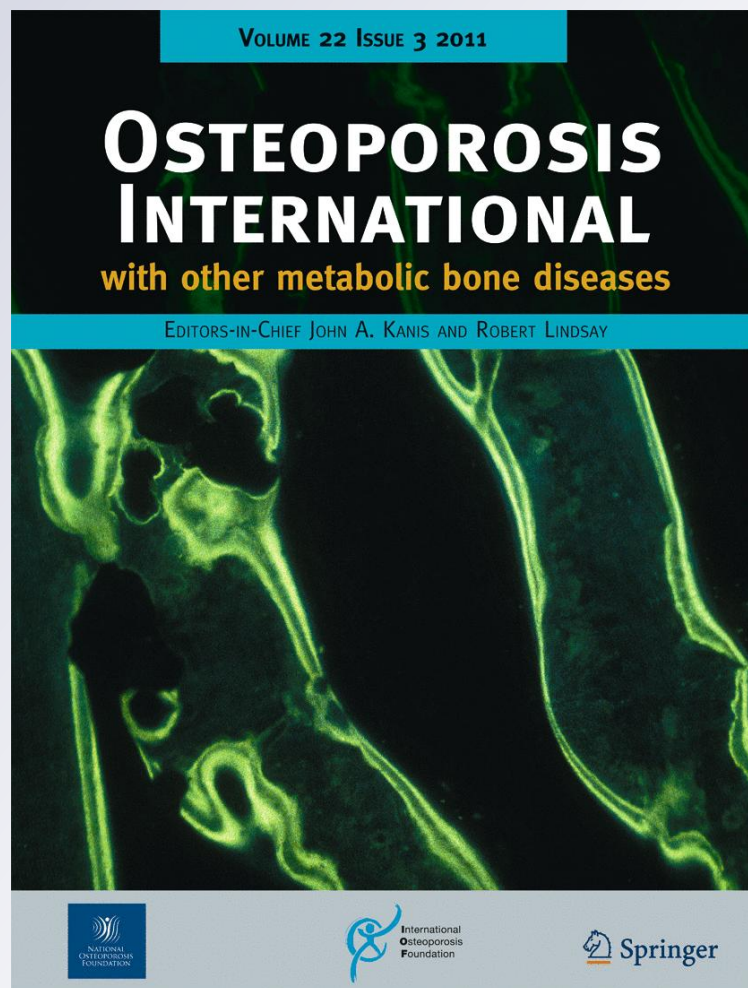


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Guidance for the adjustment of FRAX according to the dose of glucocorticoids

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Abstract

Summary We examined the effect of glucocorticoid dose on FRAX[®] derived fracture probabilities in a UK setting. A relatively simple adjustment of conventional FRAX estimates of probabilities of hip fracture and a major osteoporotic fracture can be applied to modulate the risk assessment with knowledge of the dose of glucocorticoids.

Introduction The WHO fracture risk assessment (FRAX) tool estimates 10-year probability of fracture based upon multiple clinical risk factors and an optional femoral neck BMD measurement. Ever (past and current) use of systemic glucocorticoids is a dichotomous risk factor (yes/no) and does not therefore take account of the dose of glucocorticoids. The aim of this work was to estimate the adjustment for fracture probability based upon the dose of glucocorticoids.

Methods Dose responses for fracture risk during exposure to glucocorticoids were taken from the General Practice Research Database and used to adjust the relative risks for glucocorticoids in FRAX. In addition to fracture risk, a dose response for the death hazard was estimated and both variables were used to populate the FRAX model for the UK.

Results The exposure to glucocorticoids was found to significantly affect fracture probability. The following rule was formulated. For low-dose exposure (<2.5 mg daily of prednisolone or equivalent), the probability of a major fracture is decreased by about 20% depending on age. For medium doses (2.5–7.5 mg daily), the unadjusted FRAX value can be used. For high doses (>7.5 mg daily),

probabilities can be upward revised by about 15%. Conversion factors were also determined for the adjustment of hip fracture probability.

Conclusion A relatively simple adjustment of conventional FRAX estimates of probabilities of hip fracture and a major osteoporotic fracture can be applied to modulate the risk assessment with knowledge of the dose of glucocorticoids.

Keywords Dose response · Fracture probability · Fractures · Glucocorticoids · GPRD · Osteoporosis

Introduction

In 2008, the WHO Collaborating Centre for Metabolic Bone Diseases released the fracture risk assessment tool (FRAX[®]) which estimates the 10-year probability of hip and major osteoporotic fracture (hip, clinical spine, distal forearm, and humerus) with and without information on femoral neck BMD [1, 2]. FRAX integrates seven clinical risk factors (prior fragility fracture, a parental history of hip fracture, smoking, use of systemic corticosteroids, excess alcohol intake, body mass index (BMI) and rheumatoid arthritis) which, in addition to age and sex, contribute to fracture risk independently of BMD [3]. The FRAX website (www.shef.ac.uk/FRAX/) receives about 35 million hits per year and more recently has become available on densitometers and as an iPod/iPhone application (<http://itunes.apple.com/us/app/frax/id370146412?mt=8>). FRAX has also been incorporated into practice guidelines [4–13], including those for the UK [14, 15].

With its widespread use, it is important to recognise that FRAX provides a tool for the assessment of fracture probability and not a gold standard [16, 17]. In much the same way, BMD results must be interpreted in the light of

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other clinical risk factors, so too must FRAX. For example, FRAX does not incorporate all risk factors associated with fracture that are independent of BMD, such as a history of falls [18]. A further consideration is the question of dose–response. For example, current smoking can be entered as yes or no, and does not therefore take account that there is a difference in fracture and death risk between those that smoke heavily or moderately [19, 20]. Rather, FRAX assumes an average risk, providing hazard ratios for an average number of cigarettes smoked and an average duration of smoking exposure [2]. In addition to smoking, dose response effects have been shown for alcohol intake [21], the site or number of prior fractures [22–25], and the dose and duration of exposure to glucocorticoids [26–29].

In the absence of dose–response information embedded in FRAX, some guidance concerning the quantum of effect of dose on fracture probability may aid the assessment of patients. The objective of the present study was to examine the effect of dose of glucocorticoids on fracture probability. A secondary objective was to determine whether a simple algorithm could be developed whereby fracture probabilities, determined by FRAX, might be adjusted to accommodate information on the dose of glucocorticoids.

Methods

The most extensive assessment of dose response effects of glucocorticoids on fracture risk is the study of Van Staa et al. [26–28] that examined the general practitioner records of the UK using the General Practice Research Database (GPRD)

General practice research database

GPRD comprises computerised medical records of general practitioners. We used the published data from this source that described fracture risk in patients exposed to oral glucocorticoids [26–28]. In this study, cases were defined as permanently registered patients aged 18 years or more, who received one or more prescriptions for oral glucocorticoids during the period of time from enrolment date of their practice to GPRD up to the end of study. Baseline date was the date of the first oral glucocorticoid prescription. Follow up was until fracture or 91 days after the last oral glucocorticoid prescription or the patient changed practice or death or the end of study. Controls comprised age, gender and practice-matched adult patients who received non-systemic (topical, aural and ophthalmic or nasal) glucocorticoid prescriptions. They were monitored from a randomly selected baseline date until the fracture, the patient changed practice, death or until the end of study. Outcome events comprised hip fracture (ICD 820), forearm

fracture (ICD 813), vertebral fracture (ICD 805–806) and non-vertebral fracture (ICD 800–804 and ICD 807–829)

The daily glucocorticoid dose over the total treatment period was estimated as the total amount of prescribed prednisolone (or equivalent dose) in milligrammes divided by the treatment time. Exposure was categorised as low dose (<2.5 mg/day), medium dose (2.5–7.5 mg/day) and high dose (\geq 7.5 mg/day). Relative rates of fracture were adjusted for diabetes, rheumatoid arthritis, hyperthyroidism, heart failure, seizures, anaemia, dementia, depression psychotic disorders, cardiovascular accidents, falls, history of fracture, back pain before baseline and prescription of several other medications. Relative risks are shown in Table 1. There was a significant dose–response for all fracture sites except forearm. It should be noted that the number of vertebral fractures reported was low, consistent with the variable underreporting of vertebral fractures in the UK [30]. There was no compelling evidence for an age-dependent effect on fracture risk as assessed by visual inspection [26, 28]. These estimates of fracture risk are comparable to those determined by meta-analysis of studies reporting fracture outcomes in individuals taking 5 mg of prednisolone or more [29]. Comparable figures are derived from the United States [31].

FRAX

The FRAX estimates of fracture risk use the average exposure to glucocorticoids [32] which was assumed to be equivalent to the medium dose of GPRD. However, the FRAX estimates of fracture risk were somewhat higher than that reported in GPRD. For example, the average hazard ratio for hip fracture risk was 2.62 in men and 2.07 in women in our meta-analysis [32] and 1.77 (1.55–2.02) with GPRD. Although the differences are not statistically significant, it should be noted that the controls used in GPRD were patient- and not population-based. The effect of this bias is likely to underestimate the risk of glucocorticoid exposure—offset perhaps by the FRAX cohorts using past and current use rather than predominantly current use as in the GPRD. For this reason, and in order not to disrupt the structure of FRAX, we assumed that the medium dose provided the hazard ratio of hip fracture as seen in FRAX and we adjusted the FRAX hazard ratios upward by 28% (derived from 2.27/1.77, Table 1) and downwards by 44% (0.99/1.77, Table 1) for the high and low dose, respectively, according to the differentials reported in GPRD.

The calculation of the probability of a major osteoporotic fracture requires a fracture risk estimate of the major fractures other than hip fractures [1]. The reason is that glucocorticoids and other CRFs almost certainly have different effects on the risk of fracture at different sites

Table 1 Adjusted relative risk (95% CI) of fracture compared to controls according to dose of oral glucocorticoids [26]

Fracture outcome	Low dose <i>n</i> =50 649	Medium dose <i>n</i> =104 833	High dose <i>n</i> =87 949
Nonvertebral	1.17 (1.10–1.25)	1.36 (1.28–1.43)	1.64 (1.54–1.76)
Forearm	1.10 (0.96–1.25)	1.04 (0.93–1.17)	1.19 (1.02–1.39)
Hip	0.99 (0.82–1.20)	1.77 (1.55–2.02)	2.27 (1.94–2.66)
Vertebral	1.55 (1.20–2.01)	2.59 (2.16–3.10)	5.18 (4.25–6.31)

[26, 32]. The GPRD did not report the relative risks of clinical vertebral, humerus and forearm fracture combined. It was not possible, therefore to accurately repopulate FRAX to determine the dose response effects on the probability of a major fracture. With these caveats, we assumed that the risk of a major osteoporotic fracture (without hip fracture) was equivalent to the GPRD defined non-vertebral fracture. We assumed that the underreporting of vertebral fractures and the fracture hazard associated with these would be offset in part by the inclusion of hip fractures (see Table 1). Again, in order not to disrupt the structure of FRAX, we assumed that the medium dose provided the hazard ratio as used in FRAX and we adjusted the FRAX hazard ratios upward by 21% (1.64/1.36, Table 1) and downwards by 14% (1.17/1.36, Table 1) for the high and low dose, respectively, according to the differentials reported in GPRD.

Exposure to glucocorticoids carries an increase in the risk of death [1]. It is highly plausible that the death risk associated with glucocorticoids is dose-dependent [33], in part related to the underlying disorders for which glucocorticoids are prescribed [33–35]. We assumed that the hazard ratio of death for the low dose was halved. Since the high, medium and low doses correspond approximately to tertiles of the population, the hazard ratio of the high dose group was increased by an increment that equalled the decrement in the low-dose group.

FRAX probability calculations

Ten-year probability of a major osteoporotic fracture and of a hip fracture was calculated using the UK FRAX tool (version 3.1) with and without femoral neck BMD. For the medium dose of glucocorticoid, the model used the published version. For the high and low doses, we used the adjusted risks for fracture and death as described above.

Statistics

The ratios of probabilities computed for low dose/medium dose and high dose/medium dose were calculated for men and women at 10-year intervals between the ages of 40 and 90 years. For each age and sex, we examined the ratios between fracture probabilities of all possible combinations of clinical risk factors for individ-

uals exposed to glucocorticoids (32 combinations) at BMD T-scores between +1 and -4 SD in 0.5 SD steps with a BMI between 15 and 45 kg/m² in steps of 5 kg/m² (2,464 combinations). In the absence of BMD, we examined the ratios between fracture probabilities of all possible combinations of clinical risk factors with a BMI between 15 and 45 kg/m² in steps of 5 kg/m² (224 combinations). Note that this was not a population simulation but a calculation of all possible combinations.

Results

The impact of dose on hip fracture probability

The impact of dose of glucocorticoids on hip fracture probability is shown in Fig. 1 for two individual patient scenarios in men and women. There was a modest difference in hip fracture probability between the low-dose effect compared to the no dose, reflecting the modest increase in hip fracture risk associated with the low dose (HR=1.06). As expected, probabilities increased progressively with increasing dose of glucocorticoids. Compared with the medium dose, the low dose of glucocorticoids was associated with a hip fracture probability that was approximately 40% lower. The high dose was associated with a probability approximately 25% higher than the medium dose.

When all permutations were examined, these ratios were fairly consistent comparing men and women with or without the inclusion of BMD, but varied somewhat with age (Table 2). For example, for the low-dose exposure to glucocorticoids, the average ratio with the medium dose was 0.63 in men (and the same in women) where FRAX was measured in the absence of BMD, but ranged from 0.56 at the age of 40 years to 0.73 at the age of 90 years ($p < 0.001$). For high-dose exposure, the ratio with the medium dose was also similar in men and women and varied with age such that the increment in probability decreased progressively with age ($p < 0.001$).

The impact of dose on probability of a major fracture

The impact of dose of glucocorticoids on the probability of a major fracture is shown in Fig. 2 for the two individual

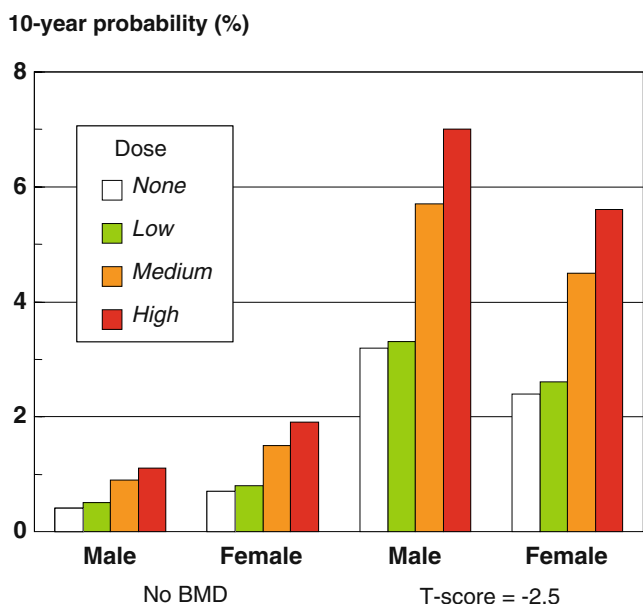


Fig. 1 Ten-year probability (%) for hip fracture in men and women according to the dose of glucocorticoids. The left-hand panels show probabilities in a male and a female at the age of 60 years, a body mass index of 25 kg/m², no clinical risk factors other than glucocorticoids and no estimate of BMD. The right-hand panels show the same clinical scenarios with the inclusion of a femoral neck BMD T-score of -2.5SD

patient scenarios in men and women shown in Fig. 1. As expected, probabilities increased progressively with increasing dose of glucocorticoids. Compared with the medium dose, the low dose of glucocorticoids was

Table 2 Ratio of hip fracture probabilities (a. low dose/medium dose and b. high dose/medium dose) in men and women with and without BMD according to age

Age (years)	No BMD		BMD	
	Men	Women	Men	Women
a. Low dose				
40	0.56	0.56	0.61	0.59
50	0.57	0.56	0.59	0.58
60	0.59	0.58	0.60	0.58
70	0.63	0.62	0.63	0.61
80	0.69	0.71	0.67	0.66
90	0.73	0.77	0.68	0.69
All ages	0.63	0.63	0.63	0.62
b. High dose				
40	1.27	1.27	1.23	1.24
50	1.25	1.27	1.24	1.26
60	1.22	1.25	1.21	1.24
70	1.15	1.19	1.16	1.21
80	1.09	1.10	1.12	1.15
90	1.08	1.06	1.12	1.12
All ages	1.18	1.19	1.18	1.21

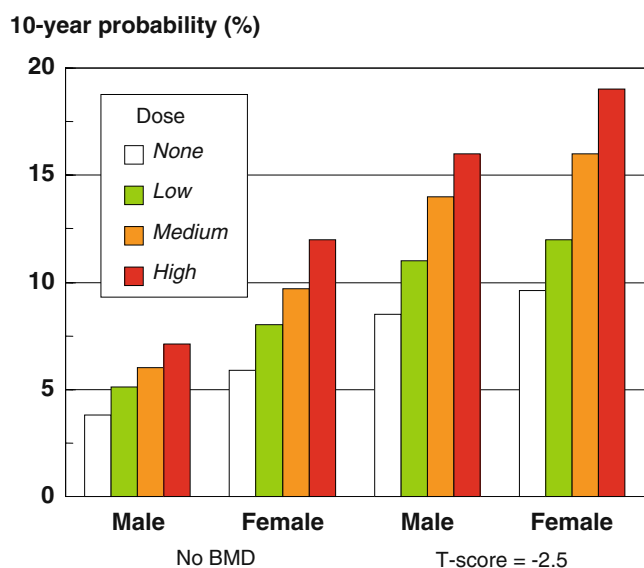


Fig. 2 Ten-year probability (%) for a major osteoporotic fracture in men and women according to the dose of glucocorticoids. The left hand panels show probabilities in a male and a female at the age of 60 years, a body mass index of 25 kg/m², no clinical risk factors other than glucocorticoids and no estimate of BMD. The right hand panels show the same clinical scenarios with the inclusion of a femoral neck BMD T-score of -2.5SD

associated with a fracture probability that was approximately 20% lower. The high dose was associated with a probability approximately 20% higher than the medium dose.

When all permutations were examined, these ratios were fairly consistent comparing men and women with or without the inclusion of BMD, but varied somewhat less with age than those observed for hip fracture (Table 3). For example, for the low-dose exposure to glucocorticoids, the average ratio with the medium dose was 0.82 in men (0.83 women) where FRAX was measured in the absence of BMD, and ranged only from 0.84 at the age of 40 years to 0.79 at the age of 90 years. For high-dose exposure, the ratio with the medium dose was also similar in men and women with or without BMD and the increment in probability decreased slightly with age.

A simplified algorithm

A summary of adjustments by age rounded off to the nearest 5% is provided in Table 4. Consider, for example, a female patient aged 70 years taking prednisolone for rheumatoid arthritis (BMI=25 kg/m²). Using the UK model, her 10-year hip fracture probability calculated with FRAX is 8.1% and the 10-year probability of a major fracture is 23%. The calculation assumes that the patient was taking an average dose of glucocorticoids (2.5–7.5 mg/day). If the actual dose was high (≥7.5 mg/day), the hip fracture probability should be uplifted by 20% and the

Table 3 Ratio of probabilities of a major osteoporotic fracture (a. low dose/medium dose and b. high dose/medium dose) in men and women with and without BMD according to age

Age (years)	No BMD		BMD	
	Men	Women	Men	Women
a. Low dose				
40	0.84	0.82	0.80	0.80
50	0.84	0.83	0.81	0.82
60	0.84	0.82	0.83	0.83
70	0.82	0.81	0.83	0.84
80	0.79	0.83	0.79	0.83
90	0.79	0.86	0.77	0.81
All ages	0.82	0.83	0.81	0.83
b. High dose				
40	1.19	1.20	1.17	1.18
50	1.18	1.20	1.17	1.18
60	1.16	1.18	1.15	1.16
70	1.12	1.13	1.12	1.14
80	1.08	1.07	1.10	1.11
90	1.07	1.04	1.10	1.09
All ages	1.13	1.14	1.13	1.14

probability of a major fracture by 15%, giving probabilities of 9.7% and 26%, respectively. Were the patient on a low dose of glucocorticoids, the respective probabilities would be 4.9% and 18%.

The age-specific adjustments given in Table 4 (simplified FRAX adjustment) were compared with values generated from the complex FRAX adjustments given in this paper for high and low doses of oral glucocorticoids. There was a close agreement between the two values. Examples are given in Fig. 3 for individuals at the ages of 50 and 80 years. At both ages, the simplified model of FRAX to compute the probabilities with a high dose of glucocorticoid overestimated the complex model to a modest degree at high fracture probabilities—an effect more marked with the inclusion of

BMD in the models. In contrast, the simplified model of FRAX to compute the probabilities with a low dose of glucocorticoid slightly underestimated the complex model at high fracture probabilities—an effect more marked with the inclusion of BMD in the models.

Discussion

In this paper, we have explored the possible impact of different doses of glucocorticoids on fracture probability. As expected, probabilities were dose-dependent with higher probabilities associated with the high dose and vice versa. Nevertheless, it is important to note that the increment in fracture probability was less than would be predicted only from the hazard ratio of fracture. For example, the hazard ratio for hip fracture between the medium and high dose (HR=1.28) would predict a 28% higher hip fracture probability whereas the calculated increment was 18%. Conversely, fracture probabilities were reduced with the low dose compared to the medium dose but by less than that expected from the hazard ratio for fracture. The reason is that glucocorticoid exposure increases the risk of death as well as for fracture and both compete, therefore in the calculation of fracture probability.

An aim of this analysis was to determine whether we could provide simple guidance in the interpretation of FRAX probabilities for the clinician faced with patients who took higher or lower than average doses of glucocorticoids. In this regard, there is good news and bad news. The good news is that dose-dependent increments or decrements in fracture probability were little affected by gender or the inclusion of BMD in the FRAX model. The bad news is that these were affected by age, again related to the competing death hazard. Notwithstanding, the effect of age was largely confined to the elderly in the case of hip fracture probabilities that permitted some simplification. There was close agreement between the simplified and more complex approach.

Table 4 Percentage adjustment of 10 year probabilities of a hip fracture or a major osteoporotic fracture by age according to dose of glucocorticoids

Dose	Prednisolone equivalent (mg/day)	Age (years)						
		40	50	60	70	80	90	All ages
Hip fracture								
Low	<2.5	-40	-40	-40	-40	-30	-30	-35
Medium ^a	2.5–7.5							
High	≥ 7.5	+25	+25	+25	+20	+10	+10	+20
Major osteoporotic fracture								
Low	<2.5	-20	-20	-15	-20	-20	-20	-20
Medium ^a	2.5–7.5							
High	≥7.5	+20	+20	+15	+15	+10	+10	+15

^a No adjustment

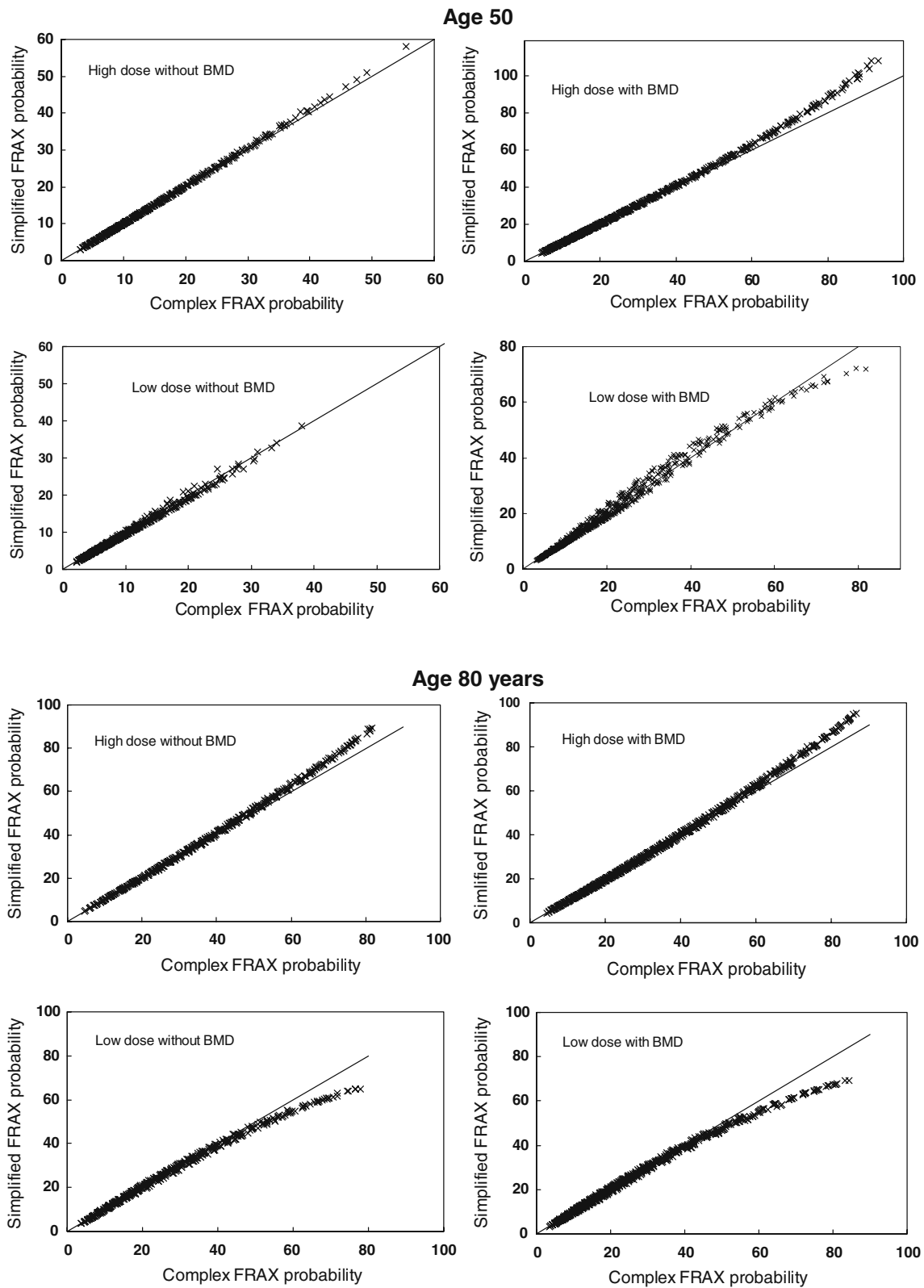


Fig. 3 The correlation between the complex FRAX adjustments and the simplified assessment of FRAX probabilities at the ages of 50 (*top panels*) and 80 years (*lower panels*) according to glucocorticoid dose and the inclusion or exclusion of BMD in the FRAX calculation. Note

that the correlations are not derived from a population sample or simulation, but from the available combinations of clinical risk factors BMI and BMD (see “Methods” section). The *solid diagonal line* shows the line of identity

The approach used in this analysis is imperfect. The correct approach would be to have available dose response information on fracture outcomes and mortality in individuals together with specific information on all FRAX related variables in all the cohorts used to synthesise FRAX. This would permit the assessment of the interdependence of the FRAX variables and allow an accurate recalibration of the FRAX model to the epidemiology of the UK. Unfortunately, such data were not available for the FRAX cohorts. Indeed, individual patient data were not available from the GPRD data from which the present analysis is derived. A further problem is that the GPRD data provided glucocorticoid exposure as a categorical variable (low, medium and high dose), so that the whole range of exposures could not be examined.

Until these deficits in the information base can be remedied, it will not be possible to incorporate fully dose–response effects of glucocorticoids into FRAX itself. Rather, “sensitivity analyses” with the best available data currently available can provide some estimate of how FRAX-generated fracture probabilities should be modulated according to the exposure to glucocorticoids. The same principles apply to other FRAX variables such as smoking, intake of alcohol, the number of prior fractures and their site where information on dose response would have clinical utility.

Over and above these considerations, there are a number of limitations in the present study that should be recognised. The additional assumptions used are detailed in the methods. The most important is that we did not have specific information on the hazard ratios for a major osteoporotic fracture and we assumed, for reasons given in the methods, that the risk of a major fracture was equivalent to the GPRD defined non-vertebral fracture. Thus, the data for a major osteoporotic fracture are less robust than for hip fracture probability. Additionally, no dose-dependent information was available on the death hazards in GPRD. The assumptions that we made on the death hazard may have been conservative [33], in which case the impact of high and low doses of glucocorticoids on fracture probability would be overestimated. Thus, higher (or lower) mortality than that assumed for the high or low dose exposure would decrease (or increase) the adjustments made to the FRAX probabilities. A further limitation of this study is the lack of independent validation.

The 10-year probability of hip fracture and probably other fractures varies markedly in different countries [36] in part related to differences in fracture risk and in part due to differences in mortality. The present analysis is based on the epidemiology of the UK. For this reason, the correction factors may not be applicable elsewhere because of differences in the death hazard. However, the present study provides a methodology whereby correction

factors can be computed for any of the countries represented by FRAX.

We conclude that a relatively simple arithmetic procedure can be applied to conventional FRAX estimates of probabilities of hip fracture and a major osteoporotic fracture to modulate the risk assessment with knowledge of dose of glucocorticoids.

Conflicts of interest None

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