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ORIGINAL ARTICLE

Updated fracture incidence rates for the Italian version of FRAX®

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Abstract
Summary In order to update data underlying the Italian version of FRAX, we computed the national hip fracture incidence in Italy from hospitalization records for the year 2008. Mortality data and 10-year probabilities of major osteoporotic fractures were also updated. This revision will improve FRAX accuracy and reliability.
Introduction The original Italian version of FRAX® was based on five regional estimates of hip fracture risk undertaken up to 20 years previously. Our objective was to update hip fracture rates for the model with more recently derived data from the whole Italian population and more recent data on mortality.
Methods We analyzed the Italian national hospitalization database for the year 2008 in order to compute age- and sex-specific hip fracture incidence rates. Re-hospitalisations of the same patients within 1 year were excluded from the analysis. Hip fracture incidence rates were computed for the age range of 40–100 years, whereas the original FRAX model lacked data on the youngest and oldest age groups. In addition, we used the national mortality data for the same year 2008 to update the model. Ten-year fracture probabilities were re-calculated on the basis of the new fracture incidence rates.
Results The new hip fracture age- and sex-specific incidence rates were close to those used in the original FRAX tool, although some significant differences (not exceeding 25–30 %) were found for men aged 65–75 years and women under 55 years of age. In general, the revision resulted in decreased estimated 10-year probabilities in the younger age groups, whilst those in the older age groups were slightly increased.
Conclusions The Italian version of FRAX has been updated using the new fracture incidence rates. The impact of these revisions on FRAX is likely to increase the accuracy and reliability of FRAX in estimating 10-year fracture probabilities.

Keywords Fractures · FRAX · Risk assessment

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Introduction

The Italian population is one of the oldest in Europe, with current life expectancy being 77.9 and 84.4 years for men and women, respectively [1]. About 20 % of the Italian population is over age 65 years and 4 % over the age of 80 years [1]. Since hip fracture incidence increases exponentially with age, hip fractures are a major public health issue in Italy.

Individual risk assessment as a criterion for treatment has been adopted in a number of areas such as cardiovascular diseases, where risk charts are commonly used [2, 3]. The goal of the WHO's new fracture prediction algorithm—named FRAX®—is to provide risk assessment for osteoporotic fractures combining clinical risk factors with or without measurements of femoral neck BMD obtained using DXA. Individual risk using the FRAX algorithm is determined from

the competing hazards of fracture and death and expressed as the 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture. The FRAX algorithms in different countries use the same clinical risk factors but the fracture probability is calibrated to each country using country-specific fracture incidence and mortality rates. Ideally, each country will derive its own rates of hip and major osteoporotic fractures which can be incorporated into FRAX.

The implementation of FRAX in Italy in 2008 was based on hip fracture rates in four cities (Verona, Siena, Rome and Parma) [4] and one region (Friuli-Venezia) in Italy [5] using data collected 8–22 years ago. There are several limitations in the use of these data. The use of regional data is not ideal since there may be substantial differences in fracture rates in different regions of the same country [6]. More recent data are also preferable to account for possible secular trends in fracture and mortality [7]. The mortality rates used were based on 1999 estimates. In addition, data on fracture and mortality were not available over the whole age range included in the FRAX model (40–100 years). These considerations suggest that FRAX models should be updated from time to time based on the availability of more recent and/or on more accurate data. Indeed, updates of FRAX have been published for the Czech Republic, USA and Turkey [8–10], and revisions for Lebanon and Belgium are posted on the FRAX web site (http://www.shef.ac.uk/FRAX/). The aim of the present study was to update the incidence and mortality rates for use in the Italian version of FRAX with data which are more current, more accurate and based on national rather than regional estimates. We also wished to assess the impact of revised rates on the estimated FRAX 10-year probabilities of hip fractures and major osteoporotic fractures.

Materials and methods

Information for all hospitalizations in Italian hospitals is recorded in the national hospital discharge records and

Table 1 Number of hip fracture cases in 2008 and incidence rate per 100,000 in Italy

Age group	No. of cases	Population size	Revised rate per 100,000	Original FRAX rate	Revised/original rate (difference, %)
Men					
40–44	628	2,465,168	25	NA	NA
45–49	666	2,157,048	31	NA	NA
50–54	678	1,910,744	35	40	−12
55–59	788	1,838,712	43	40	+7
60–64	937	1,653,133	57	50	+12
65–69	1,358	1,558,842	87	120	−27
70–74	2,177	1,306,953	167	240	−30
75–79	3,636	1,035,404	351	420	−16
80–84	4,944	676,185	731	730	+0.1
85–89	4,302	302,628	1.422	1,720	−17
90–94	1,942	93,588	2,075	2,130	−2
95–100	637	24,790	2,570	NA	NA
Subtotal men	22,693	15,026,033	151	–	–
Women					
40–44	213	2,450,106	9	NA	NA
45–49	316	2,185,216	14	NA	NA
50–54	605	1,969,855	31	40	−23
55–59	1,056	1,928,031	55	60	−8
60–64	1,666	1,770,421	94	110	−14
65–69	3,096	1,751,643	177	200	−11
70–74	5,897	1,588,755	371	370	+0.3
75–79	11,158	1,441,619	774	820	−6
80–84	17,398	1,154,195	1.507	1,470	+2
85–89	16,405	655,144	2.504	2,610	−4
90–94	7,939	260,635	3,046	3,070	−1
95–100	3,052	88,011	3,468	NA	NA
Subtotal women	68,801	17,253,932	399	–	–
Total men + women	91,494	32,279,965	283	–	–

NA not available

Table 2 Distribution (in percent) of hip fractures per age group in Italy (2008), reporting both percentage of overall incident cases and incidence in specific age groups

Age	Men		Women	
	% of all cases	% of population	% of all cases	% of population
>40	100	100	100	100
>50	85	69	99	73
>60	79	44	97	50
>70	69	23	90	30
>80	52	7	65	12
>90	11	<1	16	2

maintained centrally at the Italian Ministry of Health. This information is anonymous and includes the patient's age, diagnosis, procedures performed and length of the hospitalization. We assumed that all hip fractures resulted in hospitalization [11–17]. The analyses of hospital discharge records were carried out for the latest available year (2008) and were performed by searching for the following ICD-9CM codes of hip fracture (major diagnosis): 820.0–820.1 (femoral neck fractures), 820.2–820.3 (per-trochanteric femoral fractures) and 820.8, 820.9 and 821.1 (other femoral fractures). These data were subject to a systematic completeness and accuracy quality assessment performed by the Ministry of Health. The matching with social security codes showed a percentage of correct linkage of 99.8 % in 2008 (58,367 records matched out of 58,492). Re-hospitalisations of the same patient within the same year 2008, including admissions to rehabilitation facilities (estimated to represent 15–20 % of total hospitalizations), were excluded by the Italian Ministry of Health. Population and mortality data were obtained by the Italian Institute for Statistics, stratified by gender and 5-year age groups (40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, 90–94 and 95–100 years) [1]. Age- and sex-specific hip fracture incidence and mortality rates were computed and then compared with current rates used in FRAX. We have also revised the incidence rates of major osteoporotic fractures (vertebral, humeral and forearm fractures) by using the Italian revised hip fractures incidence rates from 2008 and the ratios between hip fracture and other major osteoporotic fractures as previously computed for the city of Malmö in Sweden [18].

Ten-year probabilities for hip fracture and major osteoporotic fractures were calculated by age and sex from the death and fracture hazard by Poisson models [19, 20]. Ten-year fracture probabilities were computed using body mass index (BMI) as a continuous function. The relationship between BMI and fracture risk was obtained from a previously published meta-analysis of 12 population-based cohorts [21]. For any given age, probabilities were derived assuming the expected mix of the

Table 3 Estimated incidence rates of major osteoporotic fractures per 100,000 in Italy for 2008 compared with those used in the original FRAX model

Age range	Vertebral fractures			Humeral fractures			Forearm fractures		
	Revised rate	Original FRAX rate	Difference (%)	Revised rate	Original FRAX rate	Difference (%)	Revised rate	Original FRAX rate	Difference (%)
Men									
50–54	165	186	−11	74	84	−12	85	96	−11
55–59	75	70	+7	27	25	+8	96	89	+8
60–64	96	85	+13	34	30	+13	60	53	+13
65–69	77	106	−27	39	54	−27	90	124	−27
70–74	168	242	−30	93	134	−31	30	43	−30
75–79	232	277	−16	88	105	−16	67	80	−16
80–84	358	358	0	117	117	0	102	102	0
85–89	526	636	−17	284	344	−17	142	172	−17
Women									
50–54	122	159	−23	124	162	−23	316	412	−23
55–59	95	104	−9	102	112	−9	274	301	−9
60–64	158	185	−15	88	103	−15	296	347	−15
65–69	200	226	−12	214	242	−12	316	358	−12
70–74	353	352	+0.3	234	233	+0.4	408	407	+0.2
75–79	511	541	−6	387	410	−6	472	500	−6
80–84	528	515	+3	347	338	+3	543	529	+3
85–89	801	835	−4.24	726	757	−4	676	705	−4

clinical risk factors. The approach uses a simpler model than FRAX in that probabilities were population-based. Thus, for any given age, probabilities were derived assuming the expected distribution of the clinical risk factors and the score derived from them [22].

Results

Table 1 shows the number of new hip fracture cases, the population base and age- and sex-specific incidence of hip fracture for 2008 in Italy. The total number of hip fracture cases in men and women aged 40 to 100 years was 91,494 (22,693 men and 68,801 women; F/M ratio = 3). Hip fracture rates were higher in men than in women up to the age of 55 years and thereafter were consistently higher in women. As expected, the incidence increased exponentially in the older age groups to approximately 2.4 % per year in men aged 95 to 100 years and to 3.2 % in women of the same age. Age-adjusted rates standardised to the world population aged 50 years or more were 140/100,000 and 334/100,000 in men and women, respectively.

Table 1 also compares the incidence rates per 100,000 inhabitants for the year 2008 with those used in the original FRAX model. In general, for women, the rates used in the original model overestimated the fracture risk compared to the more recent estimates, although the effect was small in women over the age of 70 years. The largest differences were observed in women aged 50 to 70 years old, with the maximum difference found between the ages of 50 and 54 years (–23 %). In men, the rates used in the original model underestimated the fracture risk for 2008 between 55 and 64 years of age but overestimated the risk in those over 65 years, with the largest difference observed among men aged 65–74 years (approximately 30 %). The present study also provides hip fracture incidence for men and women aged 40–49 and 95–100 years, for whom incidence data were not available for the original FRAX model.

Table 2 summarises the distribution of hip fractures by age group in Italy in 2008. Men and women aged ≥65 years accounted for about 92 % of the total number of hip fractures (n=83,941). Those between 85 and 100 years represented 37.5 % of hip fracture cases (34,277; 6,881 cases in men and 27,396 cases in women), although they accounted for only 4.4 % of the total Italian population aged 40 to 100 years. It is notable that older women ≥75 years old accounted for the vast majority of fractures (n=55,952 or 61 % of the total fractures). Very old women (aged 90–100) were about 12 % of total hip fractures (n=10,991), despite representing only 1 % of the entire population between 40 and 100 years old.

The update of hip fractures incidence rates also resulted in a change in the incidence of other major osteoporotic fractures. Table 3 shows the incidence rates of these fractures in the present study compared to those used in the original FRAX model. Differences ranged from −31 to +13 %. The greatest difference between the rates used in the original FRAX model and the present study was observed in men aged 65–74 years (up to −31 %) and in younger women aged 50–54 years (−23 %) reflecting the lower incidence of hip fracture at these ages compared with the original estimates.

Table 4 shows mortality rates due to all causes in the Italian population in 2008 compared to the mortality rates originally used in FRAX model, which were based on UN data for 1999. Mortality rates were substantially and consistently lower in both men and women aged 40–89 years old.

Table 4 Age-specific mortality rates due to all causes in 2008 (present study) and 1999 mortality rates (used in FRAX v3.3)

Age range	Revised mortality rate (2008)	Original FRAX mortality rate (1999)	Revised/original rate (difference, %)
Men			
40–44	1.21	1.84	−34
45–49	1.97	2.81	−30
50–54	3.06	4.72	−35
55–59	4.89	8.08	−39
60–64	8.28	14.04	−41
65–69	12.88	23.85	−46
70–74	21.99	38.44	−42
75–79	38.79	62.81	−38
80–84	71.56	102.27	−30
85–89	134.98	179.33[a]	−25
90–94	203.85	179.33[a]	+12
95–100	316.49	179.33[a]	+43
>100	363.80	179.33[a]	+51
Women			
40–44	0.65	0.94	−31
45–49	1.12	1.52	−26
50–54	1.75	2.37	−26
55–59	2.64	3.57	−26
60–64	4.20	5.78	−27
65–69	6.36	9.98	−36
70–74	11.07	17.54	−37
75–79	20.92	33.17	−37
80–84	43.08	63.34	−32
85–89	93.97	144.26[a]	−35
90–94	158.37	144.26[a]	
95–100	266.54	144.26[a]	
>100	422.40	144.26[a]	

[a] Mortality rate in the population aged 85 years old and over were assumed to be the same

Mortality data for oldest age groups (>85 years old) were lacking in the original FRAX model, so that mortality was underestimated in the very elderly.

Table 5 shows the effect of differences in fracture risk and mortality on fracture probabilities at different percentile of probability distribution by age category in the general population. The differences in probability estimates were relatively small. In general, the revision resulted in a lower estimated 10-year probability in the younger age groups, whilst those in the older age groups were slightly higher. For example, for a 50-year-old woman, the probability using the revised rates was about 20 % lower than if the original rates were used for both hip and major osteoporotic fractures. In 80-year-old women, the revision resulted in slightly higher 10-year probabilities (by about 10 %) compared to the original rates. Figure 1 summarises the overall impact (expressed as ratios of median fracture probability) of the revised fracture incidence and mortality data on 10-year fracture probabilities (both hip and major osteoporotic fractures), as resulted from the updated FRAX model for Italy.

Table 6 shows 10 year fracture probabilities (FRAX v3.3 and v3.4) for specific clinical scenarios in Italy and an ad hoc selection of other countries. The modest change in the FRAX revision for Italy had no effect on the rank order of fracture probabilities.

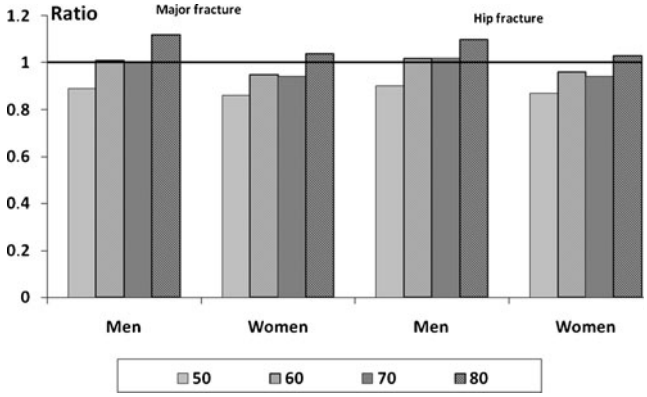

Fig. 1 Ratios of median fracture probabilities (older version 3.3 vs. revised version 3.4) of a major osteoporotic fracture and a hip fracture in White men and women for Italy

Discussion

The FRAX algorithms aim to provide individual estimates of fracture risk that would be helpful for clinical decision making in specific countries. More than 40 models are available and FRAX has already been incorporated into treatment guidelines in several countries in Europe and North America [23–28]. In addition to the development of new models, existing models should be updated when new information becomes available. In the present study, we have replaced the hip fracture rates based on regional estimates with more recent data based on national statistics for Italy. We also substituted more recent data on mortality. In addition, a significant advancement in the accuracy of the FRAX model for Italy is that data are now available on hip fracture rates at the extremes of age (below 50 and over 95 years). This is important because FRAX provides estimates of fracture risk for individuals aged between 40 and 90 years. Therefore, in order to compute the 10-year probabilities at the age of 90 years, it is preferable to have fracture incidence and mortality data up to the age of 100 years.

In the present study, we excluded re-hospitalisations of the same patient in the same year that mainly includes re-admission for the same fracture into rehabilitation hospitals. We would have missed a small minority of cases in whom a contralateral hip fracture occurred within the same year. Thus, our results should be considered as estimates more

Table 5 Ten-year probability (in percent) of a major osteoporotic fracture or a hip fracture in women at different percentiles of probability distribution at the ages shown: older FRAX Italian version 3.3 vs. revised FRAX Italian version 3.4

Age (years)	Percentile					
	10		50		90	
	Version 3.3	Revision (v 3.4)	Version 3.3	Revision (v 3.4)	Version 3.3	Revision (v 3.4)
Major fracture						
50	6	5	15	13	38	33
60	7	7	18	17	41	40
70	10	9	24	22	57	54
80	15	15	34	36	70	72
Hip fracture						
50	0.3	0.2	2.7	2.3	23	20
60	0.6	0.5	3.6	3.4 (3.4–3.5)	22	21
70	1.8	1.6	9.3	8.6 (8.4–8.8)	42	40
80	4.6	4.7	22	23 (22–23)	64	66

Table 6 Ten-year probability (sorted by rank of probability) of a major fracture and hip fracture (in percent) in men and women aged 65 years from Italy, USA and other European countries according to different individual clinical scenarios: no clinical risk factors (BMI set to 25 kg/m^2), a prior fragility fracture, femoral neck T-score −2.5 SD with no other clinical risk factors (CRFs)

	Men aged 65			Women aged 65		
	No CRFs	Prior fracture	$T = -2.5$	No CRFs	Prior fracture	$T = -2.5$
Major fracture						
Spain	2.1	4.2	4.6	3.6	7.3	5.6
France	2.6	5.3	5.7	4.5	9.0	6.9
Germany	3.3	6.6	7.1	5.8	11	8.8
Italy v.3.4	3.4	6.9	7.7	5.7	11	8.8
Italy v 3.3	3.7	7.5	8.1	6.5	13	9.8
Austria	4.9	9.7	10	8.5	17	13
UK	4.9	9.5	9.7	8.4	16	12
US[a]	5.6	11	11	9.3	18	13
Switzerland	5.6	11	11	9.5	18	14
Sweden	6.1	12	13	10	19	15
Hip fracture						
Spain	0.4	1.1	2.1	0.7	1.8	1.7
France	0.5	1.3	2.5	0.9	2.2	2.1
Germany	0.7	1.7	3.1	1.2	2.9	2.8
Italy v 3.4	0.8	1.9	3.6	1.2	3.1	2.9
Italy v 3.3	0.8	1.9	3.6	1.3	3.2	3.1
US[a]	0.8	1.9	3.5	1.2	3.0	2.9
UK	0.8	1.9	3.5	1.3	3.1	3.0
Switzerland	0.9	2.2	4.1	1.5	3.6	3.4
Austria	1.0	2.5	4.7	1.7	4.3	4.1
Sweden	1.3	3.2	6.0	2.1	5.1	4.8

[a]US Caucasian model

closely reflecting the current situation than previously used in the Italian model.

We found substantial differences in the risk of hip fracture compared with the previous regional estimates. In general, the national data showed lower hip fracture incidence rates than those used in the original FRAX implementation. It is not known whether this is due to regional differences in hip fracture rates that are well documented within countries [6] or due to a national decrease in age- and sex-specific incidence—also described in several Western countries [7]. We also showed substantial and consistent differences in mortality which was lower at all ages in 2008 than in 1999. It is of interest that the WHO mortality estimates were higher than those given by the Italian Institute for Statistics for 1999.

Despite differences in fracture risk and mortality, the effect on fracture probability was modest. This is because probability depends on the competing hazards of death and fracture risk. Lower fracture rates are expected to decrease fracture probability whereas lower mortality will increase probability of fracture. However, some significant differences (by up to 20 %) were found for probability estimates in younger women and for men aged 65 to 80 years. Based on our more comprehensive and current data, we found that—in these groups—the original rates used in the FRAX model overestimated fracture risk as much as 20 %. A significant advancement in the accuracy of the FRAX model for Italy is that data are now available on hip fracture incidence rates at the extremes of age (below 50 and over 95 years). The pattern of the results is similar to those of the US revision in that in the revised Italian FRAX model younger postmenopausal women present lower incidence rates than in the original version of the algorithm [8]. However, in USA the overestimations were generally more extreme than we found for Italy. The most extreme discrepancy we found was in Italian men between 65 and 80 years old in whom the revised incidence rates were dissimilar by as much as 30 % compared to the original FRAX data.

When comparing the 2008 mortality with that data from 1999 previously used in the original model, the rates significantly decreased in all the age groups below 85 years old. As observed after updating of the US version of FRAX, the revisions resulted in small shifts of estimated probabilities but did not modify the rank order of fracture probability in the population. In the clinical scenarios presented in this paper (Table 5), the correlation coefficients between versions 3.3 and 3.4 probabilities exceeded 0.99, so that the one can be accurately predicted from the other. In other words, an individual at the 90th percentile of risk for their gender and age would still remain at the 90th percentile of risk using the revised FRAX tool. Thus, as in the revision of the

US model [8], the consequences of improving the accuracy of the algorithm reside in the absolute probability generated and not in the rank order of risk.

In addition to the well-recognised problems in register studies, the present study has several limitations. A minority of countries that have a FRAX model also have robust information on the risk of the other major fractures (clinical spine, forearm and humerus). Where available, these are incorporated in the models (e.g. UK, USA, Switzerland, Sweden, Japan and Mexico). In the absence of information, FRAX models are based on the assumption that the age- and sex-specific pattern of these fractures is similar to that observed in Sweden. For example, if at a specific age and sex, the hip fracture risk is 50/10,000 in Sweden and 25/10,000 in an index country, then the incidence of forearm fractures in the index country is half that seen in Sweden at that age and sex. The computation of major osteoporotic fracture risk is more challenging than that of hip fractures because only a minority of them require hospital admission. In both the original implementation and in the current version of the FRAX in Italy, estimates of a major osteoporotic fracture were imputed from the ratio of hip fractures to major osteoporotic fractures in Sweden [29, 30] because of the absence of suitable empirical data. The available information suggests that the pattern of fractures is similar in the Western world and Australia, despite differences in incidence [18]. Further studies are needed in order to provide specific Italian data on the incidence of wrist, humerus, and clinical vertebral fractures. An additional improvement to FRAX might be the use of hip fracture and mortality rates by 1-year age intervals rather than the 5-year intervals. Other accuracy errors could be possibly overcome as fracture rates should ideally be based on the incidence of a first fracture at any one site, whereas current estimates are based on the incidence of fracture irrespective whether this is a first or subsequent fracture at the same skeletal site. The overestimate that arises has been characterised for Sweden [29] but not for other countries. Although the use of hospitalization records makes it possible to do this for hip fracture, the other outcome fractures used in FRAX are not consistently hospitalised.

Our study confirms previous findings from other countries showing that hip fractures are most frequently found in older people and particularly in women [11–16]. We found that about 40 % of hip fractures occurred in individuals over the age of 85 years, a group representing only 4.4 % of the Italian population aged 40 years or more. Since this segment of the population is increasing rapidly in Italy, it has important implications for the future focus of preventive strategies.

Conclusion

We have updated information on the incidence of hip fractures and mortality in Italy to allow the Italian version of FRAX to more accurately assess fracture probability. The impact of these revisions on FRAX resulted in a lowering of 10-year fracture probabilities in younger age groups and a slight increase in the older age groups. In order to keep the FRAX estimates accurate, it will be important for all countries to periodically provide updated fracture incidence and mortality data.

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