**Risk of fragility fracture among patients with gout and the impact of urate lowering therapy**

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**Competing interest**

None

**Authors Contribution**

Study concept and design: ZP, ER, CM, SH, SM, MB

Acquisition of data: SM, RW, AAS

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**Background**

Previous studies that have quantified the risk of fracture among patients with gout and assessed the potential impact of urate-lowering therapy (ULT) have provided conflicting results. Our study aims to provide better estimates of risk by minimising the impact of selection bias and confounding on the observed association.

**Methods**

We utilised data from the Clinical Practice Research Datalink which records primary care consultations of patients from across the UK. We identified incident gout patients from 1990-2004 and followed them up until 2015. Each gout patient was individually matched to four controls on age, sex and general practice. Absolute rate (AR) of fracture and hazard ratios (HR) were calculated using Cox regression models. Among patients with gout, we assessed the impact of ULT on fracture and utilised landmark analysis and propensity score matching to account for immortal time bias and confounding by indication.

**Results**

We identified 31,781 patients with incident gout matched to 122,961 controls. The AR of fracture was similar in both cases and controls (AR=53 and 55 per 10,000 person-years respectively) corresponding to the HR of 0.97 (95%CI;0.92-1.02). Our finding remained unchanged when we stratified our analysis by age and gender. We did not observe statistically significant differences in the risk of fracture among those prescribed ULT within 1 and 3 years after gout diagnosis.

**Interpretation**

Overall, gout was not associated with an increased risk of fracture. Urate-lowering drugs prescribed early during the course of disease had neither adverse nor beneficial effect on the long-term risk of fracture.

**Keywords: Gout, Fragility fractures, Urate-lowering therapy**

**Introduction**

Gout is the most common type of inflammatory arthritis, affecting 2.4% of adults in the UK**.** It has been hypothesised that, in common with other chronic inflammatory arthritides such as rheumatoid arthritis and spondyloarthropathy,(1, 2) gout may be associated with an increased risk of fracture, primarily due to the negative effects of chronic inflammation on bone, as pro-inflammatory cytokines are known to induce bone loss. However, the effects of serum urate on bone health are still under debate(3, 4) and previous studies that have assessed the impact of gout and urate-lowering therapy (ULT) on fracture risk have provided conflicting results. For instance, a population-based study from Taiwan(5) found a 17% increased risk of fracture among gout patients and reported lower fracture risk among those prescribed ULT. In contrast, a registry-based study from Denmark(6) found a 9% higher risk of fracture among people prescribed allopurinol compared to non-users whereas a US-based study(7) concluded that gout has no impact on the risk of non-vertebral fracture. Whilst former studies were based on large administrative data(5, 6), they failed to take into account life-style related factors such as body mass index and alcohol consumption, or adequately address selection bias associated with potentially delayed ULT after diagnosis(8) which may have affected their overall conclusions. Fragility fractures are associated with increased health care cost(9, 10) and a significant cause of morbidity. Therefore, the aim of this study was to precisely quantify the risk of fracture among UK gout patients and assess the potential impact of ULT on fracture risk estimates using a large population-based primary healthcare database.

**Methods**

Data source, design and setting

We used the Clinical Practice Research Datalink (CPRD)(11); a large database containing UK primary care medical records of anonymised patients (Supplementary data, section on CPRD). CPRD is representative of the general UK population in terms of age, sex, ethnicity and life-style related characteristics(12, 13). We identified individuals with a first-ever recorded Read code diagnosis of gout from general practices between 1990 and 2004 who were then followed-up until 2015. Gout diagnosis was based on a medical code assigned by the physician, which has been previously validated in CPRD and has a positive predictive value of 90%.(14) Each patient was assigned an index date corresponding to the date of their gout diagnosis and randomly matched to four controls, without gout diagnosis or evidence of ULT, on age (±3 years) and gender who were registered at the same practice and were alive and contributing data at the index date. Controls were assigned the same index date as their matched gout case. For both cases and controls, follow-up commenced from the index date. Those with a history of prior fragility fracture, less than 1 year of follow-up before the index date or less than 3 years of follow-up after index date were excluded from the study.

The event of interest was time from the index date until the first diagnosis of fracture. Medical codes for fractures at sites of major osteoporotic fracture were selected (vertebrae, humerus, wrist and hip) in addition to codes for fragility fractures of unspecified site. For the purpose of this study we were only interested in the incidence of first fracture, thus, all subsequent fracture events were ignored. Van Staa et al.(15) carried out external validation of fracture diagnosis in CPRD and found that 88% and 91% of vertebral and hip fracture diagnoses respectively were verified by physicians.

For each individual in our study, we extracted information on relevant life-style related characteristics (smoking status and alcohol consumption), body mass index (BMI) and comorbidities (defined using Charlson Index).(16) We also extracted information on selected medication use (anti-hypertensive, anti-diabetic, opioids, glucocorticoids, proton pump inhibitors (PPI), selective serotonin reuptake inhibitors (SSRI) and bisphosphonates) and history of falls. Information on comorbidities and life-style related characteristics was ascertained within five years and medication use was ascertained within 1 year before the index date. As the timing of initiation of ULT varies after gout diagnosis, we utilised landmark analysis to examine the effect of ULT on the risk of first fracture among patients with gout.(17) This method deals with immortal time bias which biases the results in favour of the treatment under study by granting a false survival advantage to the treated group. In landmark analysis(18), a fixed time after the initiation of therapy is selected for conducting survival analysis (Supplementary figure 1). Only patients alive and contributing data at landmark time were included in the analysis. The exposure (ULT) was evaluated between the index date and the landmark time whereas a fracture event was only considered after the landmark time point. Two landmark points were considered in the analysis (1 and 3 years after diagnosis) based on a previously published study.(19)Only patients prescribed more than 6 months of ULT were considered to be exposed.

Statistical analysis

We calculated the incidence of fracture as the number of first recorded fractures per 10,000 person-years. Using a Cox regression model, we calculated hazard ratios (HR) and 95% confidence intervals (CI) comparing the risk of fracture between gout cases and controls adjusted for various covariates. We accounted for clustering by practice by using robust standard errors. We imputed missing values of BMI by multiple imputation using chained equation. The proportional hazard assumption was tested using Schoenfeld residuals. We stratified our analysis by age, gender and fracture site. To assess the impact of ULT on fracture risk among those with gout, we used propensity score matching methods to account for confounding by indication. The propensity score for ULT represents the probability that a patient is prescribed ULT for at least 6 months during the exposure window given their observed covariates (described further in supplementary data: propensity score). A logistic regression model was used to estimate propensity scores and subsequently each ULT-exposed patient with gout was matched to one unexposed gout patient based on their propensity score with distance caliper distance of 0.2.(19) We used a greedy algorithm to select matches: i.e., we selected the closest matching first, then the closest remaining matching, until there were no acceptable matches. We separately compared the risk of fracture among those who received more than 6 months of ULT within 1 and 3 years exposure window compared to their matched controls not exposed to ULT during that period using Cox regression model. All analyses were conducted using Stata version 14. This study was approved by the CPRD Independent Scientific Advisory Committee (reference number 15 165RA).

**Results**

We identified 31,781 cases of incident gout who were matched to 122,961 controls. The median follow-up for our study was 10.8 years (interquartile range (IQR=6.8-13.6 years). Characteristics of the study population are summarised in Table 1. A total of 8,934 patients sustained a first fragility fracture at some point during the follow-up period. The absolute rate of fracture among gout cases and controls was 53 and 55 per 10,000 person-years respectively (Table 2). Compared to controls, we found no excess risk of fracture among patients with gout (HR=0.97 95%CI 0.92-1.02). These findings remained consistent when we stratified our analysis by age. Whilst women had higher absolute risk of fracture than men, their excess risk compared to their matched controls was not statistically significant (HR=0.96 95%CI 0.89-1.02). Compared to controls, gout patients had no increased risk of vertebral or non-vertebral fractures (Supplementary table 1). For our 1-year landmark analysis, we included 31,668 patients with incident gout (Figure 1) who did not die, transfer out of the practice or have a fracture within the exposure window. The baseline characteristics of patients exposed and unexposed to ULT within 1 year after gout diagnosis are summarised as supplementary table 2. After propensity score matching, we found no difference in the baseline characteristics by ULT exposure status which highlights the success of our matching (Supplementary table 3). There was no difference in the risk of long term fracture among those exposed and unexposed to at least 6 months of ULT within a year of their gout diagnosis (HR=1.01 95%CI 0.84-1.22) (Table 3). Similar findings were also observed in our 3-year landmark analysis.

**Interpretation**

Main findings

Utilising data from a large nationally representative cohort, we have compared the risk of fragility fracture (composite of vertebral and non-vertebral fracture) observed among patients with incident gout to the general population. Overall, gout was not associated with an increased risk of vertebral or non-vertebral facture. These findings were consistent when we stratified our analysis by age and gender. Among those with incident gout, we found that having at least 6 months of ULT within 1 and 3 years of diagnosis had neither adverse nor beneficial effect on the long-term risk of fragility fractures compared to those who received no or less than 6 months of ULT.

Strengths and limitations

Using data from UK’s primary care, we have conducted one of the largest studies with more than 25 years of follow-up to quantify the occurrence of fragility fracture among patients with gout compared to a matched group of individuals without gout in a contemporary population-based manner. Our use of a nationally representative cohort should enable our study findings to be generalisable not only to the UK but also to other developed countries with similar health care systems. Furthermore, the prospective nature of the data recording enables us to better understand the temporal relationship between exposure and outcome with minimum bias.

Our study has several limitations. Our reliance on physicians to ascertain gout diagnosis rather than using the gold standard of visualisation of monosodium urate crystals in joint fluid or identification of tophi on examination could have led to misclassification. However, gout diagnosis has been previously validated in CPRD with high accuracy(14) therefore it is unlikely that there is any major error in our findings due to misclassification of our cases. These findings are in line with another study where 83% of GP diagnosed gout cases were independently validated by a rheumatologist on clinical grounds.(20) Whilst previous studies demonstrates the high positive predictive value, it does not give the indication of negative predictive value (or sensitivity) and there is a possibility of missing cases diagnosed in specialised setting. However this is very unlikely as gout is principally managed in primary care. Furthermore, a recent study using similar database has shown higher prevalence of gout(21) than previously reported. Therefore we believe that it is unlikely that there is any major error in our findings due to misclassification of our cases. Similar misclassification may also exist for fracture diagnosis, although again recording of fracture has been validated in CPRD(15) and we believe that differential recording in the diagnosis of fracture among cases and controls is unlikely. Finally, the use of 1- and 3-year landmarks for our ULT analysis means that our findings can only be generalised to those who were alive and contributing data at those landmark points, did not develop fracture within the exposure window and were prescribed at least 6 months of ULT after their initial gout diagnosis.

Comparison with other studies

We found no association between gout and the risk of fragility fracture. This finding is in contrast to a Taiwanese study that reported a statistically significant 17% higher risk of fracture among gout patients compared to their matched controls.(5) This may be due to the difference in the study population and outcome definition used. For instance, our study primarily focused on fragility fractures whereas the Taiwanese study included all types of fractures including fracture of ankle/foot which accounted for 15% of all fractures in their gout cohort and had the largest excess risk (34%). The neutral effect of gout remained when we stratified our analysis by fracture site. This finding is consistent with other studies.(5, 7) Whilst Tzeng et al.(5) found 14% increased risk of vertebral fracture, their study failed to take into account important life-style related factors (BMI, smoking status and alcohol consumption) which may have confounded their finding. Although women are more likely to sustain fragility fractures than men, few studies provide risk estimates by gender.(5-7) A US-based study(22) reported positive associations between gout and incidence of hip and wrist fracture in women with an adjusted excess risk of 12% and 38% respectively. Whilst this refutes our findings, it used self-reported information on both gout and fracture which may have introduced bias. Furthermore, their study findings may not be generalisable to the wider population as it was exclusively based on a cohort of nurses.

We found that ULT had neither beneficial nor adverse effect on the long term risk of fragility fracture. The existing literature on the topic is conflicting(5, 6, 23) and, unlike our study, does not address the issues of immortal time bias and/or confounding by indication. For instance, Dennison et al.(6) reported 9% excess risk of osteoporotic fractures among those prescribed allopurinol compared to nonusers. Although these authors used propensity score matching, there were still significant differences in the baseline characteristics and comorbidities between exposed and unexposed groups. Moreover, their controls may have included patients without gout which may have had an impact on their observed association. In contrast, Tzeng et al(5) reported 28% lower risk of fracture among gout patients prescribed ULT compared to those not prescribed. However this study overlooked the fact that patients receiving ULT must be event-free from the time of gout diagnosis to the time of the first prescription of ULT in order to be considered exposed whereas no such requirement is necessary for the unexposed group.

Conclusions

We found no excess risk of fragility fractures among patients with gout. Our findings remained consistent when we stratified our analysis by age, gender and fracture site. Our propensity score matched landmark analyses showed that those prescribed at least 6 months of ULT within one and three years of their initial gout diagnosis had neither beneficial nor adverse effects on long term risk of fracture. These findings should be reassuring to patients, healthcare commissioners and clinicians.

**References**

1. van Staa TP, Geusens P, Bijlsma JW, Leufkens HG, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. Arthritis Rheum. 2006;54(10):3104-12.

2. Vosse D, Landewe R, van der Heijde D, van der Linden S, van Staa TP, Geusens P. Ankylosing spondylitis and the risk of fracture: results from a large primary care-based nested case-control study. Ann Rheum Dis. 2009;68(12):1839-42.

3. Mehta T, Buzkova P, Sarnak MJ, Chonchol M, Cauley JA, Wallace E, et al. Serum urate levels and the risk of hip fractures: data from the Cardiovascular Health Study. Metabolism. 2015;64(3):438-46.

4. Kim BJ, Baek S, Ahn SH, Kim SH, Jo MW, Bae SJ, et al. Higher serum uric acid as a protective factor against incident osteoporotic fractures in Korean men: a longitudinal study using the National Claim Registry. Osteoporos Int. 2014;25(7):1837-44.

5. Tzeng HE, Lin CC, Wang IK, Huang PH, Tsai CH. Gout increases risk of fracture: A nationwide population-based cohort study. Medicine (Baltimore). 2016;95(34):e4669.

6. Dennison EM, Rubin KH, Schwarz P, Harvey NC, Bone KW, Cooper C, et al. Is allopurinol use associated with an excess risk of osteoporotic fracture? A National Prescription Registry study. Archives of osteoporosis. 2015;10:36.

7. Kim SC, Paik JM, Liu J, Curhan GC, Solomon DH. Gout and the Risk of Non-vertebral Fracture. J Bone Miner Res. 2016.

8. Levesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ. 2010;340:b5087.

9. Leal J, Gray AM, Prieto-Alhambra D, Arden NK, Cooper C, Javaid MK, et al. Impact of hip fracture on hospital care costs: a population-based study. Osteoporos Int. 2016;27(2):549-58.

10. National Osteoporosis Society. Effective Secondary Prevention of Fragility Fractures: Clinical Standards for Fracture Liaison Services2015 20/10/2017. Available from: <https://staging.nos.org.uk/media/1776/clinical-standards-report.pdf>.

11. Clinical Practice Research Database: Medicine and Healthcare Products Regulatory Agency; [December, 29, 2015]. Available from: <http://www.cprd.com/intro.asp>.

12. Crooks C. Epidemiology of upper gastrointestinal bleeding studying its causes and outcomes using case control studies and surivival analyses. Ph.D. Thesis. : University of Nottingham; 2013.

13. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44(3):827-36.

14. Meier CR, Jick H. Omeprazole, other antiulcer drugs and newly diagnosed gout. Br J Clin Pharmacol. 1997;44(2):175-8.

15. Van Staa TP, Abenhaim L, Cooper C, Zhang B, Leufkens HG. The use of a large pharmacoepidemiological database to study exposure to oral corticosteroids and risk of fractures: validation of study population and results. Pharmacoepidemiol Drug Saf. 2000;9(5):359-66.

16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

17. Dafni U. Landmark analysis at the 25-year landmark point. Circulation Cardiovascular quality and outcomes. 2011;4(3):363-71.

18. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. J Clin Oncol. 2013;31(23):2963-9.

19. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Effect of allopurinol on all-cause mortality in adults with incident gout: propensity score-matched landmark analysis. Rheumatology (Oxford). 2015;54(12):2145-50.

20. Roddy E, Zhang W, Doherty M. Concordance of the management of chronic gout in a UK primary-care population with the EULAR gout recommendations. Ann Rheum Dis. 2007;66(10):1311-5.

21. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Ann Rheum Dis. 2015;74(4):661-7.

22. Paik JM, Kim SC, Feskanich D, Choi HK, Solomon DH, Curhan GC. Gout and Risk of Fracture in Women: A Prospective Cohort Study. Arthritis & rheumatology (Hoboken, NJ). 2016.

23. Basu U, Goodbrand J, McMurdo ME, Donnan PT, McGilchrist M, Frost H, et al. Association between allopurinol use and hip fracture in older patients. Bone. 2016;84:189-93.

**Tables**

**Table 1: Basic characteristic of the study population**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Controls  (n=122,961) | | Gout cases  (n=31,781) | | Standardised difference† |
|  | **N** | **%** | **N** | **%** |  |
| Mean age (SD) | 63.1 | (12.2) | 63.5 | (12.5) | 0.04 |
| Gender male | 89,978 | 73.2 | 23,180 | 72.9 | 0.00 |
| Median follow-up (IQR) | 10.8 | (6.8-13.6) | 10.8 | (6.7-13.4) | 0.03 |
|  |  |  |  |  |  |
| **Body mass index, kg/m2** |  |  |  |  |  |
| Normal (18.5-24.9) | 34,319 | 27.9 | 5,773 | 18.2 | 0.41 |
| Underweight (<18.5) | 1,151 | 0.9 | 129 | 0.4 |  |
| Overweight (25.0-29.9) | 37,142 | 30.2 | 11,641 | 36.6 |  |
| Obese (≥30) | 14,852 | 12.1 | 7,597 | 23.9 |  |
| Missing | 35,497 | 28.9 | 6,641 | 20.9 |  |
|  |  |  |  |  |  |
| **Smoking status** |  |  |  |  |  |
| Never/Ex-smokers | 100,109 | 81.4 | 26,978 | 84.9 | 0.09 |
| Current smokers | 22,852 | 18.6 | 4,803 | 15.1 |  |
|  |  |  |  |  |  |
| **Alcohol consumption, Units per weeks** |  |  |  |  |  |
| Never/Ex-drinker | 15,143 | 12.3 | 3,632 | 11.4 | 0.30 |
| Current 1-9 | 50,568 | 41.1 | 12,181 | 38.3 |  |
| Current ≥10 | 23,819 | 19.4 | 9,909 | 31.2 |  |
| Unknown | 33,431 | 27.2 | 6,059 | 19.1 |  |
|  |  |  |  |  |  |
| History of falls | 3,558 | 2.9 | 1,143 | 3.6 | 0.04 |
|  |  |  |  |  |  |
| **Charlson index** |  |  |  |  |  |
| 0 | 96,284 | 78.3 | 22,419 | 70.5 | 0.19 |
| 1-2 | 23,377 | 19 | 7,872 | 24.8 |  |
| 3-4 | 2,885 | 2.3 | 1,231 | 3.9 |  |
| ≥5 | 415 | 0.3 | 259 | 0.8 |  |
|  |  |  |  |  |  |
| **Medications** |  |  |  |  |  |
| Glucocorticoid | 3,931 | 3.2 | 1,506 | 4.7 | 0.08 |
| Opioids | 11,269 | 9.2 | 4,658 | 14.7 | 0.17 |
| Bisphosphonates | 556 | 0.5 | 125 | 0.4 | 0.01 |
| SSRIs | 3,979 | 3.2 | 1,122 | 3.5 | 0.02 |
| Statins | 8,811 | 7.2 | 3,999 | 12.6 | 0.18 |
| Anti-hypertensive | 29,634 | 24.1 | 14,233 | 44.8 | 0.44 |
| Anti-diabetic | 4,894 | 4 | 1,173 | 3.7 | 0.02 |
| PPIs | 8,339 | 6.8 | 3,366 | 10.6 | 0.14 |
| NSAIDs | 18,892 | 15.4 | 22,264 | 70.1 | 1.33 |
| Aspirin | 14,141 | 11.5 | 5,735 | 18 | 0.19 |

NSAIDs: Nonsteroidal anti-inflammatory drugs, SSRI: Selective serotonin reuptake inhibitor, PPI: Proton pump inhibitors, IQR: Interquartile range, SD: standard deviation. †Standardised difference = difference in means or proportion divided by standard error; Imbalance defined as absolute value greater than 0.20 (small effect size)

**Table 2: Absolute and relative rate of Fragility fracture among cases compared to controls**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Variables | Unexposed | | Exposed | | | |
|  | **N** | **Rateⱡ (95%CI)** | **N** | **Rateⱡ (95% CI)** | **HR unadjusted (95%CI)** | **HR adjusted\*** |
| Overall | 7,164 | 54.7 (53.5-56.0) | 1,770 | 52.9 (50.5-55.6) | 0.97 (0.92-1.02) | 0.95 (0.89-1.01) |
| **Age in years (Quartile)** |  |  |  |  |  |  |
| 1 | 683 | 18.3 (16.9-19.7) | 179 | 18.6 (16.1-21.6) | 1.02 (0.86-1.20) | 0.90 (0.73-1.10) |
| 2 | 1,147 | 32.2 (30.3-34.0) | 296 | 32.7 (29.2-36.7) | 1.01 (0.90-1.16) | 0.92 (0.79-1.07) |
| 3 | 2,020 | 61.7 (59.1-64.5) | 505 | 61.7 (56.6-67.4) | 1.02 (0.92-1.12) | 1.01 (0.91- 1.14) |
| 4 | 3,314 | 132.4 (127.9-136.9) | 790 | 119.6 (111.6-128.3) | 0.92 (0.85-1.00) | 0.94 (0.86-1.03) |
|  |  |  |  |  |  |  |
| **Gender** |  |  |  |  |  |  |
| Male | 3,016 | 30.9 (29.4-32.0) | 793 | 31.5 (29.4-33.8) | 1.02 (0.94-1.10) | 0.99 (0.90-1.09) |
| Female | 4,148 | 124.7 (121.0-128.5) | 977 | 117.7 (110.53-125.3) | 0.96 (0.89-1.02) | 0.94 (0.87-1.01) |

\*Adjusted for age, alcohol consumption, smoking status, BMI, Charlson index, opioids, fall, glucocorticoids, NSAIDs, aspirin PPI, antidiabetic, antihypertensive drugs and SSRI

ⱡPer 10,000 person years

Note: Multiple imputation was used to replace missing values of BMI using chain equation approach based on all baseline characteristics. Five imputed datasets were created and results were combined across all datasets using Rubin’s rule to obtain final estimates.

**Table 3: Risk of fracture at 1 and 3 year landmark (propensity score matched)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | 1 year landmark analysis | | | 3 year landmark analysis | | |
|  | **ULT not prescribed**  **Rate\* (95%CI)** | **ULT prescribed**  **Rate (95%CI)** | **HR (95%CI)** | **ULT not prescribed**  **Rare (95%CI)** | **ULT prescribed**  **Rate (95%CI)** | **HR (95%CI)** |
|  |  |  |  |  |  |  |
| Overall | 62.0 (54.3-70.8) | 62.7 (55.0-71.6) | 1.01 (0.84-1.22) | 65.3 (58.5-72.8) | 65.2 (58.5-72.7) | 1.00 (0.85-1.16) |
| Vertebral | 8.3 (5.8-12.0) | 7.7 (3.7-8.8) | 0.68 (0.39-1.20) | 9.0 (6.7-12.1) | 6.5 (4.6-9.1) | 0.71 (0.45-1.12) |
| Non-vertebral fracture | 47.1 (40.4-54.9) | 51.9 (44.9-60.0) | 1.10 (0.89-1.36) | 50.6 (44.7-57.3) | 52.1 (46.1-58.9) | 1.03 (0.87-1.22) |
| Wrist | 19.2 (15.1-24.4) | 21.1 (16.8-26.5) | 1.10 (0.79-1.53) | 17.9 (14.6-22.1) | 18.0 (14.6-22.1) | 1.00 (0.74-1.34) |
| Hip | 18.4 (14.4-23.5) | 23.1 (18.6-28.7) | 1.25 (0.90-1.75) | 24.3 (20.3-29.0) | 25.2 (21.2-30.1) | 1.04 (0.81-1.34) |
| Humerus | 9.5 (6.5-13.3) | 7.7 (5.3-11.2) | 0.81 (0.49-1.35) | 8.4 (6.2-11.4) | 8.90 (6.6-11.4) | 1.06 (0.70-1.62) |

\*per 10,000 person-year

**Figure legend**

Figure 1: Study population flow diagram.