# Risk of Major Osteoporotic Fracture (Hip, Vertebral, Radius, Humerus) After First, Second and Third Fragility Fracture in a Swedish General Population Cohort

Emma Jonsson,[1] Oskar Ström,[1,2] Anna Spångéus,[3] Kristina Åkesson,[4]
Fredrik Borgström,[1,2] Jonas Banefelt,[1] Emese Toth,[5] Cesar Libanati,[5] Mata Charokopou[5]

[1]Quantify Research, Stockholm, Sweden, [2]LIME/MMC, Karolinska Institutet, Stockholm, Sweden, [3]Department of Endocrinology, Medicine and Health, Linköping University Hospital, Linköping, Sweden, [4]Department of Orthopaedics, Skåne University Hospital, Malmö and Lund University, Lund, Sweden, [5]UCB BioPharma SPRL, Brussels, Belgium

PMS13

## Background

- It is well known that sustaining a fragility fracture leads to an increase in the risk of a subsequent fracture.[1,2]
- Studies have indicated that the increase in fracture risk is not linear over time and is highest within the 2 years following the initial fracture.[3,4]
- It is less clear how the risk of a subsequent fracture changes following second or third fracture.
- Understanding a patient's risk of future fracture over time is important for disease management and can inform clinical and economic decision-making in the field of osteoporosis.

## Objective

- **To estimate risk of subsequent major osteoporotic fracture (MOF) over time for women experiencing their first, second or third fragility fracture compared with matched non-fracture controls.**

## Methods

- This is a retrospective observational cohort study of data included in Swedish National Registers between 1998 and 2015.
- Women aged >49 years with 1, 2 or 3 fragility fractures (index fractures) between 2006 and 2012 were included. Women with Paget's disease or malignancies were excluded.
- Each fracture was matched by gender and birth year to three non-fracture controls from the general population.
- Index fractures were grouped as hip, vertebral and any fracture.
- To avoid miscoding fractures at the same body site at follow-up, fractures were counted as a new fracture only if they occurred ≥6 months (inpatients) and ≥12 months (outpatients) after the previous fracture. A 3-month limit between subsequent inpatient fractures at the same body site was tested using a sensitivity analysis.
- Incidence rates and hazard ratios after index fracture were estimated in single failure parametric survival spline models[5] and adjusted for several baseline covariates[a] and for attained age.

## Results

### Patient characteristics at baseline

- The analyses included 229,259 women with one index fracture (6% vertebral; 21% hip), 39,494 women with two index fractures (12% vertebral; 25% hip) and 7,655 women with three index fractures (14% vertebral; 26% hip) (**Table 1**).

### Subsequent and cumulative incidence of fracture

- Cumulative 1-, 2- and 5-year incidence of first subsequent MOF was 6%, 12% and 25%, respectively (**Figure 1**).
- Cumulative incidence of MOF in women with two prior fractures was 10%, 19% and 40% after 1, 2 and 5 years, respectively.
- Cumulative incidence of a third subsequent MOF was similar to that of the first subsequent MOF. Data in this group were limited to a 3-year follow-up due to lack of data availability (median follow-up = 1.5 years).
- Risk of a subsequent MOF was highest in the first 6 months following index fracture and declined over 5 years (**Figure 2**).
- After an index vertebral fracture, risk of a subsequent MOF was higher than for other index-fracture types. Risk of a subsequent MOF in those women with an index vertebral fracture was lower in the adjusted versus unadjusted models (**Figure 3**).
- Risk of a subsequent MOF was more strongly related to age in women with an index hip fracture versus other index fracture types (data not shown).
- In the index hip fracture group, risk of a subsequent MOF was higher in women aged 50–64 years versus those aged 65–74 and ≥75 years (**Figure 4**).

### Study limitations

- Data for women with three prior fractures were limited to a 3-year follow-up due to the small sample size.
- Clinical data that may influence fracture risk, such as bone density measurements, were not available in these analyses and therefore limit our interpretation of the results.
- No formal statistical comparisons were made between first, second and third index fracture groups, thus subsequent fracture risk between these groups should not be compared.
- As data were collected from routine clinical practice, the number of vertebral fractures in these analyses is likely to be an underestimate of the number that would be detected by morphometric analysis.

[a]Baseline covariates: secondary osteoporosis, dependency (defined as use of a multi-dose drug dispensing service within the past 12 months), and in the previous 12 months: Charlson comorbidity index, osteoporosis treatment, glucocorticoid use, days of hospitalisation (all-cause), number of outpatient physician specialist visits (all-cause), exposure to drugs increasing risk of falls and number of different medications prescribed.

## Table 1. Baseline characteristics

| | 1st to 2nd fracture | | 2nd to 3rd fracture | | 3rd to 4th fracture | |
|---|---|---|---|---|---|---|
| | One prior fracture (N=229,259) | Controls* | Two prior fractures (N=39,494) | Controls* | Three prior fractures (N=7,655) | Controls* |
| Age at index date, mean (SD) | 74.0 (12.5) | 72.2 (11.9) | 79.3 (11.4) | 77.1 (11.2) | 81.8 (10.3) | 79.5 (10.2) |
| Charlson comorbidity index, mean (SD) | 0.4 (0.7) | 0.3 (0.6) | 0.6 (0.8) | 0.4 (0.7) | 0.7 (0.9) | 0.4 (0.7) |
| Dependency,[†] % | 15.4 | 7.6 | 30.0 | 12.3 | 42.6 | 14.7 |
| Rheumatoid arthritis, % | 2.4 | 1.7 | 2.9 | 1.7 | 3.2 | 1.7 |
| Osteoporosis medications within the last 12 months before index date, % | 17.4 | 8.4 | 22.2 | 18.1 | 25.1 | 18.0 |
| Secondary osteoporosis, % | 6.0 | 6.2 | 7.0 | 6.6 | 8.3 | 6.4 |
| Glucocorticoid use within the last 12 months before index date, % | 3.5 | 2.4 | 5.0 | 2.9 | 6.2 | 3.3 |
| Days of all-cause hospitalisation during the past 12 months, mean (SD) | 2.7 (10.5) | 1.2 (6.4) | 7.2 (14.5) | 1.8 (7.6) | 10.8 (19.0) | 1.9 (7.4) |
| Number of outpatient physician specialist visits during the last 12 months (all-cause), mean (SD) | 1.5 (4.4) | 1.1 (2.9) | 2.5 (5.9) | 1.3 (3.0) | 3.1 (7.7) | 1.3 (3.1) |
| Exposure to drugs increasing the risk of falls during the last 12 months, % | 73.5 | 65.8 | 85.7 | 73.3 | 90.8 | 77.0 |
| Number of different medications prescribed within the last 12 months, mean (SD) | 6.1 (5.2) | 5.0 (4.6) | 8.2 (5.8) | 5.8 (4.8) | 9.6 (6.0) | 6.1 (4.8) |

*Sampled from a pool of 260,401 women from the general population without prior fracture at the index date. [†]Dependency was defined as use of a multi-dose drug dispensing service within the past 12 months. SD, standard deviation.

## Figure 1. Cumulative incidence of a subsequent MOF in women with 1, 2 or 3 prior fractures
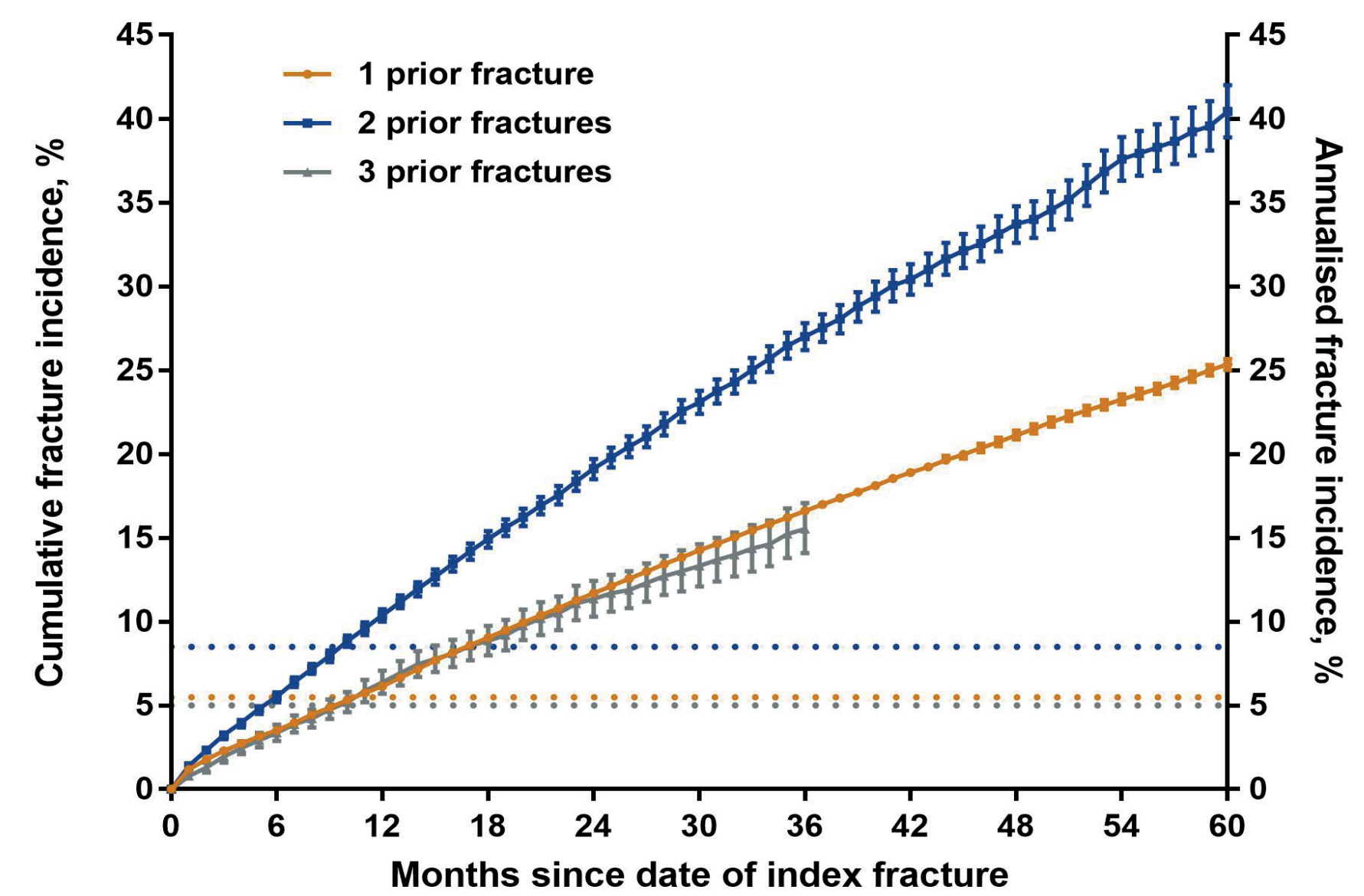


Plot shows cumulative mean fracture incidence ± 95% confidence interval. Horizontal dotted lines show the annualised mean incidence over the entire follow-up period (5.3% [1 prior fracture]; 8.5% [2 prior fractures]; 5.0% [3 prior fractures]). MOF, major osteoporotic fracture.

## Figure 2. Hazard ratio of a subsequent MOF in women with index fracture at any site versus non-fracture controls
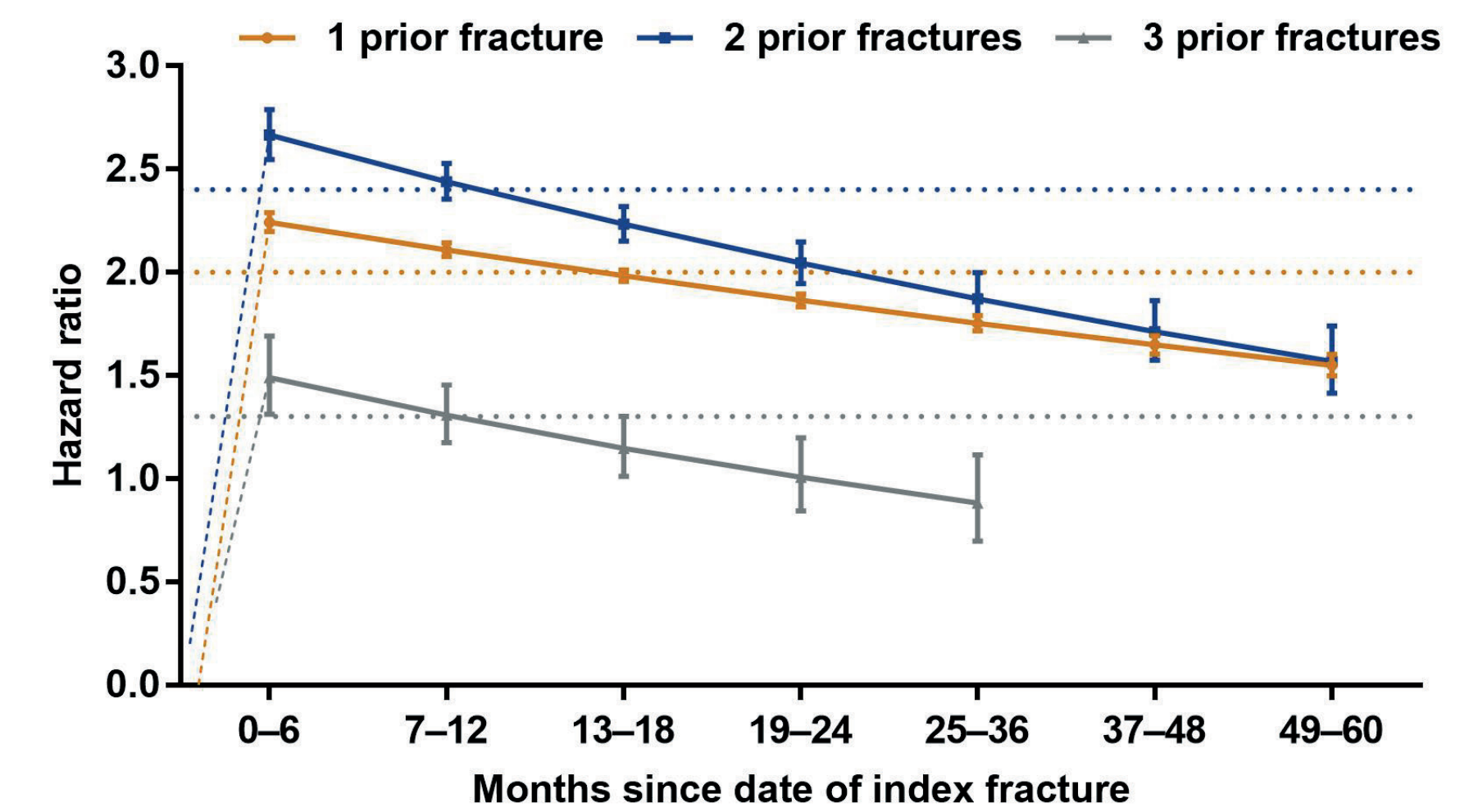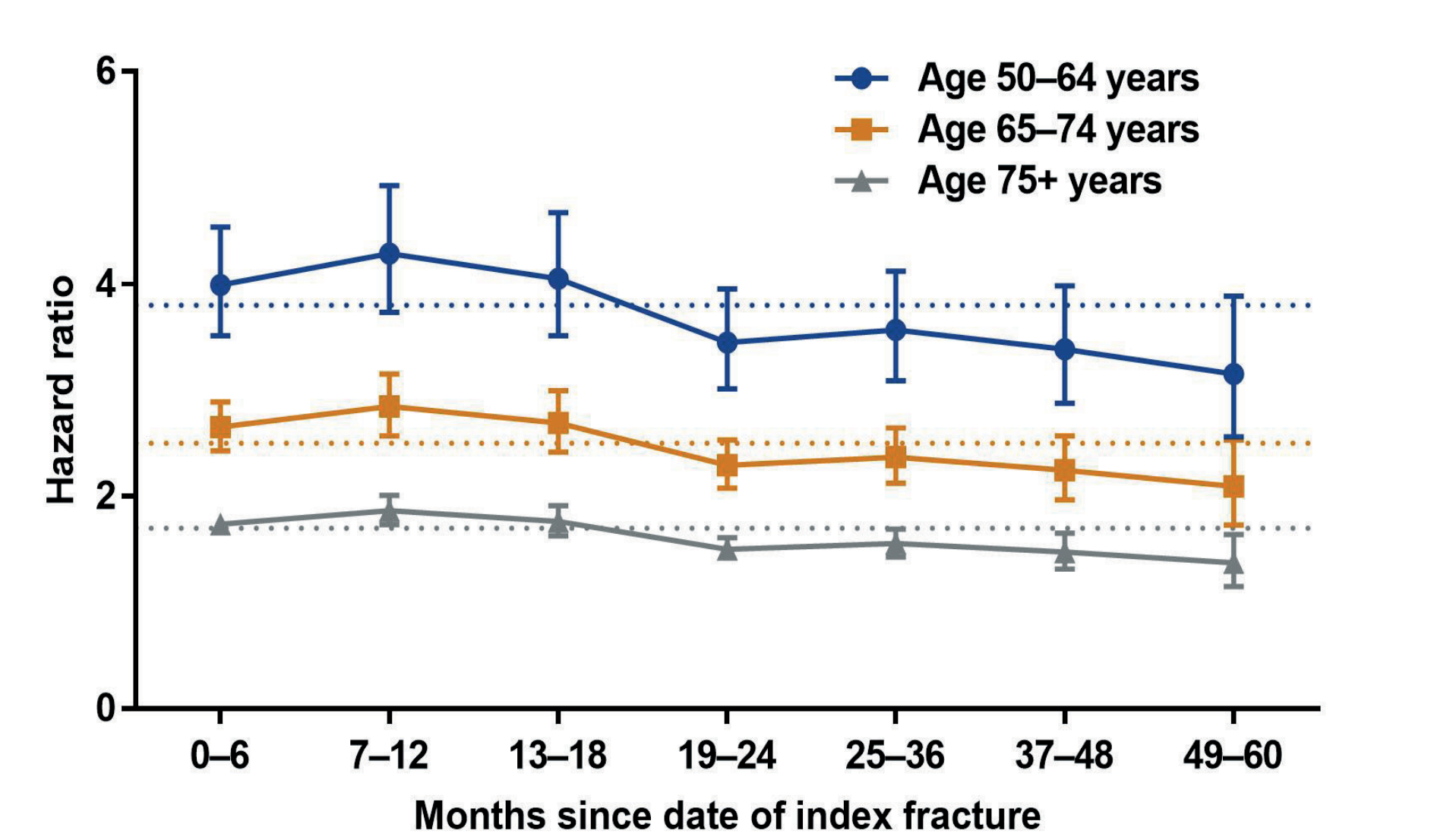


Adjusted hazard ratios, 6-month limit on inpatient fracture and 12-month limit on outpatient fracture of same type. Hazard ratios beyond 36 months for the group with 3 prior fractures are not shown due to small sample size. Horizontal dotted lines show the mean hazard ratio over the entire follow-up period (2.0 [1 prior fracture]; 2.4 [2 prior fractures]; 1.3 [3 prior fractures]). Vertical dashed lines represent the theoretical increase in risk of a subsequent MOF from time = 0.

## Figure 3. Hazard ratio of a subsequent MOF in women with index vertebral fracture versus non-fracture controls
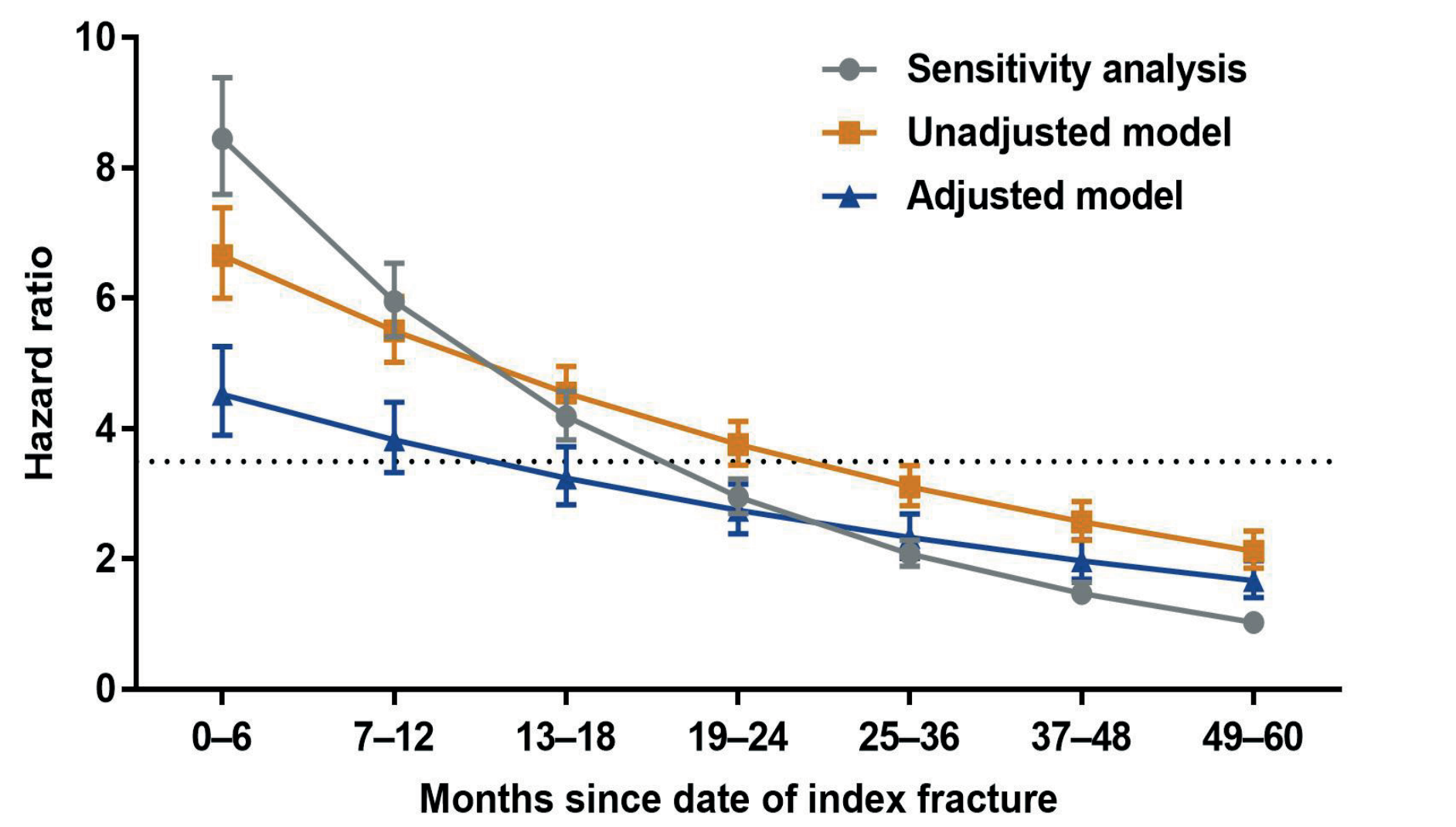


Data show hazard ratios with and without adjustment for baseline covariates and also an unadjusted sensitivity analysis using a 3-month limit for recording subsequent fractures at the same site. Horizontal dotted line shows the mean hazard ratio over the entire follow-up period (3.5 [adjusted model]).

## Figure 4. Hazard ratio of a subsequent MOF by age in women with index hip fracture versus non-fracture controls



Adjusted results, using a 6-month limit on prior inpatient fracture and 12-month limit on prior outpatient fracture of same type. Horizontal dotted lines show the mean hazard ratios over the entire follow-up period (3.8 [Age 50–64 years]; 2.5 [Age 65–74 years]; 1.7 [Age 75+ years]).

## Conclusions

- In this large sample of women with multiple fractures, the risk of a subsequent MOF was highest within the first 2 years after the previous fracture.
- After controlling for various baseline characteristics such as age, dependency and glucocorticoid use, there remains an increased risk in women with multiple fractures compared with non-fracture controls.
- The risk of a subsequent MOF was higher following an index vertebral fracture than index hip fracture or any index fracture.
- After adjustment for baseline covariates, the risk of a subsequent MOF was higher in women with two prior fractures than those with one prior fracture. However, in women with three prior fractures, the risk of a subsequent MOF was lower than with one or two prior fractures. While not tested in this study, competing mortality may be a contributory factor to this finding. Further research will be required to understand this outcome.

### References

1. Klotzbuecher CM, et al. J Bone Miner Res 2000;15:721–39.
2. Gehlbach S, et al. J Bone Miner Res 2012;27:645–53.
3. Van Geel TACM, et al. Curr Osteoporos Rep 2010;8:118–22.
4. Johansson H, et al. Osteoporos Int 2017;28:775–80.
5. Royston P and Parmar MK. Stat Med 2002;21:2175–97.