*Number of prior fractures v4*

**Adjusting** **conventional FRAX estimates of fracture probability according to the number of prior fractures**

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**Abstract**

*Summary* The risk of a recurrent fragility fracture is high following a first fracture and higher still with more than one prior fracture. This study provides adjustments to FRAX-based fracture probabilities accounting for the number of prior fractures.

*Introduction* Prior fractures increase subsequent fracture risk. The aim of this study was to quantify the effect of the number of prior fractures on the 10-year probability of fracture determined with FRAX®.

*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. Ten-year probabilities of hip fracture and major osteoporotic fracture (MOF) were determined according to the number of prior osteoporotic fractures over a 20-year interval from the hazards of death and fracture. Fracture probabilities were also computed for a prior osteoporotic fracture irrespective of the number of previous fractures. The probability ratios provided adjustments to conventional FRAX estimates of fracture probability according to the number of prior fractures.

*Results* Probability ratios to adjust 10-year FRAX probabilities of a hip fracture and MOF increased with the number of prior fractures but decreased with age in both men and women. Probability ratios were similar in men and women, and for hip fracture and MOF. Mean probability ratios according to the number of prior fractures for all scenarios were 0.95, 1.08, 1.21 and 1.35, for 1,2, 3 and 4 or more prior fractures, respectively. Thus, a simple rule of thumb Is to downward adjust FRAX-based fracture probabilities by 5% in the presence of a single prior fracture and to uplift probabilities by 10, 20, and 30% with a history of 2, 3 and 4 or more prior fractures, respectively.

*Conclusion* The probability ratios provide adjustments to conventional FRAX estimates of fracture probability according to the number of prior fractures.

**Key words**: FRAX adjustment ∙ Fracture probability ∙ Prior fracture ∙ Risk assessment

**Introduction**

In 2008, the then World Health Organization (WHO) Collaborating Centre at Sheffield, UK released FRAX®, a fracture risk assessment tool for estimating individualized 10-year probability of hip and major osteoporotic fracture (MOF; hip, clinical spine, distal forearm or proximal humerus) [1]. The FRAX tool integrates seven dichotomous clinical risk factors (prior fragility fracture, parental hip fracture, smoking, systemic glucocorticoid use, excess alcohol intake, rheumatoid arthritis, and other secondary causes of osteoporosis) which, in addition to age, sex and body mass index (BMI), contribute to a 10-year fracture probability estimate independently of bone mineral density (BMD) [1, 2]. BMD at the femoral neck is an optional input variable. FRAX tools are country specific to take account of the heterogeneity of fracture risk and mortality worldwide [3]. Since its release, 86 models have been made available for 78 countries covering more than 80% of the world population [4]. The tool provides metrics which are increasingly used in health technology assessment [5, 6, 7] and regulatory guidance [8].

Prior fragility fracture, a well-established risk factor for a future fracture [9, 10, 11, 12, 13], is already accommodated within FRAX [1]. The population relative risk of having a hip fracture or other osteoporotic fracture is approximately 2-fold higher for most types of prior fracture. However, the increase in risk is not constant with age. For example, a large meta-analysis showed that a prior fracture history was a significant risk factor for hip fracture at all ages, but the population relative risk was highest at younger ages and decreased progressively with age [13]. Also, the risk of a subsequent osteoporotic fracture is particularly acute immediately after an index fracture and wanes progressively with time [14, 15, 16]. The waning of risk with time is also age-dependent [17]. Although these additional refinements of risk are not currently captured in FRAX, exploratory arithmetic adjustments have been developed which can be applied to conventional FRAX estimates of probabilities of hip fracture and a MOF [18, 19]. These and other adjustments to FRAX will shortly be accessible in FRAXplus through the FRAX web portal.

Several prior fractures carry a risk greater than a single prior fracture [20, 21, 22, 23, 24, 25], but the impact on FRAX-based probabilities is not known. The aim of the present study was to determine the impact of the number of prior fractures on fracture probability and a means to adjust FRAX-based probabilities.

**Methods**

*Study cohort*The total 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 [26, 27]. The study was approved by the National Bioethics Committee and the Data Protection Authority in Iceland. All participants gave written consent.

The current study is based on 18,872 participants who attended during the recruitment period in 1967–1991, comprising 9,116 men and 9,756 women as previously described [18]. The present analysis was confined to 2783 individuals who had sustained one or more fractures in the previous 20 years. Thus, the baseline for analysis was 20 years after enrolment to the study with a mean follow up time of 11.2 years until death, emigration, or December 31st, 2012, yielding a total of 31,170 person-years of observation.

*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, as were fractures at skeletal sites not considered to be associated with osteoporosis (e.g. face, skull, hands, feet) [28]. The register has been shown to have a capture rate of about 97% for hip, forearm, and clinical vertebral fractures [29]. The circumstances of the trauma leading to the fracture were assessed, but all fractures were counted regardless of trauma since high-trauma fractures are associated with low bone mineral density and future fracture risk to the same extent as fractures without high-trauma [30]. 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. In a sensitivity analysis to further explore the potential impact of double counting, hazard ratios for fracture were compared where two or more consecutive fractures at the same site were additionally excluded from analysis.

Prior fractures comprised those at skeletal sites considered to be associated with osteoporosis [28]. Outcome fractures comprised clinical vertebral fracture (ICD 10 codes S12.0-S12.2, S12.7, S22.0-22.1, S32.0), humeral fractures (S42.2-42.3), distal forearm fracture (S52.5-52.6) and hip fracture (S72.0-S72.2), collectively termed major osteoporotic hip fracture (MOF) and hip fracture alone.

*Fracture probabilities.*

FRAX computes the 10-year probability of hip or major osteoporotic fracture. In the case of a prior fracture, FRAX does not characterise the number of prior fractures so that the coefficient reflects an exposure to an average number of prior fractures. In order to determine an adjustment to FRAX for the actual number of prior fractures, fracture probabilities were calculated using the Reykjavik study as previously described from the hazards of death and fracture [31, 32]. In this way, the 10-year probability of fracture, for example, after a single prior fracture, two prior fractures or three prior fractures etc was compared with the 10-year probability of a prior fragility fracture irrespective of their number (in keeping with that provided in the current FRAX algorithm). It is important to note that the probability models used were based on purpose-built models similar, but not identical, to FRAX. The ratio of the two probabilities provided an adjustment to FRAX hereafter referred to as the probability ratio or adjustment ratio.

A modification of the Poisson regression model [33, 34] was used to study the relationship between sex, age, and the number of previous fractures on the one hand and on the other hand, the risk of a future MOF or hip 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 baseline fracture + β3 · current age + β4 · number of previous fracture). The beta coefficients reflect the importance of the variables, and βx = 0 denotes that the corresponding variable does not contribute to fracture risk. All associations were adjusted for age and time since baseline. For the sensitivity analysis, the hazard function for a further fracture (MOF or hip fracture) was calculated in men and women with no prior fracture and after 1, 2, and 3 or more prior fractures.

**Results**

Characteristics of the population studied are given in Table 1. Mean age at recruitment to the Reykjavik study was 52 years. Thus, age at baseline for the present analysis was 20 years on with a mean age of 73 years and a range of 53-99 years. As expected, more women than men had sustained a prior fragility fracture (2065 vs. 718). During follow up, 1021 MOFs were sustained of which 476 were fractures at the hip.

**Table 1.** Characteristics of the population with one or more prior osteoporotic fractures.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Mean | SD | Range | n | % |
| Men |  |  |  | 718 | 26 |
| Women |  |  |  | 2065 | 74 |
| Age at recruitment (years) | 52.3 | 7.8 | 33-79 | 2783 |  |
| Age at baseline (years) | 73.2 | 7.8 | 53-99 | 2783 |  |
| Previous MOF |  |  |  | 2123 | 76.3 |
| Number of prior fractures |  |  |  |  |  |
|  1 |  |  |  | 1907 | 68.5 |
|  2 |  |  |  | 586 | 21.1 |
|  3 |  |  |  | 179 | 6.4 |
|  > 4 |  |  |  | 111 | 4.1 |
| Follow up (years) | 11.2 | 6.8 | 0.0-25.1 | 2783 |  |
| MOF during follow up |  |  |  | 1021 | 36.7 |
| Hip fracture during follow up |  |  |  | 476 | 17.1 |

Fracture probabilities were calculated between the ages of 60 and 85 years since there were few individuals outside this age range (37 men and 78 women age <60 years, and 23 men and 146 women age >85 years). Ten-year probabilities of MOF and hip fracture are given in Tables 2 and 3, respectively. Fracture probabilities were higher in women than in men. In the case of MOF, fracture probabilities rose with age, though above the age of 80 years they decreased due to the competing effect of mortality. When 10-year fracture probability was calculated in all participants irrespective of the number of prior fractures, the probability was marginally higher than in men or women with a single prior fracture. For example, in women age 65 years, the 10-year probability of a MOF was 30.2% when no account was taken of the number of prior fractures (see Table 2). In women of the same age but with a single prior fracture, the probability was marginally lower at 28.2%. Thereafter, fracture probability rose with increasing number of prior fractures in men and in women, irrespective of age.

**Table 2**. Ten- year probability of a major osteoporotic fracture by age in men and women with a prior fragility fracture irrespective of the number of prior fractures and according to the number of prior fractures.

|  |  |  |
| --- | --- | --- |
|  |  | Number of prior fractures |
|  | Age (years) | Any number | 1 | 2 | 3 | ≥4 |
| Men  |  60  |  14.6  | 14.1 | 16.7 | 19.7 | 23.0 |
|  |  65  |  16.5  | 15.6 | 18.6 | 21.8 | 25.2 |
|  |  70  |  18.3  | 17.5 | 20.3 | 23.4 | 26.8 |
|  |  75  |  19.4  | 18.6 | 21.2 | 23.9 | 26.6 |
|  |  80  |  18.9  | 18.1 | 20.1 | 22.0 | 23.9 |
|  |  85  |  16.3  | 15.9 | 17.1 | 18.2 | 19.3 |
|  |  |  |  |  |  |  |
| Women |  60  |  26.6  | 25.0 | 29.3 | 34.1 | 39.4 |
|  |  65  |  30.2  | 28.2 | 32.8 | 37.9 | 43.3 |
|  |  70  |  33.7  | 31.4 | 36.2 | 41.2 | 46.5 |
|  |  75  |  36.5  | 34.2 | 38.7 | 43.3 | 48.0 |
|  |  80  |  37.3  | 35.2 | 38.9 | 42.6 | 46.1 |
|  |  85  |  34.9  | 33.3 | 36.0  | 38.4  | 40.6 |
|  |  |  |  |  |  |  |

**Table 3**. Ten- year probability of a hip fracture by age in men and women with a prior fragility fracture irrespective of the number of prior fractures and according to the number of prior fractures.

|  |  |  |
| --- | --- | --- |
|  |  | Number of prior fractures |
|  | Age (years) | Any number | 1 | 2 | 3 | ≥4 |
| Men  |  60  |  2.4  | 2.4 | 2.8 | 3.2 | 3.7 |
|  |  65  |  4.3  | 4.1  | 4.8  | 5.5  | 6.3  |
|  |  70  |  6.9  | 6.6 | 7.6  | 8.6 | 9.7 |
|  |  75  |  9.6  | 9.3  | 10.4 | 11.5  | 12.6  |
|  |  80  |  11.6  | 11.3 | 12.2 | 13.0  | 13.8  |
|  |  85  |  12.1  | 12.0 | 12.4  | 12.8  | 13.1  |
|  |  |  |  |  |  |  |
| Women |  60  |  3.5  | 3.3  | 3.9  | 4.5  | 5.3  |
|  |  65  |  6.2  | 5.8  | 6.8  | 7.9  | 9.1  |
|  |  70  |  10.3  | 9.6  | 11.0  | 12.6  | 14.4  |
|  |  75  |  14.8  | 13.8  | 15.7  | 17.6  | 19.6  |
|  |  80  |  19.0  | 18.0 | 19.8  | 21.5  | 23.2  |
|  |  85  |  21.6  | 20.8  | 22.1  | 23.2  | 24.1  |

The probability ratio, representing the ratio of 10-year probability with a given number of prior fractures versus the probability irrespective of the number of prior fractures, is shown in figure 1. In men and women with a single prior fracture, the probability ratio was marginally lower than unity, but rose progressively as the number of prior fractures increased. Probability ratios decreased with age, an effect that was more marked the greater the number of prior fractures.



**Fig.1.** Probability ratios for a major osteoporotic fracture (MOF) and hip fracture (HF) in men and in women by age according to the number of prior fractures.

There were differences in probability ratios between men and women but the differences were of statistical significance rather than of clinical significance. For MOF, the mean probability ratio in women was lower by 0.023 than in men (p<0.001, 95% CI: 0.021- 0.026). For hip fracture the ratio in women was 0.025 lower than in men (p<0.001, 95% CI: 0.022-0.028). Similarly, there was a statistically significant difference between the probability ratios for MOF and hip fracture (p<0.001) but the difference was small and of no clinical significance (mean difference overall 0.0010 with a SD of 0.011 (95% CI: 0.0006-0.0014).

In the sensitivity analysis, hazard ratios for fracture outcomes did not differ when two or more consecutive fractures at the same site were excluded from analysis. This held true for men and for women, for hip fracture and MOF. Data are shown for women in Figure 2.



**Fig. 2** Hazard ratio (HR) for a major osteoporotic fracture (left panel) and hip fracture (right) according to the number of prior osteoporotic fractures. The unshaded bars provide values where two or more consecutive fractures at the same site were excluded from analysis to avoid double counting.

**Discussion**

This study shows that the risk of a hip fracture and MOF increases with the number of prior fragility fractures. Several studies have shown similar effects. The increase in risk is particularly marked when the prior fracture and outcome fractures are radiographic spine fractures [20, 21, 22, 23, 24]. In these studies, the increment in risk between a first and second fracture ranged from 1.40 to 3.06 in women (Table 4). The impact of the number of prior clinical fractures on subsequent fracture outcomes is less well studied. The increment in risk is more modest where prior fractures are osteoporotic fracture which in women ranged from 1.05 to 1.26 [25], similar to the increments found in the present study (see Table 4).

**Table 4** Risk ratio for a subsequent fracture in the presence of two prior fractures versus a single prior fracture at the sites shown. Vertebral fracture refers to radiographic vertebral deformities.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Prior fracture | Outcome fracture | 2 vs. 1 prior fracture | Average age(Years)  | Sex | Publication |
| Vertebral | Vertebral | 2.28 | 69 | F | Gallacher 2005 [23] |
| Vertebral | Vertebral | 1.68 | 69  | F | Black 1999 [20] |
| Vertebral | Vertebral | 1.53-1.84a | 66  | F | Siris 2007 [24] |
| Vertebral | Vertebral | 3.06 | 65  | M and F | Lunt 2003 [22] |
| Vertebral | Vertebral | 1.40 | 67  | F | Delmas 2003 [21] |
| Vertebral | Forearm | 1.02 | 69  | F | Black 1999 [20] |
| Vertebral | Nonvertebral | 1.22 | 69  | F | Black 1999 [20] |
| Vertebral | Hip | 1.10 | 69  | F | Black 1999 [20] |
| Vertebral | Any | 1.05-1.12a,c | 66  | F | Siris 2007 [24] |
| Nonvertebral | Nonvertebral | 2.20c | 69  | F | Gallacher 2005 [23] |
| Osteoporotic | Osteoporotic | 1.26 | 67  | F | Agarwal 2021 [25] |
| Osteoporotic | Osteoporotic | 0.75 | 69  | M | Agarwal 2021 [25] |
| Osteoporotic | Hip | 1.25 | 67  | F | Agarwal 2021 [25] |
| Osteoporotic | Major osteoporotic | 1.16b | 65  | M | Present study |
| Osteoporotic | Hip | 1.17b | 65  | M | Present study |
| Osteoporotic | Major osteoporotic | 1.15b | 65  | F | Present study |
| Osteoporotic | Hip | 1.17b | 65  | F | Present study |
| a Range dépendent on T-score |
| b Range dependent on age |
| c >2 vs. 1 fracture |

As expected, 10-year fracture probabilities increased progressively as the number of prior fractures increased. Probability ratios (the ratio of 10-year probability with a given number of prior fractures versus the probability irrespective of the number of prior fractures) permit the adjustment of FRAX-based probabilities with knowledge of the number of prior osteoporotic fractures. In the case of a single prior fracture, FRAX is marginally downward adjusted. The reason is that FRAX takes no account of the number of prior fractures. Rather, it assumes an average number of prior fractures which, in the present study, was 1.48. Thereafter, FRAX is progressively upward adjusted as the number of prior fractures increase.

Although the magnitude of the adjustment varied according to the number of prior fractures, for the most part the adjustment was similar in men and women, and for MOF and hip fracture probability. This permits a simplification of the adjustment algorithm for clinical use. The mean probability ratio according to the number of prior fractures for all scenarios in Figure 1 were 0.95, 1.08, 1.21, and 1.35 for 1,2, 3 and 4 and more prior fractures, respectively. Thus, a simple rule of thumb would be to downward adjust FRAX-based fracture probabilities by 5% in the presence of a single prior fracture and to uplift probabilities by 10, 20, and 30% with a history of 2, 3 and 4 or more prior fractures, respectively. The rule makes the assumption that differences in fracture probability (MOF or hip fracture), sex and age are similar. Inspection of figure 1, however, indicates that constancy of the probability ratio by age to be an oversimplification, particularly the higher the number of prior fractures. For this reason, computer-based algorithms could provide a more accurate assessment of the adjustment for the number of prior fractures.

Many practice guidelines recommend treatment in individuals who have sustained a fragility fracture [35]. It might be argued that, if patients with a prior fracture are to be treated, then adjustment for number of prior fractures is not worthwhile in that the adjustment to FRAX would not change the decision to treat an individual. However, several considerations should temper this view. First, some assessment guidelines restrict the indication for treatment to a prior hip fracture alone, prior hip or vertebral fractures, to multiple fractures, or to fracture patients only in the presence of densitometric osteoporosis [24, 36, 37, 38, 39, 40]. Second, patients may be reclassified from high risk to very high risk, a dichotomisation recognised by the International Osteoporosis Foundation (IOF), the European Society for Clinical and Economic Evaluation of Osteoporosis and Osteoarthritis (ESCEO) [41], American Association of Clinical Endocrinologists, American College of Endocrinology [42] and more recently by the National Osteoporosis Guideline Group (NOGG) in the UK [43, 44. Those designated at very high risk are considered to be candidates for anabolic treatment followed by antiresorptive treatment as first line rather than treatment with inhibitors of bone resorption alone. Anabolic agents, including new agents such as abaloparatide and romosozumab, or established agents such as teriparatide, have demonstrably more rapid and greater fracture risk reductions than antiresorptive treatments [45, 46, 47]. Finally, the discussion of fracture probabilities is of value in the interaction of patients and health care professionals which may in turn promote adherence to medication [48].

Strengths of this study were the random sampling of a large population, the detail placed on fracture ascertainment, the long duration of observation [27] and the high accuracy for the ascertainment of fractures [29]. However, there were also, some limitations which should be considered in the interpretation of the results. First, the probability calculations and the ratios derived therefrom were determined without the inclusion of bone mineral density or other FRAX risk factors for fracture, an omission that requires further study. Notwithstanding, the increased fracture risk associated with a prior fracture is largely independent of bone mineral density [12]. A further limitation is the lack of external validation in terms of probability ratios. The increase in fracture risk, however, was comparable to other independent studies. Moreover, the increase in fracture risk associated with a prior fracture is remarkably constant worldwide. Notwithstanding, confirmation in further studies in different populations is warranted. Finally, a 20-year horizon for fracture history was chosen and it is possible that other horizons could yield different fracture risks. The omission of some fractures in our sensitivity analysis suggests that the effect, if any, is likely to be small.

For the present study, we relied on within cohort probability calculations rather than on FRAX. This was required because a proportion of individuals with a prior fracture would have other risk factors whereas FRAX, developed for individual rather than population assessment, does not accommodate proportional exposure to clinical risk factors. Despite the differences in absolute probabilities, the risk ratio for a prior fracture versus no prior fracture was near identical in the present study to that of FRAX [18]. This supports a view that the probability ratios derived in the present study can be applied to adjust FRAX estimates of fracture probability in all FRAX models.

Ideally, FRAX should incorporate the number of prior fragility fractures as an input variable. However, the incorporation of this variable into FRAX would demand international confirmation with prospective databases that had more or less complete information on all FRAX risk factors. Such data do not (yet) exist. For this reason, our intent is to develop an ‘add on’ to FRAX in much the same way as is undertaken for Trabecular Bone Score, to allow for exploratory examination of the impact of prior fracture number as well as recency of fracture, glucocorticoid dose etc under the banner of FRAXplus®.

We conclude that that it is feasible to use a simple arithmetic procedure

to adjust major osteoporotic fracture and hip fracture risk predictions from FRAX based upon the number of prior fractures. This will shift some individuals into a different risk category and thereby facilitate identification and treatment of those who would most benefit.

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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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