

Calibration of FRAX® 3.1 to the Dutch population with data on the epidemiology of hip fractures

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Abstract

Summary The FRAX tool has been calibrated to the entire Dutch population, using nationwide (hip) fracture incidence rates and mortality statistics from the Netherlands. Data used for the Dutch model are described in this paper.

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Introduction Risk communication and decision making about whether or not to treat with anti-osteoporotic drugs with the use of T-scores are often unclear for patients. The recently developed FRAX models use easily obtainable clinical risk factors to estimate an individual's 10-year probability of a major osteoporotic fracture and hip fracture that is useful for risk communication and subsequent decision making in clinical practice. As of July 1, 2010, the tool has been calibrated to the total Dutch population. This paper describes the data used to develop the current Dutch FRAX model and illustrates its features compared to other countries.

Methods Age- and sex-stratified hip fracture incidence rates (LMR database) and mortality rates (Dutch national mortality statistics) for 2004 and 2005 were extracted from Dutch nationwide databases (patients aged 50+ years). For other major fractures, Dutch incidence rates were imputed, using Swedish ratios for hip to osteoporotic fracture (upper arm, wrist, hip, and clinically symptomatic vertebral) probabilities (age- and gender-stratified). The FRAX tool takes into account age, sex, body mass index (BMI), presence of clinical risk factors, and bone mineral density (BMD).

Results Fracture incidence rates increased with increasing age: for hip fracture, incidence rates were lowest among Dutch patients aged 50–54 years (per 10,000 inhabitants: 2.3 for men, 2.1 for women) and highest among the oldest subjects (95–99 years; 169 of 10,000 for men, 267 of 10,000 for women). Ten-year probability of hip or major osteoporotic fracture was increased in patients with a clinical risk factor, lower BMI, female gender, a higher age, and a decreased BMD T-score. Parental hip fracture accounted for the greatest increase in 10-year fracture probability.

Conclusion The Dutch FRAX tool is the first fracture prediction model that has been calibrated to the total Dutch population, using nationwide incidence rates for hip fracture and mortality rates. It is based on the original

FRAX methodology, which has been externally validated in several independent cohorts. Despite some limitations, the strengths make the Dutch FRAX tool a good candidate for implementation into clinical practice.

Keywords FRAX · Hip fracture · Osteoporosis · Osteoporotic fracture · 10-year fracture probability

Introduction

Osteoporosis is a devastating disease resulting in substantial health care costs and increased mortality. In Europe, osteoporotic fractures affect one in two women and one in five men aged 50 years and older [1]. In Europe, total health care costs associated with these fractures have been estimated to be around €30 billion [1]. In 2000, an estimated 5.8 million disability-adjusted life years were caused by osteoporotic fractures worldwide [2]. Among patients who have sustained a hip fracture, one in five will die within the first year after the fracture, whilst one in three of those surviving needs assistance with walking [3, 4]. Because of this huge burden, assessment of an individual's risk of fracture is important so that a prophylactic intervention can be effectively targeted.

As of July 1, 2010, the FRAX[®] tool has been calibrated to the total Dutch population (<http://www.sheffield.ac.uk/FRAX>). FRAX uses easily obtainable clinical risk factors, with or without femoral neck bone mineral density (BMD), to estimate 10-year fracture probability [5]. It has been constructed using primary data from nine population-based cohorts around the world. The gradients of fracture risk have been validated externally in 11 independent cohorts with a similar geographic distribution [6]. FRAX is a platform technology using Poisson models that integrate risk variables, fracture risk, and death risk over a 10-year interval. Using the incidence rates of hip and osteoporotic fractures and mortality rates, FRAX can be calibrated to create a country-specific model [7]. With the introduction of the online Dutch FRAX tool, it is important to understand the origin of the data for further validation if needed. Furthermore, the possibilities of the Dutch FRAX tool and its strengths/limitations compared to other Dutch models need to be discussed. The objective of this paper is to describe the data used to develop the current Dutch FRAX model.

Methods

Data sources

For the calibration of FRAX, we used two different sources of data: (1) the national hospitalization registry of the Netherlands and (2) the Dutch national mortality statistics.

Hip fractures in the Netherlands were identified using the national hospitalization registry (“Landelijke Medische Registratie, LMR”) [8]. The vast majority of patients who sustain a hip fracture are recorded as inpatient hospitalizations. The LMR is therefore the best option to estimate national incidence rates of hip fractures in the Netherlands. Up to 2004, the completeness of the LMR has been shown to be very high (98.9% in 2004) [9], and the database has been widely used for various research purposes [10–18]. Since 2005, however, the number of missing records in the LMR has increased, probably as a result of the stepwise introduction of a new reimbursement system in hospitals. The proportion of missing records was estimated at 3.3% in 2005, 10.5% in 2006, and 12.0% in 2007 [9]. The register is held by several licensees; in this paper, we have used LMR data from Statistics Netherlands for the years 2004/2005. The reason for choosing 2004 and 2005 was that we considered a 1.1% rate of under-recording as acceptable, but not a >10% (from 2005 on) missing rate. Data for 2004 were delivered in an aggregated report by Statistics Netherlands.

In contrast to hip fractures, incidence of osteoporotic fractures could not be determined using national registries (including LMR), because a dedicated registry with routinely recorded osteoporotic fractures does not exist in the Netherlands. Therefore, the World Health Organization Collaborating Centre for Metabolic Bone Disease used the population of Sweden in order to impute incidence rates of major osteoporotic fractures in the Netherlands [19, 20]. In Malmö, radiography referrals are recorded for all fractures that come to medical attention. For each age and sex category, incidence rate ratios for major osteoporotic fractures to hip fractures were calculated in this Swedish population [20]. It was assumed that these age- and gender-specific ratios found in Malmö are comparable to those in the Netherlands. This assumption has also been used for many of the FRAX models with incomplete epidemiological information. Available information suggests that the age- and gender-stratified pattern of fracture is very similar in the Western world and Australia, although it should be noted that incidence rates for vertebral fracture as judged by vertebral morphometry may be underestimated in some of these data sources [19].

Mortality rates were extracted using the national mortality registry, available from Statistics Netherlands. When a patient dies, doctors and coroners are obliged to fill out a death certificate. The national mortality registry has a high degree of completeness because of the legal requirement.

Study population and outcomes

Using the LMR data from 2004/2005, Statistics Netherlands computed the age- and gender-specific incidence rates of hip fracture (International Classification of Disease 9,

ICD9) code 820. Cases were defined as patients (aged 50+ years) who were hospitalized for a hip fracture in 2004/2005 and who had not been hospitalized for a hip fracture in the previous 5 years. Incidence rates were estimated as follows: the number of men and women in 5-year age intervals with at least one hip fracture in 2004 and 2005 was divided by the age- and sex-specific population of the Netherlands at the average midpoint of 2004 and 2005. We included hip fracture cases of persons who had been recorded in the national patient register as a Dutch resident for the full calendar year. We excluded those who had immigrated or emigrated during 2004/2005 [21]. In order to estimate the incidence of other osteoporotic fractures in the Netherlands, we used Swedish population-based data (Malmö), as described previously by Kanis et al. [19, 20]. First osteoporotic fracture diagnoses were identified, using files at the Department of Diagnostic Radiology in Malmö (1987–1993). Osteoporotic fractures included those of the hip, forearm, proximal humerus, and clinically symptomatic vertebral fractures. Past records were examined to exclude patients who had previously sustained a fracture of the same type. Multiple osteoporotic fractures at different sites were counted separately. Age- and gender-specific ratios for osteoporotic fracture to hip fracture were calculated and used to transform the Dutch hip fracture incidence rates to those for osteoporotic fractures [7, 19]. Mortality statistics for the year 2005 were retrieved from the website of Statistics Netherlands (www.statline.nl).

Calibration

The development and validation of FRAX[®] has been extensively described by Kanis et al. and McCloskey et al. [5, 22, 23]. The risk factors used were based on a systematic set of meta-analyses of population-based cohorts

worldwide. For the construct of a FRAX model for the Netherlands, data from the following sources are required: (1) beta coefficients of the risk factors in the original FRAX model and (2) incidence rates of hip fracture, and mortality rates, for an individual country. The relative importance of the beta coefficients for death and fracture was assumed to be similar in the Netherlands, as has been shown across several European countries [6]. However, absolute age-specific fracture risk and mortality rates differ from country to country [5]. Consequently, for each age category, the hazard function was calibrated to match the mean risk (both fracture risk and mortality rate) for that specific age group in the Netherlands, without altering the relative importance of the beta coefficients [5].

Comparison of Dutch hip fracture incidence rates with those in other world regions

In order to compare Dutch hip fracture probabilities with those of other regions of the world, the remaining lifetime probability of hip fracture from the age of 50 years was calculated for men and women, as described by Kanis et al. and Johnell et al. [24, 25]. In the present analysis, values for the Netherlands were compared with those of China (with and without inclusion of Hong Kong), Mexico, Portugal, Spain, France, UK, Turkey, USA, and Sweden.

Results

Table 1 shows 1-year age- and gender-stratified incidence rates of hip fracture for the Netherlands (2004 and 2005), as well as the incidence of osteoporotic fractures, based on the Malmö transformation. Hip fracture incidence was lowest in patients aged 50–54 years old (per 10,000 inhabitants: 2.3 for men and 2.1 for women) and highest among the

Table 1 Dutch age- and gender-stratified 1-year incidence rates of hip fracture (true data; 2004/2005) and (imputed) osteoporotic fracture (imputed using Swedish data) per 10,000 inhabitants in 2004/2005 as modeled in FRAX

	Age category (years)	1-year incidence hip fracture by FRAX (per 10,000 inhabitants)		1-year imputed incidence osteoporotic fracture by FRAX (per 10,000 inhabitants)	
		Male	Female	Male	Female
	50–54	2.3	2.1	16.8	23.3
	55–59	3.0	4.2	17.1	33.0
	60–64	4.6	8.1	17.5	46.5
	65–69	8.9	15.3	28.3	68.1
	70–74	16.9	28.6	45.9	99.8
Modeled Dutch incidence rates for osteoporotic fractures imputed, using real-life Dutch incidence rates for hip fractures, and Swedish (age- and gender-stratified) hip to osteoporotic fracture incidence rate ratios	75–79	32.3	53.6	74.4	146.2
	80–84	61.6	100.5	120.5	214.1
	85–89	117.6	188.2	195.4	313.6
	90–94	141.0	224.3	240.4	385.9
	95–99	169.0	267.3	295.8	474.9

oldest subjects (95–99 years) (169.0 of 10,000 and 267.3 of 10,000 for men and women, respectively). With increasing age, there was a rise in proportion of all fractures primarily accounted for by hip fractures, with the highest proportion in the oldest patients (among osteoporotic fractures, 57.1% were hip fractures in males, 56.3% in females).

Age- and gender-stratified mortality rates for the total Dutch population are shown in Table 2. Mortality rates increased with higher ages, with rates of 4,245 per 10,000 male inhabitants and 3,532 per 10,000 female residents in the oldest age category (≥ 95 years).

In Table 3, 10-year probabilities of osteoporotic fractures are shown for Dutch men and women per age and gender category in the absence or presence of at least a single clinical risk factor (each row), without entering information on BMD, keeping BMI constant at 25 kg/m². Parental history of hip fracture was the strongest clinical risk factor in the elderly: a 90-year-old woman with a BMI of 25 kg/m², and a parental hip fracture as single clinical risk factor, had a 26% 10-year probability of osteoporotic fracture (20% for hip fracture), whilst the risk was only 13% for a female of equal age and BMI without a parental hip fracture. When compared to a male patient with the same clinical risk factors, the 10-year probability of fracture was halved (13% for osteoporotic fracture, 11% for hip fracture). In younger age categories, much smaller differences between the two genders were observed: the 10-year probability of osteoporotic fracture was 3.7% in a 50-year-old female with a BMI of 25 kg/m² and a parental hip fracture as single clinical risk factor (0.2% for hip fracture), as compared to 3.0% in a 50-year-old male with comparable clinical risk factors (0.1% for hip fracture).

Tables 4 and 5 show the effect of BMD on the 10-year probabilities of osteoporotic and hip fracture in men and women aged 60 years old (Table 4) and aged 80 years old (Table 5) with a BMI of 25 kg/m², rheumatoid arthritis, and

a parental history of hip fracture. Fracture risk increased with decreasing T-score. When BMD was entered into the model, the difference in probabilities between men and women became less marked than without BMD. There was also a large range of probabilities noted as a function of the T-score. Thus, probability was markedly underestimated in individuals with low T-scores (for elderly patients, i.e., 80 years old, only at T-scores below -2 SD), when information on BMD was not used in the model.

Table 6 shows that Northern European countries (including the Netherlands) yielded the highest lifetime probabilities for hip fracture (with the highest rate seen in Sweden) in individuals from the age of 50 years. In contrast, much lower incidence rates were recorded in China, Mexico, and Mediterranean countries.

Discussion

In this paper, we describe the FRAX[®] model developed for the Netherlands, which can be used to assess individual 10-year probabilities of hip fracture, as well as any osteoporotic fracture in Dutch patients. It has been calibrated to the total Dutch population, based on nationwide incidence rates for hip fracture and mortality. The model became available in July 2010 at the FRAX[®] website (<http://www.sheffield.ac.uk/FRAX>).

Previous clinical risk scores in Holland have been developed in cohorts that were representative for only a small Dutch region, and these risk scores have not been validated externally. Pluijm et al. proposed a clinical risk score to estimate fracture risk in Dutch women, using information from two different Dutch cohort studies [26]. Although the risk score is simple to use, there are some limitations to the model. The cohorts included patients from small regions and may therefore not be representative of the country. Although one of the two models included multiple cities throughout the country, the majority of fracture cases originated from a specific area in the city of Rotterdam, which is not comparable to patients from the general population [26]. Furthermore, men had not been included in these cohorts, limiting the use of the risk score to women only. Finally, there may have been substantial under-recording of several risk factors for fracture (such as rheumatoid arthritis, smoking, alcohol intake, and oral glucocorticoid use) in these GP-based cohorts. Compared to pharmacy dispensing data (representative sample of the total Dutch population, with a similar age), the prevalence of oral glucocorticoid use was found to be 1.5–2.2-fold lower in these GP-based registries (2%) [16]. More recently, van Geel et al. developed a fracture risk model in a cohort comprising postmenopausal women, inhabitants of the southern part of the Netherlands [27]. This clinical risk score is the simplest to use, as it only includes three

Table 2 Dutch age- and gender-stratified mortality rates (per 10,000 inhabitants) in 2005

Age category (years)	Mortality rate (per 10,000 inhabitants)	
	Male	Female
50–54	41.0	31.1
55–59	65.1	46.5
60–64	113.7	69.4
65–69	190.9	103.1
70–74	330.6	181.5
75–79	584.7	328.2
80–84	1,005.2	607.6
85–89	1,710.1	1,193.8
90–94	2,690.0	2,085.7
≥ 95	4,245.0	3,532.0

Table 3 Age- and gender-stratified 10-year probabilities (percent) of osteoporotic fracture in absence or presence of at least a single clinical risk factor, without information on BMD

	Males					Females				
	Age (years)									
Clinical risk factor	50	60	70	80	90	50	60	70	80	90
No risk factor	1.5	2.3	3.6	5.5	5.5	1.8	3.4	6.9	12	13
Previous fracture	3.2	4.7	7.0	9.0	8.8	4.1	7.1	13	20	21
Parental hip fracture	3.0	4.4	6.0	12	13	3.7	6.6	11	24	26
Current smoking	1.6	2.4	3.9	6.0	5.8	2.0	3.7	7.7	14	14
Glucocorticoid use ^a	2.4	3.7	5.7	8.1	7.7	3.1	5.7	11	20	19
Rheumatoid arthritis	2.0	3.1	5.2	8.3	8.5	2.5	4.8	9.8	18	19
Secondary osteoporosis ^b	2.0	3.1	5.2	8.3	8.5	2.5	4.8	9.8	18	19
Alcohol use ^c	1.8	2.8	4.6	7.3	7.5	2.2	4.2	8.7	16	17

BMI is set at 25 kg/m²

^a Current exposure to oral glucocorticoids or prior exposure for a period of at least 3 months at a daily dose of at least 5 mg prednisolone (or equivalent doses of other glucocorticoids)

^b Includes patients diagnosed with diabetes mellitus type I, osteogenesis imperfecta, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition or malabsorption, and chronic liver disease

^c Exposure to at least three units of alcohol daily (one unit equals 8–10 g alcohol)

risk factors in the final model. A major strength, compared to the other Dutch fracture models, is the consideration of the time window in which a prior fracture could have occurred. Like the model described by Pluijm et al., the van Geel model also is limited to women only and may not be representative for the entire country. A third model, introduced by the Dutch Institute for Healthcare Improvement (CBO), aims to identify high-risk patients for fracture by calculating a fracture risk score based on weighted widely recognized risk factors [28]. However, in contrast to the other Dutch fracture models, these weights are based on expert opinion and have not been developed and validated in clinical studies using Dutch patients' data. Therefore, these estimated weights may not reflect real-life weights. This CBO model is currently used in the national Dutch guidelines for fracture prevention [28]. The use of FRAX in these guidelines is limited: FRAX risk assessment is only

recommended in patients with multiple clinical risk factors (CBO score ≥ 4), and a T-score between -2.0 SD and -2.5 SD, but without evidence of a recent fracture.

The importance of calibrating FRAX to an individual country is illustrated by the marked differences in lifetime risks of hip fracture in 50-year-old males and females between countries worldwide. In line with previous reports, we found much higher incidences for hip fracture in European countries (including the Netherlands), as compared to those in countries like China, Mexico, and those in the Mediterranean area [29–31]. Possible explanations for this decreased incidence rate in the latter countries as compared to the Netherlands include lower life expectancy, in particular in Latin America (as most hip fractures occur after the age of 65 years) [30], variations in reversible lifestyle factors, and genetics [32, 33]. High prevalence rates in Scandinavian countries (including Sweden) may to

Table 4 BMD- and gender-stratified 10-year probabilities of osteoporotic and hip fracture for a 60-year-old patient with a BMI of 25 kg/m², rheumatoid arthritis, and a parental history of hip fracture

BMD	Males		Females	
	10-year probability (%) of		10-year probability (%) of	
T-score	Osteoporotic fracture	Hip fracture	Osteoporotic fracture	Hip fracture
Not taken into account	5.9	0.8	8.9	1.3
1	4.5	0.1	6.1	0.1
0	5.2	0.3	6.9	0.2
-1	6.6	0.7	8.1	0.5
-2	9.5	2.2	11	1.6
-3	15	6.5	17	5.0
-4	28	18	29	15

Table 5 BMD- and gender-stratified 10-year probabilities of osteoporotic and hip fracture for an 80-year-old patient with a BMI of 25 kg/m², rheumatoid arthritis, and a parental history of hip fracture

BMD	Males		Females	
	10-year probability (%) of		10-year probability (%) of	
	Osteoporotic fracture	Hip fracture	Osteoporotic fracture	Hip fracture
T-score				
Not taken into account	19	16	36	29
1	5.6	3.1	7.1	2.3
0	8.2	5.4	11	4.9
-1	12	9.2	17	10
-2	19	16	27	20
-3	30	26	45	38
-4	43	40	67	62

some degree be explained by icy condition in the winter [34] and high smoking frequency/alcohol intake (in particular in Denmark) [35].

The use of FRAX as a clinical tool demands a consideration of intervention thresholds. These thresholds, determined by fracture probability, should be recommended based on clinical imperatives and validated by the cost-effectiveness of a possible FRAX-based strategy. In the UK, the National Osteoporosis Guideline Group has described management algorithms that are based on FRAX [36]. These guidelines describe fracture risk thresholds at which BMD assessment or osteoporosis treatment should be carried out. In a post hoc analysis, they demonstrated cost-effectiveness of this strategy, based on a willingness to pay (WTP) threshold set at £20,000 for each quality-adjusted life year gained [37]. However, these intervention thresholds may not apply to the Netherlands, since the cost of osteoporosis and BMD measurement, and the WTP in the Netherlands, may differ from those in the UK. In addition, the willingness to trade-off risks for benefits of

fracture prevention may vary among individual patients. Using FRAX, both the clinician and the patient can discuss fracture probability and weigh the risks and benefits of starting fracture prevention (although Dutch cost-effectiveness studies need to be conducted to determine clear intervention thresholds).

As of 2010, it remains unclear whether the implementation of FRAX screening indeed would lead to reduced fracture rates, compared to conventional patient management, though a substantial body of indirect evidence suggests that FRAX identifies individuals who respond to pharmacotherapy [38]. In order to assess the clinical usefulness of FRAX screening, the “Screening of Older Women for Prevention of Fracture” trial is currently being conducted [39]. In this British trial, effectiveness (reduction of fracture incidence) and cost-effectiveness of FRAX screening in women aged 70–85 years are being evaluated. In the Netherlands, the Salt Osteoporosis Study is currently being carried out to assess the 3-year efficacy of FRAX-based screening in women aged 65 years or more with at least one clinical risk factor for fracture [40]. The randomized clinical trial will compare the fracture incidence in patients who have been screened for high fracture risk using FRAX[®] (and have received treatment options based on this) with the fracture incidence of patients who received care based on current Dutch guidelines.

The major strength of FRAX[®] is that it has been developed in nine different cohorts and has been externally validated in 14 studies comprising of several million individuals [6, 41–43]. In addition, higher predictive validity for fracture outcome is obtained by combining both data on clinical risk factors and BMD levels. A meta-analysis showed that the combination of clinical risk factors and BMD provides higher specificity and sensitivity than either alone [6]. Current models are limited to either the use of clinical risk factors or BMD alone, possibly diminishing their predictive validity [6, 26, 27]. A third strength is the use of a continuous scale for age and body weight, as fracture risk increases even above the fixed age and body weight thresholds used by many other models [44, 45].

Table 6 Lifetime probability of hip fracture in males and females from the age of 50 years

Country	Lifetime risk at ≥50 years (%)	
	Males	Females
China	1.9	2.4
Mexico	3.8	8.5
China (Hong Kong)	4.1	8.8
Portugal	3.6	10.1
Spain	4.2	12.0
France	3.6	12.7
UK	4.8	14.0
Turkey	3.5	14.6
USA	6.0	15.8
Netherlands (present study)	5.2	17.3
Sweden	13.1	28.5

Furthermore, in contrast to the current local Dutch models, the Dutch FRAX tool has been calibrated to the total Dutch population, using nationwide incidence rates for hip fracture and mortality rates.

A limitation of the Dutch FRAX[®] is that, as of 2010, the tool has not been prospectively validated in the Netherlands (i.e., the predictive value of FRAX in the Netherlands). Notwithstanding, the model is constructed using national rather than regional information on hip fracture and death rates. An additional limitation is that the incidence rates of hip fracture were derived from the year 2004/2005 and were therefore not completely up to date. Unfortunately, Dutch national hip fracture data are no longer reliable after 2005. Due to a change in law, Dutch hospitals are no longer required to record their hospitalization rates by ICD9 code and send them to the national registry [9]. In order to overcome this limitation, a future study has been designed, in which hip fracture rates will be updated by linkage of various Dutch epidemiological registries.

A third limitation of FRAX in general is that it makes no use of several other important clinical risk factors for fracture (such as previous vertebral fractures, a history of falls, vitamin D deficiency, and use of psychotropic drugs) [10, 11, 18, 46, 47]. Although the model does take prior fractures into account, the number and recency of these fractures have not been included as predictors in the model, because of the lack of data available in the construct cohorts [19], but they probably are important. For instance, a Dutch retrospective cohort study showed that the incidence of new clinical fractures was higher among patients who had sustained multiple baseline fractures, when compared to those who had sustained only a single fracture at baseline [48]. In addition, in the FRAX[®] model, current use of oral glucocorticoids was not specified by cumulative or daily dose, which may be more accurate to use in order to predict osteoporotic fractures [49, 50]. To overcome this limitation, a recent study has shown a methodology to adjust conventional FRAX estimates of hip and osteoporotic fracture probabilities based on knowledge of the daily glucocorticoid dose in an individual patient [51].

The FRAX model assumes that the weight of each clinical risk factor on the risk of death and fracture is the same as that derived from the cohorts used in the construction of FRAX rather than on empirical data from the Dutch population. In the absence of national data, the assumption is reasonable, particularly since the weight of the clinical risk factors has been validated in an international perspective [6].

Finally, in contrast to the UK, cost-effectiveness has not been evaluated in the Netherlands, using FRAX[®] as a decision tool for BMD assessment or to start drug treatment [36]. Therefore, it is currently unclear at which fracture risk

threshold interventions (such as BMD measurement or treatment with calcium and bisphosphonate) should be recommended in the Netherlands. Furthermore, fracture risk estimation by FRAX is limited to treatment-naïve patients only.

In conclusion, this paper describes the development of the Dutch FRAX model. This tool allows the estimation of 10-year absolute risks of hip and osteoporotic fracture in Dutch residents. The calibrated model is based on the original FRAX methodology, which has been externally validated in several independent cohorts. It is the first model that has been calibrated to the total Dutch population, using nationwide incidence rates for hip fracture and mortality rates. Despite some limitations [19, 52], its strengths make the Dutch FRAX tool a good candidate for implementation into clinical practice.

Conflicts of interest Arief Lalmohamed, Anthonius de Boer, and Frank de Vries work at a division that received unrestricted funding for pharmacoepidemiological research from GlaxoSmithKline, the private–public-funded Top Institute Pharma (www.tipharma.nl), includes co-funding from universities, government, and industry), the Dutch Medicines Evaluation Board, and the Dutch Ministry of Health. John Kanis, Helena Johansson, Johannes Jacobs, and Willem Lems have no competing interests with regard to this work.

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References

1. Poole KE, Compston JE (2006) Osteoporosis and its management. *BMJ* 333:1251–1256
2. Cummings SR, Melton LJ (2002) Epidemiology and outcomes of osteoporotic fractures. *Lancet* 359:1761–1767
3. Morrison RS, Chassin MR, Siu AL (1998) The medical consultant's role in caring for patients with hip fracture. *Ann Intern Med* 128:1010–1020
4. Wolinsky FD, Fitzgerald JF, Stump TE (1997) The effect of hip fracture on mortality, hospitalization, and functional status: a prospective study. *Am J Public Health* 87:398–403
5. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E (2008) FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 19:385–397
6. Kanis JA, Oden A, Johnell O, Johansson H, De Laet C, Brown J et al (2007) The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 18:1033–1046
7. Johansson H, Kanis JA, McCloskey EV, Oden A, Devogelaer JP, Kaufman JM et al (2010) A FRAX(R) model for the assessment of fracture probability in Belgium. *Osteoporos Int* 22:453–461

8. Bouter LM, van Dongen MCJM, Zielhuis GA (2005) Epidemiologisch onderzoek, 5th edn. Bohn Stafleu van Loghum, Nederland, p 41
9. de Bruin A, Ariel A, Verweij G, Israëls A (2009) Methode van bijschatten van StatLinetablel Ziekenhuispatiënten naar diagnose. Statistics Netherlands (CBS), Den Haag
10. Verdel BM, Souverein PC, Egberts TC, van Staa TP, Leufkens HG, de Vries F (2010) Use of antidepressant drugs and risk of osteoporotic and non-osteoporotic fractures. *Bone* 47:604–609
11. Pouwels S, van Staa TP, Egberts AC, Leufkens HG, Cooper C, de Vries F (2009) Antipsychotic use and the risk of hip/femur fracture: a population-based case-control study. *Osteoporos Int* 20:1499–1506
12. Pouwels S, Lalmohamed A, van Staa T, Cooper C, Souverein P, Leufkens HG et al (2010) Use of organic nitrates and the risk of hip fracture: a population-based case-control study. *J Clin Endocrinol Metab* 95:1924–1931
13. Pouwels S, Lalmohamed A, Souverein P, Cooper C, Veldt BJ, Leufkens HG et al (2010) Use of proton pump inhibitors and risk of hip/femur fracture: a population-based case-control study. *Osteoporos Int* 22:903–910
14. Pouwels S, Lalmohamed A, Leufkens B, de Boer A, Cooper C, van Staa T et al (2009) Risk of hip/femur fracture after stroke: a population-based case-control study. *Stroke* 40:3281–3285
15. de Vries F, Souverein PC, Cooper C, Leufkens HG, van Staa TP (2007) Use of beta-blockers and the risk of hip/femur fracture in the United Kingdom and the Netherlands. *Calcif Tissue Int* 80:69–75
16. de Vries F, Pouwels S, Lammers JW, Leufkens HG, Bracke M, Cooper C et al (2007) Use of inhaled and oral glucocorticoids, severity of inflammatory disease and risk of hip/femur fracture: a population-based case-control study. *J Intern Med* 261:170–177
17. de Vries F, Pouwels S, Bracke M, Leufkens HG, Cooper C, Lammers JW et al (2007) Use of beta-2 agonists and risk of hip/femur fracture: a population-based case-control study. *Pharmacoepidemiol Drug Saf* 16:612–619
18. Arbouw ME, Movig KL, van Staa TP, Egberts AC, Souverein PC, de Vries F (2010) Dopaminergic drugs and the risk of hip or femur fracture: a population-based case-control study. *Osteoporos Int* 22:2197–204
19. Kanis JA, Hans D, Cooper C, Baim S, Bilezikian JP, Binkley N et al (2011) Interpretation and use of FRAX in clinical practice. *Osteoporos Int* 22:2395–2411
20. Kanis JA, Johnell O, Oden A, Sembo I, Redlund-Johnell I, Dawson A et al (2000) Long-term risk of osteoporotic fracture in Malmo. *Osteoporos Int* 11:669–674
21. Statistics Netherlands (2011) StatLine—hip fracture incidence rates, explanation methodology. Available at statline.cbs.nl. Accessed on 24 June 2011
22. McCloskey EV, Johansson H, Oden A, Kanis JA (2009) From relative risk to absolute fracture risk calculation: the FRAX algorithm. *Curr Osteoporos Rep* 7:77–83
23. Kanis JA, on behalf of the World Health Organization Scientific Group (2008) Assessment of osteoporosis at the primary health-care level. Technical report. WHO Collaborating Centre, University of Sheffield, UK
24. Kanis JA, Johnell O, De Laet C, Jonsson B, Oden A, Oglesby AK (2002) International variations in hip fracture probabilities; implications for risk assessment. *J Bone Miner Res* 17:1237–1244
25. Johnell O, Kanis JA (2006) An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 17:1726–1733
26. Pluijm SM, Koes B, de Laet C, Van Schoor NM, Kuchuk NO, Rivadeneira F et al (2009) A simple risk score for the assessment of absolute fracture risk in general practice based on two longitudinal studies. *J Bone Miner Res* 24:768–774
27. van Geel TA, Nguyen ND, Geusens PP, Center JR, Nguyen TV, Dinant GJ et al (2010) Development of a simple prognostic nomogram for individualising 5-year and 10-year absolute risks of fracture: a population-based prospective study among postmenopausal women. *Ann Rheum Dis* 70:92–97
28. Dutch Institute for Healthcare Improvement (CBO) (2011) Richtlijn Osteoporose en fractuurpreventie, derde herziening. CBO, Utrecht
29. Yan L, Zhou B, Prentice A et al (1999) Epidemiological study of hip fracture in Shenyang Peoples Republic China. *Bone* 24:151–155
30. Zingmond DS, Melton LJ III, Silverman SL (2004) Increasing hip fracture incidence in California Hispanics, 1983 to 2000. *Osteoporos Int* 15:603–610
31. Morales Torres J, Gutierrez-Urena S (2004) The burden of osteoporosis in Latin America. *Osteoporos Int* 15:625–632
32. Dennison E, Mohamed MA, Cooper C (2006) Epidemiology of osteoporosis. *Rheum Dis Clin North Am* 32:617–629
33. Cooper C, Cole ZA, Holroyd CR, Earl SC, Harvey NC, Dennison EM, Melton LJ, Cummings SR, Kanis JA, and the IOF CSA Working Group on Fracture Epidemiology (2011) Secular trends in the incidence of hip and other osteoporotic fractures. *Osteoporos Int* 22:1277–1288
34. Emaus N, Olsen LR, Ahmed LA, Balteskard L, Jacobsen BK, Magnus T et al (2011) Hip fractures in a city in Northern Norway over 15 years: time trends, seasonal variation and mortality: The Harstad Injury Prevention Study. *Osteoporos Int* 22:2603–2610
35. Juel K (2000) Increased mortality among Danish women: population based register study. *BMJ* 321:349–350
36. Compston J, Cooper A, Cooper C, Francis R, Kanis JA, Marsh D et al (2009) Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. *Maturitas* 62:105–108
37. Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A et al (2008) Case finding for the management of osteoporosis with FRAX—assessment and intervention thresholds for the UK. *Osteoporos Int* 19:1395–1408
38. Kanis JA, McCloskey E, Johansson H, Oden A, Leslie WD (2011) FRAX® with and without BMD. *Calcif Tissue Int* (In press)
39. University of East Anglia (2010) Screening of older women for prevention of fracture (SCOOP) study. Available at: <http://www.scoopstudy.ac.uk/>. Accessed Nov. 18, 2010
40. VU University Medical Center, Stichting ArtsenLaboratorium en Trombosedienst (SALT) (2010) Stepped screening of fracture risk. A case finding and treatment program for women of 65 years of age and older in primary care. Available at: <http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=2430>. Accessed Dec. 23, 2010
41. Fraser L-A, Langsetmo L, Berger C, IG Goltzman D, Adachi JD, and the CaMos Research Group et al (2011) Fracture prediction and calibration of a Canadian FRAX® tool; a population-based report from CaMos. *Osteoporos Int* 22:829–837
42. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA (2010) Manitoba bone density program. Independent clinical validation of a Canadian FRAX((R)) tool: fracture prediction and model calibration. *J Bone Miner Res* 25:2350–2358
43. Hippisley-Cox J, Coupland C (2009) Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractures Scores. *Br Med J* 339:b4229
44. Siris ES, Brenneman SK, Barrett-Connor E, Miller PD, Sajjan S, Berger ML et al (2006) The effect of age and bone mineral density on the absolute, excess, and relative risk of fracture in postmen-

- opausal women aged 50–99: results from the National Osteoporosis Risk Assessment (NORA). *Osteoporos Int* 17:565–574
45. De Laet C, Kanis JA, Oden A, Johanson H, Johnell O, Delmas P et al (2005) Body mass index as a predictor of fracture risk: a meta-analysis. *Osteoporos Int* 16:1330–1338
 46. van den Brand MW, Samson MM, Pouwels S, van Staa TP, Thio B, Cooper C et al (2009) Use of anti-depressants and the risk of fracture of the hip or femur. *Osteoporos Int* 20:1705–1713
 47. Cauley JA, Hochberg MC, Lui LY, Palermo L, Ensrud KE, Hillier TA et al (2007) Long-term risk of incident vertebral fractures. *JAMA* 298:2761
 48. van Helden S, Cals J, Kessels F, Brink P, Dinant GJ, Geusens P (2006) Risk of new clinical fractures within 2 years following a fracture. *Osteoporos Int* 17:348–354
 49. De Vries F, Bracke M, Leufkens HG, Lammers JW, Cooper C, Van Staa TP (2007) Fracture risk with intermittent high-dose oral glucocorticoid therapy. *Arthritis Rheum* 56:208–214
 50. Leib ES, Saag KG, Adachi JD, Geusens PP, Binkley N, McCloskey EV et al (2011) Official positions for FRAX[®] clinical regarding glucocorticoids: the impact of the use of glucocorticoids on the estimate by FRAX[®] of the 10 year risk of fracture from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX[®]. *J Clin Densitom* 14:212–219
 51. Kanis JA, Johansson H, Oden A, McCloskey EV (2011) Guidance for the adjustment of FRAX according to the dose of glucocorticoids. *Osteoporos Int* 22:809–816
 52. Hans DB, Kanis JA, Baim S, Bilezikian JP, Binkley N, Cauley JA et al (2011) Joint official positions of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX: executive summary of the 2010 Position Development Conference on Interpretation and Use of FRAX in Clinical Practice. *J Clin Densitom* 14:171–180