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**The effect on subsequent fracture risk of age, sex and prior fracture site by recency of prior fracture**

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**Abstract**

*Summary* The risk of a recurrent fragility fracture varies by age and sex, as by site and recency of sentinel fracture.

*Introduction* The recency of prior fractures affects subsequent fracture risk. Variable recency may obscure other factors that affect subsequent fracture risk. The aim of this study was to quantify the effect of a sentinel fracture by site, age and sex where the recency was held constant.

*Methods* The study used data from the Reykjavik Study fracture register that documented prospectively all fractures at all skeletal sites in a large sample of the population of Iceland. Fracture incidence was compared to that of the general population determined at fixed times after a sentinel fracture (humeral, clinical vertebral, forearm, hip, and minor fractures). Outcome fractures comprised a major osteoporotic fracture and hip fracture.

*Results* Sentinel osteoporotic fractures were identified in 9504 men and women. Of these, 3616 individuals sustained a major osteoporotic fracture as the first subsequent fracture, of whom 1799 sustained a hip fracture. Hazard ratios for prior fracture were consistently higher in men than in women and decreased progressively with age. Hazard ratios varied according to the site of sentinel fracture with higher ratios for hip and vertebral fracture than for humerus, forearm or minor osteoporotic fracture.

*Conclusion* The risk of a recurrent fragility fracture varies by age, sex and site of sentinel fracture when recency is held constant.

Key words: Fracture risk ∙ Recency of fracture ∙ Prior fracture ∙ Risk assessment ∙ Sentinel fracture

**Introduction**

Prior fragility fracture is a well-established risk factor for a future fracture [1, 2, 3, 4, 5, 6, 7]. The summary relative risk of having a hip fracture or other osteoporotic fracture is approximately 2-fold higher for most types of prior fracture. However, a number of additional factors appear to affect the increase in risk. These include the recency of fracture [8, 9, 10, 11, 12, 13, 14, 15] age [2, 15], sex [5], and the site of the sentinel fracture [1].

Despite the many studies available, there are many inconsistencies in the conclusions offered. For example, a large meta-analysis indicated no difference for subsequent fracture risk between men and women [2] as also subsequently reported [13] whereas others have shown an increased risk in men [5, 3, 16, 17]. In a similar vein, there is inconsistent evidence for site specificity. The pooled estimates in meta-analyses suggest that women with prior fractures have twice the risk of future fractures compared with those without prior fractures [1, 2]. In contrast, prior spine fracture is reported as a stronger predictor of hip fracture than a distal forearm fracture [3] and a prior hip fracture a strong harbinger of future hip fracture [4]. More recently, fracture risk and probability adjustments for FRAX were shown to differ according to the site of a recent prior fracture [18, 19].

It is difficult to disentangle the various reported associations. For example, is the higher risk variously reported in men after fracture compared with women due to the shorter duration of observation or the study of younger men?

The aim of the current study was to examine the extent by which the risk of subsequent major osteoporotic or hip fracture varied by age, sex and site of prior fracture for a fixed recency of prior fracture using a well-defined Icelandic Reykjavik Study database.

**Methods**

*Study cohort*The study cohort consists of 30,795 men and women, comprising all residents in the greater Reykjavik Area on December 1, 1967, born between 1907 and 1935 (both years included), which represented 55% of the total Icelandic population in this age range at that time [20, 21]. The current analysis is based on 18,872 participants (71.8 % of the cohort) who attended during the recruitment period in 1967–1991, comprising 9,116 men and 9,756 women. Individuals were followed-up for a median time of 28 years until death, emigration or December 31st, 2012, yielding a total of 510,265 person-years of observation. The study was approved by the National Bioethics Committee and the Data Protection Authority in Iceland. All participants gave informed written consent.

*Assessment of fractures*

The Reykjavik Study fracture register documented all incident fractures and their date of occurrence in all participants from their entry into the study until December 31, 2012. All medical records for the participants, including referral letters if needed, were manually examined and verified. All fractures were registered according to the International Classification of Diseases (ICD version 10 or ICD version 9). Avulsions less than 5×6 mm, fractures secondary to malignancy and stress fractures were excluded. The register has been shown to have a capture rate of about 97% for hip, forearm, and clinical vertebral fractures [22]. Subclinical vertebral fractures were not documented. The circumstances of the trauma leading to the fracture were assessed, but all fractures were counted regardless of trauma. In order to minimise double counting, subsequent consecutive fractures that occurred at the same site were excluded where the interval between fractures was less than 30 days.

Five categories of sentinel fracture were defined, comprising clinical vertebral fracture (ICD 10 codes S12.0-S12.2, S12.7, S22.0-22.1, S32.0), proximal humeral fracture (S42.2-42.3), distal forearm fracture (S52.5-52.6) hip fracture (S72.0-S72.2) and ‘minor’ osteoporotic fracture. Minor osteoporotic fractures comprised sites associated with osteoporosis [23], excluding the major osteoporotic fractures (clinical vertebral, proximal humeral, distal forearm and hip fracture). Specifically, minor osteoporotic fractures comprise those at the ribs, pelvis, midshaft and distal femur, distal humerus, proximal forearm, tibia and fibula (in women), clavicle, scapula and sternum [23]. Fractures at the ankle, face, foot, hand, patella and skull were regarded as non-osteoporotic fractures. Fractures at the tibia were considered an osteoporotic fracture in women but not in men. For brevity, distal forearm and proximal humerus fractures are termed forearm and humerus fractures.

*Fracture incidence*

The hazard function for a second major osteoporotic fracture (MOF; comprising clinical spine, hip, humerus or forearm fracture) or hip fracture after a first forearm, vertebral, humerus, hip or minor fracture was calculated. A modification of the Poisson regression model [24, 25] was used to study the relationship between sex, age, and the site of the previous fracture by recency of prior fracture. Note that the model determined the hazard function for fracture and not fracture probability. Follow up was measured in person years and the observation period of each participant was divided in intervals of one month. The hazard function was assumed to be exp(β0 + β1 · sex + β2 · current time from fracture + β3 · current age). The beta coefficients reflect the importance of the variables, and βx = 0 denotes that the corresponding variable does not contribute to fracture risk.

The fracture risk with time after previous fracture was investigated with spline functions with time since previous fracture as a continuous variable. When analysing time to second fracture only the first fracture after the sentinel fracture was counted. When studying the association between risk of a second fracture and the time since first fracture, spline functions were fitted using knots at 0.5, 2.5 and 15 years after the first fracture. The splines were second-order functions between the breakpoints and linear functions at the tails resulting in a smooth curve. The hazard functions for fracture were compared to that of the general population of the same age and sex to derive hazard ratios and 95% confidence intervals (95% CI).

*Time horizon*

The impact of recency of fracture on hazard ratios in the Reykjavik Study cohort has been previously published at least for major osteoporotic fractures as an outcome [15, 18]. For the purpose of this paper we assessed the contribution of sex, age and site of sentinel fracture at a fixed time of 10 years after the sentinel fracture unless otherwise noted. The impact of recency on minor and all osteoporotic fractures has not been previously reported and is briefly described.

**Results**

Sentinel osteoporotic fractures were identified in 9504 men and women at the sites shown in Table 1. Of these, 3616 individuals sustained a major osteoporotic fracture as the first subsequent fracture, of whom 1799 experienced a hip fracture as the first subsequent fracture.

**Table 1.**  Baseline characteristics and fracture outcomes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Hip | Vertebral | Humerus | Forearm | Minor  |
| *Men* |  |  |  |  |  |
| Number  | 576 | 362 | 248 | 393 | 905 |
| Age (years) + SD a | 53.6±8.3 | 52.7±8.6 | 51.2±7.4 | 50.7±8.0 | 50.3±8.0 |
| Age (years) + SD b | 79.5±8.6 | 74.0±11.1 | 72.6±10.6 | 70.5±10.8 | 70.2±11.1 |
| MOF during follow up  |  |  |  |  |  |
| Number  | 117  | 106 | 75 | 127 | 218 |
| Incidence (/100,000) | 685  | 1011 | 1016  | 1055 | 783 |
| 95% CI | 567-821 | 828-1223 | 799-1273 | 879-1255 | 682-894 |
| HF during follow up |  |  |  |  |  |
| Number  | 79 | 47 | 46 | 59 | 114 |
| Incidence (/100,000) | 458  | 430  | 600  | 466  | 395  |
| 95% CI | 362-571 | 316-571 | 439-800 | 354-601 |  326-474 |
| *Women* |  |  |  |  |  |
| Number  | 1498 | 1003 | 844 | 1971 | 1704 |
| Age (years) + SD a | 55.3±8.7 | 54.2±8.8 | 52.9±8.5 | 52.2±8.3 | 52.9±8.6 |
| Age (years) + SD b | 79.6±8.8 | 74.7±9.6 | 74.2±9.9 | 69.5±10.3 | 73.6±11.2 |
| MOF during follow up  |  |  |  |  |  |
| Number  | 459  | 485 | 396 | 901 | 732 |
| Incidence (/100,000) | 1065  | 1800  | 1644  | 1594  | 1500  |
| 95% CI | 970-1167 | 1644-1968 | 1486-1814 | 1492-1702 | 1393-1612 |
| HF during follow up |  |  |  |  |  |
| Number  | 273 | 224 | 190 | 420 | 347 |
| Incidence (/100,000) | 614  | 761  | 726  | 671  | 655  |
| 95% CI | 544-692 | 664-867 | 627-837 | 608-738 | 588-727 |

HF, hip fracture; MOF, major osteoporotic fracture
a At baseline.
b at sentinel fracture

*Effect of age*

Ten years following a sentinel fracture, hazard ratios for a subsequent MOF decreased progressively with age in both women (Fig. 1) and men (Fig. 2 The gradient with age was particularly marked in the case of hip and vertebral sentinel fractures. For example, the hazard ratio for MOF after a vertebral fracture was 5.6 at the age of 40 years, decreasing to 1.5 at the age of 90 years (Table 2). For minor osteoporotic fracture, the respective hazard ratios were 2.6 and 1.5. Despite the decrease in hazard ratio with age, the risk of MOF was consistently above unity. In the case of subsequent hip fracture, hazard ratios decreased progressively with age for all sentinel fracture sites (Table 3). The gradient with age was particularly marked in the case of a sentinel hip fracture. In women at the age of 40 years, the hazard ratio for a subsequent hip fracture was 47.6 which fell to 1.1 at the age of 90 years. At the younger age, the 95 % confidence intervals were large (25-89), but the lower estimate was still markedly increased.

*Effect of sex*

At 10 years following a sentinel fracture, hazard ratios for a subsequent MOF fracture were consistently and significantly greater in men than in women. The increase in hazard ratio for men, relative to women, with sentinel vertebral fracture was 1.79 (95% CI = 1.42-2.17), for hip fracture 1.27 (95% CI = 1.03-1.55), for forearm fracture 1.34 (95% CI = 1.11-1.62), for humerus fracture 1.57 (95% CI = 1.22, 2.01) and 2.09 (95% CI = 1.80-2.45) for a minor fracture.

For the outcome of hip fracture, the difference between men and women was significant only for vertebral fracture (HR for men relative to women=1.47; 95 % CI = 1.07-2.02) and minor osteoporotic fracture (HR=1.48; 95 % CI = 1.20-1.84).

*Effect of fracture site*

All sentinel fractures were associated with a significantly increased risk of a subsequent fracture. Hazard ratios for major osteoporotic fracture varied according to the site of sentinel fracture with higher ratios for hip and vertebral fracture than for humerus, forearm or minor osteoporotic fracture. In women at the age of 40 years, for example, the highest hazard ratios were seen for a sentinel hip or vertebral fracture (HR= 6.4 and 5.6,



**Fig. 1** Hazard ratio and 95% confidence interval (vs general population of same age and sex) for subsequent MOF 10 years after a prior fracture at the sites shown in women.

**Fig. 2** Hazard ratio and 95% confidence interval (vs general population of same age and sex) for subsequent MOF 10 years after a prior fracture at the sites shown in men.

Respectively) (Table 2). Intermediate values were seen for humerus and forearm fractures (HR = 3.8 and 3.1, respectively). When all osteoporotic sentinel fractures were considered the hazard ratio for major osteoporotic fracture was 2.9 (Fig. 3). The same rank order was seen at all ages and in men, albeit with higher hazard ratios in men. In the case of hip fracture outcome, there was a similar rank order of effect but for a sentinel hip fracture, the hazard ratios for a subsequent hip fracture were very large (Table 3)



Fig. 3 Hazard ratio and 95% confidence interval (vs general population of same age and sex) for subsequent MOF associated with a sentinel fracture in women age 40 years.

*Recency of fracture*

As previously shown, the increased risk of MOF following a sentinel hip, vertebral, humerus and forearm fracture decreased with time. A similar phenomenon was seen with ‘minor osteoporotic fractures’ in both men and women (Fig. 4). The weight of minor sentinel fractures was less than that for sentinel fractures at other sites and greater in men than in women at all time points.

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**Fig 4**. Hazard ratio (vs general population of same age and sex) for a MOF after a sentinel fracture at the sites shown for men and woman at the age of 60 years at the time of the sentinel fracture

**Discussion**

Many studies have found that a recent occurrence of fracture is a greater risk factor for subsequent fracture than a history of earlier fracture, demonstrated for

vertebral fracture [8, 12], hip, humeral and forearm fractures [2, 5, 8, 15, 18,] and when these fracture sites were combined [9, 14, 26]. Recently, probability adjustments for FRAX were shown to differ according to the recency of fracture [19]. The question arises whether other factors that are associated with a prior fracture are confounded by the large effect of recency of fracture. The strength of the present study was that it was possible to study the long-term determinants of fracture risk after a first sentinel fracture where recency could be held constant. For this end, a time horizon of ten years after a sentinel fracture was chosen, though the same qualitative conclusions would be found with shorter time horizons.

The principal findings are that the risk (relative to that in the general age and sex matched population) of an MOF or hip fracture following a sentinel fracture is markedly higher in men than in women, is higher at younger ages and differs according to the site of the sentinel fracture. None of these findings are new but, to our knowledge, no previous publications have reported all these associations in the same study. This finding supports a view that many previous studies were confounded by the recency of fracture.

The greater relative risk of refracture in men compared with women (despite a lower absolute risk [15] was marked. At the age of 60 years, for example, a sentinel hip fracture in a woman was associated with a significant increase in the risk of a subsequent MOF with a HR of 3.5 (95% CI = 2.6-4.6). For a man at the same age, the hazard ratio was more than double (HR 7.7; 95% CI = 5.6-10.6). Similar differences between men and women were seen at all ages and for all sentinel fractures. It is notable that two meta-analyses did not show differences between men and women in subsequent fracture risk [1, 2]. The analysis of Klotzbeucher [1] did not consider age or recency of fracture. The meta-analysis of Kanis et al [2] was based on the primary individual data and included the covariates of time since start of follow up, current age, prior history of fracture and sex. There was no significant difference in risk ratio between men and women. It is of interest that the point estimates were consistently greater in men than in women though, perhaps related to age, of relatively small magnitude. For example, a prior fracture was associated with an increase in subsequent hip fracture risk of 1.97 (1.12–3.48) for men and 1.56 (1.23–1.98) in women. Very strong sex dependent effects, similar to that in the present study, have been reported in population surveys of Malmo, Sweden [5] and Edinburgh, Scotland [17].

A further finding of the present study was the important impact of age. Hazard ratios decreased markedly with age for all sentinel fractures. For a sentinel vertebral fracture, for example, the hazard ratio for a subsequent MOF was 5.6 (3.8-8.4) in women at the age of 40 years. This fell progressively with age to 1.5 (1.2-1.8) at the age of 90 years. The same phenomenon was observed in individuals with a recent fracture (within 2 years), albeit in the same cohort as that currently studied [18, 19]. Many studies have not sought or reported age-dependent effects but, where examined showed an effect similar to that of the present study [2, 5, 16, 17]. The meta-analysis of Kanis [2], used in the creation of FRAX, found age-dependent effects for hip fracture outcome but a non-significant trend for a subsequent MOF. In the present study we report hazard ratios and not fracture probabilities. The latter consider the competing death hazard. However, neglecting the death hazard would underestimate the hazard ratios. Thus, the age dependent effects that we report cannot be explained by not considering the risk of death.

The third major finding from the present study was the differential significance of the site of sentinel fracture. Prior vertebral and hip fractures carried the most weight with respect to subsequent fracture risk. Humeral and forearm sentinel fractures carried intermediate weight. Minor osteoporotic fractures carried the least weight. A sentinel hip fracture carried a high risk of subsequent fractures, especially hip fracture. There is also published evidence for site specificity [1, 3, 4, 5]. For example, the pooled estimate in a meta-analysis reported that women with prior fractures had twice the risk of future fractures compared with those without prior fractures. However, prior spine fractures carried a 4 to 19-fold increase in risk for subsequent spine fractures fracture than a distal forearm fracture [1]. Prior spine fracture was a stronger predictor of hip fracture than a distal forearm fracture in women (but not in men) [3].

The pattern of incident fractures changes with age but this cannot explain the decreasing relative risk with age. MOFs account for approximately 45% of incident osteoporotic fractures in men at the ages 50-54 rising to 54% in the age group 85-89 years. For women, the respective proportions are 70% and 64%. However, the proportion of sentinel hip and vertebral fractures (with the greatest risk for MOF) increases with age in men from 27% of all osteoporotic fractures to 56% and from 19% to 47% in women [23]. Thus, the effect of age on subsequent fracture risk is not driven by the changing pattern of fracture with age.

The question arises of the implications for risk assessment, specifically for the use of FRAX. FRAX uses eight clinical risk factors. Of these, one of the strongest risk factors is a history of a prior fragility fracture. Fracture probabilities are approximately doubled in the presence of a prior fracture depending on age and sex [27, 28]. The present study confirms many observations, summarized in meta-analyses, that the risk of fracture is approximately doubled after a first fracture [1, 2]. For all prior fractures combined, the relative risk of any subsequent fracture was 2.2 (95% CI 1.9–2.6) in the meta-analysis of Klotzbeucher, which was confined mainly to women. This estimate is very consistent with the long-term observations in the present study. In women, the relative risk of a MOF following any sentinel fracture ranged from 1.4 to 2.9, depending on age (Table 2). The relatively modest increase in long-term risk contrasts the very marked increases in risk with a recent sentinel fracture. The added risk provided by taking fracture recency into account is substantial, particularly in younger individuals and guidance for the adjustment of conventional probability assessments has recently become available [19]. The present study highlights other factors of importance for risk assessment that are not presently accommodated by FRAX. These include the differences in risk between men and women, age in the case of probability of MOF, and the differential effects of the site of sentinel fracture. Whether these findings can inform future iterations of FRAX will depend on the granularity of population-based cohort studies. The present study can at least inform investigators of the relevant questions to ask.

Strengths in this study were the random sampling of the population, the detail placed on fracture ascertainment, the long duration of observation [20, 21] and the high accuracy for the ascertainment of fractures [22]. However, there were also, some limitations to this study. Despite the extensive information on fracture, age, sex, mortality, dates and sites of fracture, there was no information on other clinical risk factors that contribute to the assessment of fracture risk. Additionally, we did not study subclinical vertebral fracture. A further limitation is that the study was a single country study but the consistency of the findings with the published literature suggest that the findings are of international relevance. Notwithstanding, independent verification of these findings from other countries is appropriate.

In conclusion, a low-energy sentinel fragility fracture confers an increased risk of sustaining a second low-energy fracture later in life, with the relative risk of refracture particularly raised in men and younger individuals. Finally, sentinel fractures at different sites are associated with differences in subsequent fracture risk. These observations should inform the future interpretation of fracture risk.

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**Compliance with ethical standards**

The study was approved by the National Bioethics Committee and the Data Protection Authority in Iceland. All participants gave informed written consent.

**Conflicts of interest**

V Gudnason, G Sigurdsson, K Siggeirsdottir, E Liu, L Vandenput and H Johansson have no competing interests to declare.

N. Harvey has received consultancy, lecture fees and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, Servier, Shire, UCB, Kyowa Kirin, Consilient Healthcare, Radius Health and Internis Pharma.

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JA Kanis is the architect of FRAX® but has no financial interest.

M Lorentzon has received lecture fees from Amgen, Lilly, Meda, Renapharma, UCB Pharma, and consulting fees from Amgen, Radius Health, UCB Pharma, Renapharma and Consilient Health, all outside the presented work

**References**

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| 1. | Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA, 3rd, Berger M (2000) Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res 15: 721-739. |
| 2. | Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, Eisman J, Fujiwara S, Garnero P, Kroger H, McCloskey EV, Mellstrom D, Melton III LJ, Pols H, Reeve J, Silman A, Tenenhouse A (2004) A meta-analysis of previous fracture and subsequent fracture risk. Bone; 35: 375-382 |
| 3. | Haentjens P, Johnell O, Kanis JA, Bouillon R, Cooper C, Lamraski G, Vanderschuren D, Kauffman J-M, Boonen S (2004) Gender-related differences in short and long-term absolute risk of hip fracture after Colles’ or spine fracture: Colles’ fracture as an early and sensitive marker of skeletal fragility in men. J Bone Miner Res 19: 1933-1944 |
| 4. | Hansen L, Petersen KD, Eriksen SA, Langdahl BL, Eiken PA, Brixen K, Abrahamsen B, Jensen JE, Harslof T, Vestergaard P (2015) Subsequent fracture rates in a nationwide population-based cohort study with a 10-year perspective. Osteoporos Int 26: 513-9. |
| 5. | Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Pettersen C, De Laet C, Jonsson B (2004) Fracture risk following an osteoporotic fracture. Osteoporos Int 15: 175-179. |
| 6. | Finsen V, Benum P (1986) Past fractures indicate increased risk of hip fracture, Acta Orthop Scand 57: 337-339. |
| 7. | Gunnes M, Mellstrom D, Johnell O (1998) How well can a previous fracture indicate a new fracture? A questionnaire study of 29,802 postmenopausal women. Acta Orthop Scand 69: 508– 12. |
| 8. | Johnell O, Oden A, Caulin F, Kanis JA (2001) Acute and long-term increase in fracture risk after hospitalization for vertebral fracture. Osteoporos Int 12: 207-214. |
| 9. | Giangregorio LM, Leslie WD (2010) Manitoba Bone Density Program. Time since prior fracture is a risk modifier for 10-year osteoporotic fractures. J Bone Miner Res 25: 1400-5. |
| 10. | Dretakis KE, Dretakis EK, Papakitsou EF, Psarakis S, Steriopoulos K (1998) Possible predisposing factors for the second hip fracture. Calcif Tissue Int 62: 366–369 |
| 11. | Nymark T, Lauritsen JM, Ovesen O, Röck ND, Jeune B (2006) Short time-frame from first to second hip fracture in the Funen County Hip Fracture Study. Osteoporos Int. 2006;17(9):1353-7. |
| 12. | Lindsay R, Silverman SL, Cooper C, Hanley DA, Barton I, Broy SB, Licata A, Benhamou L, Geusens P, Flowers K, Stracke H, Seeman E (2001) Risk of new vertebral fracture in the year following a fracture. JAMA 285: 320-323 |
| 13. | Ryg J, Rejnmark L, Overgaard S, Brixen K, Vestergaard P (2009) Hip fracture patients at risk of second hip fracture: a nationwide population-based cohort study of 169,145 cases during 1977-2001. J Bone Miner Res 24: 1299-307 |
| 14. | van Geel TACM, van Helden S, Geusens PP, Winkens B, Dinant G-J (2016) Clinical subsequent fractures cluster in time after first fractures. Ann Rheum Dis 68: 99–102 |
| 15. | Johansson H, Siggeirsdóttir K, Harvey NC, Odén A, Gudnason V, McCloskey E, Sigurdsson G, Kanis JA (2017) Imminent risk of fracture after fracture. Osteoporos Int 28:775-780 |
| 16. | Van Staa TP, Leufkens HGM, Cooper C (2002) Does a fracture at one site predict later fractures at other sites? A British cohort study. Osteoporos Int 13: 624-629 |
| 17. | Robinson CM, Royds M, Abraham A, McQueen MM, Court-Brown CM, Christie J (2002) Refractures in patients at least forty-five years old. A prospective analysis of twenty-two thousand and sixty patients. J Bone Joint Surg Am 84: 1528–33. |
| 18. | Kanis JA, Johansson H, Odén A, Harvey NC, Gudnason V, Sanders K, Sigurdsson G, Siggeirsdottir K, Borgström F, McCloskey EV (2018) Characteristics of recurrent fractures. Osteoporosis International 29: 1747-1757. |
| 19. | Kanis JA, Johansson H, Harvey NC, Gudnason V, Sigurdsson G, Siggeirsdottir K, Lorentzon M, Liu M, Vandenput L, McCloskey E (2020) Effects of the recency of sentinel fractures on conventional estimates of fracture probability using FRAX. Osteoporosis International. |
| 20. | Bjornsson OJ, Davidsson. D., Olafsson H et al (1979) Report XVIII. Health Survey in the Reykjavik Area. — Men. Stages I–III, 1967–1968, 1970–1971 and 1974–1975. Participants, Invitation, Response etc. The Icelandic Heart Association, Reykjavík |
| 21. | Bjornsson G, Bjornsson OJ, Davidsson D et al (1982) Report abc XXIV. Health Survey in the Reykjavik Area. – Women. Stages I-III, 1968–1969, 1971-1972 and 1976-1978. Participants, Invitation, Response etc. The Icelandic Heart Association, Reykjavík  |
| 22. | Siggeirsdottir K, Aspelund T, Sigurdsson G, Mogensen B, Chang M, Jonsdottir B, Eiriksdottir G, Launer LJ, Harris TB, Jonsson BY, Gudnason V (2007) Inaccuracy in self-report of fractures may underestimate association with health outcomes when compared with medical record based fracture registry. Eur J Epidemiol 22: 631-639. |
| 23. | Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A (2001) The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int 12:417–427 |
| 24. | Breslow NE, Day NE (1987) Statistical methods in cancer research, vol 2. IARC Scientific Publications, no 32, Lyon 131–135 |
| 25. | Albertsson-Wikland K, Martensson A, Savendahl L Niklasson A, Bang P, Dahlgren J, Gustafsson J, Kriström B, Norgren S, Pehrsson NG, Odén A (2016) Mortality is not increased in recombinant human growth hormone-treated patients when adjusting for birth characteristics. J Clin Endocrinol Metab 101: 2149-2159. |
| 26. | Söreskog E, Ström O, Spångéus A, Åkesson KE, Borgström F, Banefelt J, Toth E, Libanati C, Charokopou M (2000) Risk of major osteoporotic fracture after first, second and third fracture in Swedish women aged 50 years and older. Bone 134:115286. doi: 10.1016/j.bone.2020.115286.  |
| 27. | Kanis JA on behalf of the World Health Organization Scientific Group (2007) Assessment of osteoporosis at the primary health-care level. Technical Report. WHO Collaborating Centre, University of Sheffield, UK. Available at <http://www.shef.ac.uk/FRAX/index.htm> |
| 28. | Kanis JA, Johnell O, Oden A, Johansson H, McCloskey EV (2008b) FRAX™ and the assessment of fracture probability in men and women from the UK. Osteoporos Int 19: 385-397. |

**Table 2.** Risk of a MOF (Hazard ratio with 95% CI) 10 years after a sentinel fracture at the sites shown.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Vertebral | Hip | Forearm | Humerus  | Minor osteoporotic | Any osteoporotic |
|  | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| Women |  |  |  |  |  |  |  |  |  |  |  |  |
| 40 |  5.6 |  3.8-8.4 |  6.4 | 4.1-10.2  |  3.1 | 2.3-4.1  |  3.8 | 2.4-6.1  | 2.6 | 1.9-3.6 |  2.9 |  2.4- 3.7 |
| 50 |  4.3 | 3.1-5.9  |  4.7 | 3.3-6.8  |  2.6 | 2.0-3.2  |  3.2 | 2.3-4.6  | 2.3 | 1.8-3.0 |  2.5 |  2.1- 3.0 |
| 60 |  3.3 | 2.6-4.2  |  3.5 | 2.6-4.6  |  2.1 | 1.8-2.5  |  2.7 | 2.1-3.6  | 2.1 | 1.8-2.5 |  2.2 |  1.9- 2.5 |
| 70 |  2.5 | 2.0-3.1  |  2.6 | 2.1-3.2  |  1.8 | 1.6-2.0  | 2.3  | 1.9-2.8  | 1.9 | 1.6-2.2 |  1.8 |  1.7- 2.1 |
| 80 |  1.9 | 1.6-2.3  |  1.9 | 1.5-2.3  |  1.5 | 1.3-1.7  |  1.9 | 1.6-2.3  | 1.7 | 1.5-1.9 |  1.6 |  1.4- 1.8 |
| 90 |  1.5 | 1.2-1.8  |  1.4 | 1.1-1.7  |  1.3 | 1.1-1.5  | 1.6  | 1.3-2.1  | 1.5 | 1.3-1.8 |  1.4 |  1.2- 1.6 |
| Men |  |  |  |  |  |  |  |  |  |  |  |  |
| 40 |  9.0 | 5.9-13.7  | 14.3 |  8.9-23.0 |  6.4 | 4.5-9.0  |  6.9 | 4.2-11.1  |  3.5 |  2.5- 4.8 |  5.0 |  3.9- 6.3 |
| 50 |  6.9 | 4.8-9.7  |  10.5 | 7.1-15.5  |  5.3 | 4.0-7.1 |  5.8 | 3.9-8.6  |  3.1 |  2.4- 4.0 |  4.2 |  3.5- 5.1 |
| 60 |  5.2 | 3.9-7.0  |  7.7 | 5.6-10.6  |  4.5 | 3.5-5.7  |  4.9 | 3.5-6.8  |  2.8 |  2.3- 3.4 |  3.6 |  3.1- 4.3 |
| 70 |  4.0 | 3.1-5.2 |  5.6 | 4.3-7.4  |  3.7 | 3.0-4.6  |  4.1 | 3.1-5.5  |  2.5 |  2.1- 3.0 |  3.1 |  2.7- 3.6 |
| 80 | 3.1 | 2.4-3.9  |  4.1 | 3.2-5.4  |  3.1 | 2.5-3.8  |  3.5 | 2.6-4.6  |  2.3 |  1.9- 2.7 |  2.7 |  2.3- 3.1 |
| 90 |  2.3 | 1.7-3.1  |  3.0 | 2.3-4.0  |  2.6 | 2.1-3.3  |  2.9 | 2.1-4.0  |  2.0 |  1.6- 2.5 |  2.3 |  1.9- 2.7 |

**Table 3.** Risk of a hip fracture (Hazard ratio with 95% CI) 10 years after a sentinel fracture at the sites shown.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Vertebral | Hip | Forearm | Humerus  | Minor osteoporotic | Any osteoporotic |
|  | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| Women |  |  |  |  |  |  |  |  |  |  |  |  |
| 40 |  9.3 | 4.6-18.9  |  46.7 | 24.5-88.8  |  3.4 | 2.0-5.8  |  7.4 | 3.4-15.9  | 5.7 | 3.3-9.7 |  4.7 |  3.2- 6.9 |
| 50 |  6.1 | 3.5-10.7  |  22.1 | 13.3-36.8  |  2.7 | 1.8-4.1  |  5.2 | 2.8-9.4  | 4.2 | 2.8-6.4 |  3.6 |  2.7- 4.8 |
| 60 |  4.0 | 2.7-6.1  |  10.5 | 7.1-15.4  |  2.1 | 1.6-2.9  |  3.6 | 2.3-5.6  | 3.1 | 2.3-4.2 |  2.7 |  2.2- 3.3 |
| 70 |  2.7 | 2.0-3.6  |  5.0 | 3.7-6.6  |  1.7 | 1.4-2.1  |  2.5 | 1.8-3.4  | 2.3 | 1.8-2.9 |  2.0 |  1.8- 2.4 |
| 80 |  1.7 | 1.4-2.2  |  2.4 | 1.8-3.0  | 1.4  | 1.2-1.6  |  1.8 | 1.4-2.3  | 1.7 | 1.4-2.0 |  1.5 |  1.3- 1.8 |
| 90 |  1.1 | 0.9-1.5  |  1.1 | 0.8-1.5  |  1.1 | 0.9-1.4  |  1.2 | 0.9-1.6  | 1.2 | 1.0-1.6 |  1.2 |  1.0- 1.4 |
| Men |  |  |  |  |  |  |  |  |  |  |  |  |
| 40 | 12.4 | 5.9-25.8  | 92.4 | 47.9-178.0 | 5.6 | 3.1-10.1  | 14.6 | 6.7-31.8  | 7.5 | 4.4-12.7 |  7.3 |  5.0-10.9 |
| 50 |  8.1 | 4.5-14.8  |  43.7 | 25.7-74.5  |  4.5 | 2.8-7.3  |  10.2 | 5.4-19.1  | 5.5 | 3.6-8.4 |  5.5 |  4.1- 7.6 |
| 60 |  5.3 | 3.3-8.6  | 20.7 | 13.6-31.6  |  3.6 | 2.4-5.3  |  7.1 | 4.3-11.6  | 4.1 | 2.9-5.7 |  4.2 |  3.3- 5.3 |
| 70 |  3.5 | 2.4-5.2  |  9.8 | 7.0-13.8  |  2.9 | 2.1-4.0  |  5.0 | 3.4-7.4  | 3.0 | 2.3-3.9 |  3.2 |  2.6- 3.8 |
| 80 |  2.3 | 1.6-3.3  |  4.6 | 3.4-6.4  |  2.3 | 1.7-3.1  |  3.5 | 2.4-5.0  | 2.2 | 1.7-2.9 |  2.4 |  2.0- 2.9 |
| 90 |  1.5 | 1.0-2.3  |  2.2 | 1.5-3.1  |  1.8 | 1.3-2.6  |  2.4 | 1.6-3.7  | 1.6 | 1.2-2.2 |  1.8 |  1.4- 2.3 |