	<0.001	2.2 (2.1–2.4)	<0.001
Current smoking	7.1	1.1 (1.0–1.2)	0.11	1.2 (1.1–1.4)	<0.001
Alcohol intake ≥21 units/week	9.3	1.5 (1.0–2.3)	0.05	1.7 (1.1–2.5)	0.01
Fair/poor general health	9.3	1.7 (1.5–1.8)	<0.001	1.6 (1.5–1.7)	<0.001
Fallen in the last year	8.7	1.7 (1.6–1.9)	<0.001	1.7 (1.6–1.8)	<0.001
Highest education level	6.2	0.9 (0.8–1.0)	0.11	1.0 (0.9–1.1)	0.76
Self-reported osteoporosis	10.4	2.0 (1.8–2.1)	<0.001	1.8 (1.7–2.0)	<0.001
Hypertension	6.8	1.1 (1.0–1.2)	0.004	1.0 (0.9–1.1)	0.91
Heart disease	8.7	1.5 (1.3–1.6)	<0.001	1.3 (1.2–1.4)	<0.001
High cholesterol	6.7	1.1 (1.0–1.1)	0.16	1.0 (1.0–1.1)	0.43
Asthma	7.8	1.2 (1.1–1.4)	<0.001	1.3 (1.1–1.4)	<0.001
COPD	9.4	1.6 (1.4–1.7)	<0.001	1.5 (1.3–1.7)	<0.001
Osteoarthritis	7.7	1.4 (1.3–1.5)	<.001	1.3 (1.2–1.4)	<.001
Rheumatoid arthritis	10.4	1.7 (1.2–2.3)	0.002	1.6 (1.2–2.2)	0.003
Stroke	9.1	1.4 (1.2–1.7)	<0.001	1.2 (1.1–1.5)	0.009
Inflammatory bowel	9.0	1.4 (1.2–1.8)	0.001	1.4 (1.1–1.7)	0.002
Age			<0.001		
55–64 years	5.2	Referent		-	-
65–74 years	6.2	1.2 (1.1–1.3)		-	-
75–84 years	8.8	1.8 (1.6–1.9)		-	-
≥85 years	11.6	2.3 (2.0–2.7)		-	-
BMI			0.26		0.59
<18.5 kg/m^2	7.5	Referent			

	2-year fracture rate (%)	Unadjusted HR (95% CI) for incident fracture	P value	Age-adjusted HR (95% CI) for incident fracture	P value
18.5–24.9 kg/m^2	6.7	0.9 (0.7–1.2)		1.0 (0.7–1.3)	
25–29.9 kg/m^2	6.5	0.9 (0.7–1.1)		0.9 (0.7–1.2)	
≥30 kg/m^2	6.1	0.8 (0.6–1.1)		0.9 (0.7–1.2)	
Prior fracture	11.6	2.4 (2.3–2.6)	<0.001	2.2 (2.1–2.4)	<0.001
Current smoking	7.1	1.1 (1.0–1.2)	0.11	1.2 (1.1–1.4)	<0.001
Alcohol intake ≥21 units/week	9.3	1.5 (1.0–2.3)	0.05	1.7 (1.1–2.5)	0.01
Fair/poor general health	9.3	1.7 (1.5–1.8)	<0.001	1.6 (1.5–1.7)	<0.001
Fallen in the last year	8.7	1.7 (1.6–1.9)	<0.001	1.7 (1.6–1.8)	<0.001
Highest education level	6.2	0.9 (0.8–1.0)	0.11	1.0 (0.9–1.1)	0.76
Self-reported osteoporosis	10.4	2.0 (1.8–2.1)	<0.001	1.8 (1.7–2.0)	<0.001
Hypertension	6.8	1.1 (1.0–1.2)	0.004	1.0 (0.9–1.1)	0.91
Heart disease	8.7	1.5 (1.3–1.6)	<0.001	1.3 (1.2–1.4)	<0.001
High cholesterol	6.7	1.1 (1.0–1.1)	0.16	1.0 (1.0–1.1)	0.43
Asthma	7.8	1.2 (1.1–1.4)	<0.001	1.3 (1.1–1.4)	<0.001
COPD	9.4	1.6 (1.4–1.7)	<0.001	1.5 (1.3–1.7)	<0.001
Osteoarthritis disease	7.7	1.4 (1.3–1.5)	<.001	1.3 (1.2–1.4)	<.001
Celiac disease	8.9	1.4 (1.0–2.0)	0.08	1.4 (1.0–2.0)	0.08
Parkinson's disease	16.0	2.6 (1.9–3.6)	<0.001	2.2 (1.6–3.1)	<0.001
Age			<0.001		
55–64 years	5.2	Referent		-	-
65–74 years	6.2	1.2 (1.1–1.3)		-	-
75–84 years	8.8	1.8 (1.6–1.9)		-	-
≥85 years	11.6	2.3 (2.0–2.7)		-	-
BMI			0.26		0.59
<18.5 kg/m^2	7.5	Referent			
18.5–24.9 kg/m^2	6.7	0.9 (0.7–1.2)		1.0 (0.7–1.3)	
25–29.9 kg/m^2	6.5	0.9 (0.7–1.1)		0.9 (0.7–1.2)	
≥30 kg/m^2	6.1	0.8 (0.6–1.1)		0.9 (0.7–1.2)	
Prior fracture	11.6	2.4 (2.3–2.6)	<0.001	2.2 (2.1–2.4)	<0.001

	2-year fracture rate (%)	Unadjusted HR (95% CI) for incident fracture	*P* value	Age-adjusted HR (95% CI) for incident fracture	*P* value
Current smoking	7.1	1.1 (1.0–1.2)	0.11	1.2 (1.1–1.4)	<0.001
Alcohol intake ≥21 units/week	9.3	1.5 (1.0–2.3)	0.05	1.7 (1.1–2.5)	0.01
Fair/poor general health	9.3	1.7 (1.5–1.8)	<0.001	1.6 (1.5–1.7)	<0.001
Fallen in the last year	8.7	1.7 (1.6–1.9)	<0.001	1.7 (1.6–1.8)	<0.001
Highest education level	6.2	0.9 (0.8–1.0)	0.11	1.0 (0.9–1.1)	0.76
Self-reported osteoporosis	10.4	2.0 (1.8–2.1)	<0.001	1.8 (1.7–2.0)	<0.001
Hypertension	6.8	1.1 (1.0–1.2)	0.004	1.0 (0.9–1.1)	0.91
Heart disease	8.7	1.5 (1.3–1.6)	<0.001	1.3 (1.2–1.4)	<0.001
High cholesterol	6.7	1.1 (1.0–1.1)	0.16	1.0 (1.0–1.1)	0.43
Asthma	7.8	1.2 (1.1–1.4)	<0.001	1.3 (1.1–1.4)	<0.001
COPD	9.4	1.6 (1.4–1.7)	<0.001	1.5 (1.3–1.7)	<0.001
Osteoarthritis	7.7	1.4 (1.3–1.5)	<.001	1.3 (1.2–1.4)	<.001
Multiple sclerosis	12.0	1.9 (1.4–2.6)	<0.001	2.0 (1.5–2.8)	<0.001
Cancer	7.3	1.1 (1.0–1.3)	0.01	1.1 (1.0–1.2)	0.18
Diabetes (type 1)	9.6	1.5 (1.3–1.8)	<0.001	1.4 (1.2–1.6)	<0.001

Abbreviations: BMI: body mass index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; HR: hazard ratio.

Table 2

Co-morbidity index for key co-morbidities studied (n=40,614).

Co-morbidity	HR (95% CI)	Points
Heart disease	1.2 (1.0–1.3)	10
Osteoarthritis	1.2 (1.1–1.3)	13
COPD	1.2 (1.1–1.4)	15
Multiple sclerosis	1.7 (1.2–2.6)	37
Parkinson's disease	1.9 (1.3–2.8)	44

Abbreviations: CI: confidence interval; COPD: chronic obstructive pulmonary disease; HR: hazard ratio.

Table 3

Calibration of fracture prediction model with co-morbidity index and observed 2-year fracture rates (n=40,633).

Co-morbidity index points	Women, % (*n*)	Mean 2-year predicted fracture rate,[a] %	Observed 2-year fracture rate,[b] % (*n*)
0–9	51 (20,677)	5.1	5.4 (1242)
10–13	35 (14,188)	6.7	6.7 (1079)
14–23	8 (3446)	8.4	8.4 (340)
24–38	5 (2032)	9.8	9.8 (244)
39–119	1 (290)	14.8	17.4 (60)

[a] From the Cox regression model of 2-year incident fracture with FRAX risk factors and the co-morbidity index as predictors. A total of 19 women with incomplete covariate information were dropped from the final model.

[b] Kaplan-Meier method.