



Original Full Length Article

Assessing 5-year incidence rates and determinants of osteoporotic fractures in primary care

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ARTICLE INFO

Article history:

Received 1 February 2011

Revised 11 July 2011

Accepted 22 September 2011

Available online 02 October 2011

Edited by: Felicia Cosman

Keywords:

Osteoporotic fracture

Primary care

Incidence rate

Risk factors

ABSTRACT

Purpose: To assess the gender and age-related 5-year incidence rates of osteoporotic fractures, and their related predictors, in a primary care setting.

Methods: We obtained information from the Health Search–CSD Longitudinal Patients Database (HSD). This is an Italian General Practice data repository which comprises information given by computer-based patient records of a selected group of over 900 Primary Care Physicians (PCPs).

We selected all patients aged 50 to 85 years, who were actively included into the PCP's list at the beginning of the enrolment period (1st January 2002–31st December 2003). We excluded individuals who were registered in the PCPs' list for less than 1 year before the entry date (Index date) into the cohort, as well as those who were diagnosed with Paget disease or malignant neoplasm. Participants were followed up until the occurrence of osteoporotic fracture, one of the exclusion criteria, or the end of the study period.

Results: The 5-year rates (per 1000 person-years) of any osteoporotic fracture were 11.56 (95% C.I. 11.33 to 11.77) among females, and 4.91 (95% C.I. 4.75 to 5.07) among males. For hip fractures, the overall incidence rates were 3.23 (95% C.I. 3.11 to 3.34) among females and 1.21 (95% C.I. 1.12 to 1.28) among males, respectively. Advanced age, history of fracture, use of corticosteroids, rheumatoid arthritis, BMI ≤ 20, presence of osteoporosis, gastrointestinal and chronic hepatic disease, depression, chronic obstructive pulmonary disease, use of anticonvulsants and a higher number of co-medications, increased the risk of any osteoporotic fractures.

Conclusions: The use of primary care data confirms a higher incidence of osteoporotic fractures among females vs. males as well as in older individuals. Predictors of osteoporotic fractures were consistent with FRAX® algorithm. Given the clinical utility of a simple score for the assessment of absolute fracture risk among osteoporotic patients, its assessment and validation in the Italian HSD could potentially provide an applicable prediction tool.

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Introduction

Osteoporosis is a systemic condition characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and, consequently, an increased risk of fracture. Osteoporotic fractures represent an increasing cause of morbidity in the older populations and a considerable burden to health services in many regions of the world [1–4].

Hence, there is the need to improve methods for accurate identification of individuals at high risk of fractures, who might benefit from a preventive or therapeutic intervention. Indeed, although Bone Mass

Density (BMD) measurement at the femoral neck with Dual energy X-ray Absorptiometry (DXA) is a strong predictor of the osteoporotic fracture risk [5], there have been several issues associated with its use as a clinical diagnostic test, because of its relevant cost and low sensitivity [6]. Several fractures occur in women with normal BMD [7], and the evidence suggests that risk prediction algorithms that do not include BMD, seem to possess an equal effectiveness [8]. Along this line, less expensive and more practical methods for identifying those individuals at high risk of osteoporotic fractures is a healthcare requirement. These methods should ideally be based on models which have developed similar questions in diverse populations, which are representative of the specific healthcare setting.

Recently, computer-based algorithms (FRAX®) have been developed (www.shef.ac.uk/FRAX) under the auspices of the World Health Organization (WHO). This algorithm provides 10-year probabilities of hip fracture and other major osteoporotic fractures (i.e., spine and

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forearm). This prediction tool seems to possess a higher sensitivity to detect those at high risk of fracture [9], besides suggesting which intervention threshold should be developed [10]. However, a necessary prerequisite for the implementation of prediction score are data on the epidemiology of fragility fractures and the potential risk factors which underlie this risk. To this purpose, little is known on the general practice setting.

Furthermore, since the incidence of fracture and the prevalence of associated risk factors will change over time, the methods to derive the risk prediction algorithms need to be dynamic, so that they can be modeled over time. Longitudinal primary care databases have the advantage of having large and broadly representative populations with historical data, constantly updated and retrospectively traced to a decade in the majority of practices. In this context, they have been demonstrated to provide complete and reliable information aimed at developing and validating clinical risk score of fractures [11].

Thus, the aim of this study was to assess – in a primary care setting – the 5-year gender and age specific absolute risk of osteoporotic fractures (hip, vertebral and others) taken as a whole, only those of hip, and the related predictors.

Methods

Data source

We obtained information from the Health Search–CSD Longitudinal Patients Database (HSD), an Italian General Practice (GP) database that comprises data given by computer-based patient records of a selected group of over 900 Primary Care Physicians (PCPs). PCPs voluntarily agreed to collect patient information and to attend specific training courses for data entry. The HSD contains patients' demographic details that are linked through the use of an encrypted code with clinical records (diagnoses, referrals, and tests results), drug prescriptions (drug name, date of the filled prescription, and number of days' supply), prevention records, hospital admissions, and the date of death. To be considered for participation in epidemiological studies, PCPs should meet "up-to-standard" quality criteria pertaining to the levels of coding, prevalence of well-known diseases, mortality rates, years of recording and the evaluation of missing values [12].

A number of studies have been published confirming the research validity of the HSD information in conducting epidemiological research [13–15].

When this study was initiated, 500 PCPs homogeneously distributed across all Italian areas, covering a patient population of 1,088,229 individuals, fitted the up-to-standard quality criteria.

Study cohort

We enrolled all patients who were actively included into the PCPs list at the beginning of the enrolment period (1st January 2002–31st December 2003). To be eligible patients had to be registered with one of the participating PCPs for at least 1 year before the entry (Index date) into the study cohort, and to be aged between 50 and 85 years.

To estimate the osteoporotic-related fractures, we excluded patients who had been diagnosed with alternative causes of bone fragility, such as Paget disease (International Classification Disease, 9th revision, Clinical Modification-ICD9CM-code: 731.x) or malignant neoplasm (ICD9CM: 140–208.x), before the Index date. Subjects were followed up from the Index date until the occurrence of these events, whichever came first: osteoporotic fracture, diagnosis of tumor and/or Paget disease, death, PCP's change, and end of the study period.

According to data availability, participants' mean age (major than 60 years), and medical literature [4,16–18] patients were followed up to 5 years.

Outcomes

Osteoporotic fractures were ascertained through the physician's coded diagnosis [4,16,17,19] during follow-up and were defined as an incident event of hip (ICD9CM: 733.14, 820.x, 821.0 and 821.2), vertebral (733.13, 805.x) and other fractures such as humerus (733.11, 812.x), radius and ulna (733.12, 813.x), shinbone and fibula (733.16, 823.x), and pelvis (808.x).

Covariates

In our analysis we examined a series of explanatory variables. All of them are known to affect the risk of fracture [6,9,20] according to FRAX® score. They comprise history osteoporotic fractures, chronic use of corticosteroids (ATC H02* and at least 120 Defined Daily Dose (DDD) within one year before the Index date), rheumatoid arthritis (ICD9CM 714.x and 720.0 or at least two prescriptions of anti-rheumatic drugs [ATC M01C*, L04AA*, L01BA01] six months before the Index date), Body Mass Index (BMI) and current smoking.

We have also included additional features potentially associated with fracture risk, such as doctor-diagnosis of osteoporosis (733.0x), hypogonadism (257.2x), neurologic diseases (340.x, 335.2x, 356.x, 359.x, 271.x, 358.x and 740 through 759.x), organ transplant (V42.x), type 1 diabetes (250.x1 and 250.x3), hyperthyroidism (242.0, 242.1, 242.8 and 242.9), gastrointestinal diseases (530.x through 534.x), chronic hepatic diseases (571.x), Chronic Pulmonary Obstructive Disease (COPD: 491.2x and 496.x), asthma (493.x) and depression (311.x, 296.2x and 296.3x) [2,11,18,21–26].

Finally, we have also included certain medications as covariates likely related to fracture risk: they comprised use of anticonvulsants (N03A*) and the number of distinct drugs being prescribed six months before the Index date.

Data analysis

On the basis of the study outcomes, we adopted two different cohorts.

In the first one, we also excluded patients with previous osteoporotic fractures before the Index date from the aforementioned "Study cohort". Herein, we provided age and sex-specific incidence rates of 5-year overall osteoporotic fractures, and solely those of hip, as cases per 1000 person-years.

In the second one, to investigate the possible risk factors, we maintained the overall "Study cohort".

The prevalence of any predictor and the demographic characteristics of the study cohort were then evaluated according to a descriptive analysis for man and women, separately. We used the chi-square test to evaluate the potentially significant differences in baseline characteristics between genders.

Multivariable Poisson regression models, adjusting for selected baseline factors, were constructed to derive continuous hazard functions. Separate models have been carried out for women and men. The outputs were the estimated 5-year risk of fractures combination (vertebral, hip and others) and only for hip fractures. Any covariate was selected according to statistical and/or clinical meaning as shown by univariate analysis and current medical literature, respectively. In particular, any feature apt to identify patient's chronic status at baseline was investigated. Hence, the final models retained age categories, history of fracture, BMI (≤ 20 vs. higher), rheumatoid arthritis, current smoking (as per FRAX® score), osteoporosis diagnosis, neurologic disease, hyperthyroidism, gastrointestinal and chronic hepatic disease, depression, asthma, COPD, number of co-medications and use of anticonvulsants. We performed a goodness-of-fit test to assess the appropriateness of the Poisson regression.

Statistical significance was defined as a 2-tailed value of $p < 0.05$. Estimates of incidence rate ratio, 95% Confidence Intervals (CIs), and

probability values were generated with STATA software, version 10.1 (STATA Corp, College Station, Tex).

Results

Characteristics of the study cohort

After applying the inclusion and exclusion criteria, 271,121 subjects (122,553 males and 148,568 females) entered the analysis.

Baseline demographic and clinical features of the study population are shown in Table 1. Significant differences have been observed between males and females with regard to several characteristics. Among females, a significantly higher prevalence of previous fractures was reported when compared with males (2.42% vs. 1.21%; $p < 0.0001$).

Consistently, females showed a higher prevalence for all other FRAX® items, except for current smoking (males: 6.62% vs. females: 3.86%; %; $p < 0.0001$).

Concerning the other potential risk factors, presence of osteoporosis, hyperthyroidism, depression, asthma, as well as the use of anticonvulsants showed a greater prevalence among females than males. No significant differences between males and females have been observed about the prevalence of neurologic disease and type 1 diabetes.

Incidence rates

The 5-year incidence rates (per 1000 person-years) of any osteoporotic fracture stratified by age group and gender are depicted in

Table 1
Baseline characteristics of the study cohort according to gender.

	Men N = 122,553	Women N = 148,568	P value
Demographic characteristics			
Mean age (year)	63.4 (9.74)	65.2 (9.22)	<0.0001
Age strata			<0.0001
<=60	48,948 (39.94%)	50,482 (33.98%)	
65–69	39,727 (32.42%)	45,325 (30.51%)	
>=70	33,878 (27.64%)	52,761 (35.51%)	
FRAX® factors			
Fracture history	1489 (1.21%)	3592 (2.42%)	<0.0001
Hip fracture	318 (0.26%)	951 (0.64%)	<0.0001
Vertebral fracture	429 (0.35%)	784 (0.53%)	<0.0001
Other fractures	772 (0.63%)	1965 (1.32%)	<0.0001
Use of corticosteroids	627 (0.51%)	936 (0.63%)	<0.0001
Rheumatoid arthritis	556 (0.45%)	1595 (1.07%)	<0.0001
BMI <= 20 ^a	483 (0.39%)	1770 (1.19%)	<0.0001
Current smoking	8115 (6.62%)	5739 (3.86%)	<0.0001
Other possible risk factors			
Osteoporotic diagnosis	1009 (0.82%)	17,382 (11.70%)	<0.0001
Hypogonadism	10 (0.01%)	0 (0%)	-
Neurologic disease	1176 (0.96%)	1455 (0.98%)	= 0.601
Organ transplant	178 (0.15%)	101 (0.07%)	<0.0001
Type 1 diabetes	135 (0.11%)	153 (0.10%)	= 0.568
Hyperthyroidism	377 (0.31%)	1344 (0.90%)	<0.0001
Gastrointestinal disease	9750 (7.96%)	10,087 (6.79%)	<0.0001
Chronic hepatic disease	3796 (3.10%)	3277 (2.21%)	<0.0001
Depression	2225 (1.82%)	6160 (4.15%)	<0.0001
Asthma	2268 (1.85%)	4177 (2.81%)	<0.0001
COPD	6457 (5.27%)	3785 (2.55%)	<0.0001
Pharmacotherapy			
Anticonvulsants	1608 (1.31%)	2108 (1.42%)	= 0.017
Number of concurrent medications			<0.0001
0	47,670 (38.90%)	46,804 (31.50%)	
1	36,800 (30.03%)	52,833 (35.56%)	
2+	38,083 (31.07%)	48,931 (32.94%)	

Each feature is reported as n (%).

COPD: Chronic Obstructive Pulmonary Diseases, BMI: Body Mass Index.

^a BMI: patients with a BMI measurement within 3 years before the Index date.

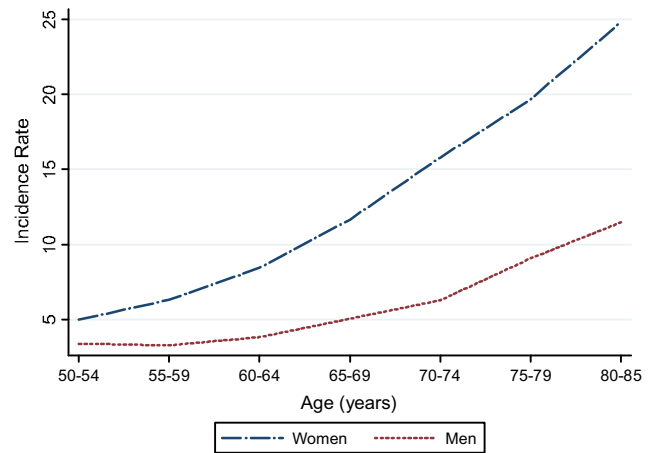


Fig. 1. Age and gender-specific 5-year incidence rates of any osteoporotic fracture (per 1000 person-years).

Fig. 1. Overall, we have found estimates ranging from 4.91 (95% C.I. 4.75 to 5.07) among males to 11.56 (95% C.I. 11.33 to 11.77) among females. Although the incidence appeared higher among women across all age groups, an increased gap has been observed from the age group 65–69 years and forward.

Concerning hip fractures (Fig. 2), the overall incidence rates were 3.23 (95% C.I. 3.11 to 3.34) and 1.21 (95% C.I. 1.12 to 1.28) among females and males, respectively. We have observed similar incidence up to 60 years between genders, whereas a sharp increase among older females was revealed until the age group 80–85.

Risk factors

The result of the multivariate Poisson regression analysis, in terms of 5-year absolute risk for any osteoporotic fracture and only for hip fractures, is shown in Table 2. As a whole, 14,225 osteoporotic fractures occurred in the study cohort, 10,542 (74.1%) among females and 3683 (25.9%) among males.

For female gender, advanced age, history of fracture, use of corticosteroids, rheumatoid arthritis, BMI <= 20, a diagnosis of osteoporosis, gastrointestinal and chronic hepatic diseases, depression, COPD, use of anticonvulsants and a higher number of medications, significantly increased the risk of any osteoporotic fractures. Concerning hip fractures, we gathered a 13.27-fold higher risk among patients

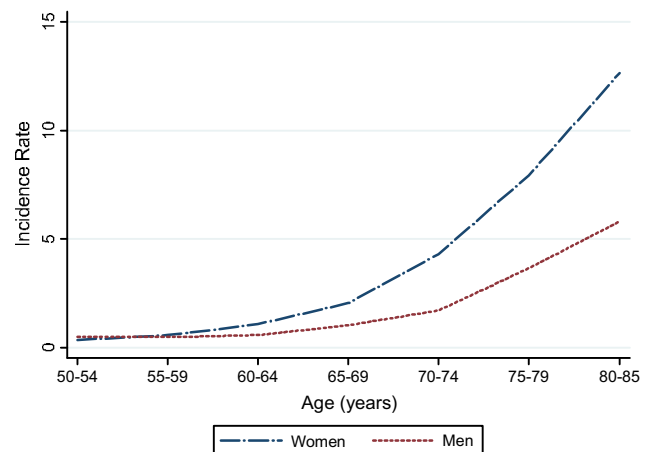


Fig. 2. Age and gender-specific 5-year incidence rates of hip osteoporotic fracture (per 1000 person-years).

Table 2
Multivariable Poisson regression of the association^a between baseline clinical characteristics and 5-year fracture risk.

	All fractures (N = 14,225)		Hip fractures (N = 3929)	
	Males (N = 3683)	Females (N = 10,542)	Males (N = 914)	Females (N = 3015)
<i>Demographic characteristics</i>				
<i>Age strata</i>				
<=60	1	1	1	1
65–69	1.26 (1.16–1.38)	1.68 (1.58–1.78)	2.06 (1.64–2.6)	2.77 (2.32–3.30)
>=70	2.31 (2.13–2.50)	3.19 (3.02–3.37)	8.06 (6.58–9.87)	13.27 (11.37–15.5)
<i>FRAX® factors</i>				
History of fracture	2.39 (1.99–2.89)	1.9 (1.75–2.06)	1.99 (1.36–2.91)	2.21 (1.93–2.52)
Use of corticosteroids	1.39 (0.98–1.97)	1.69 (1.42–2.01)	1.57 (0.86–2.88)	1.80 (1.34–2.43)
Rheumatoid arthritis	1.41 (0.97–2.05)	1.25 (1.07–1.46)	1.11 (0.49–2.50)	1.28 (0.97–1.69)
BMI <= 20 ^b	1.69 (1.18–2.43)	1.42 (1.23–1.63)	1.67 (0.86–3.25)	2.01 (1.61–2.50)
Current smoking	1.06 (0.93–1.20)	1.08 (0.97–1.20)	1.13 (0.87–1.47)	1.13 (0.91–1.39)
<i>Other possible risk factors</i>				
Osteoporotic diagnosis	1.57 (1.23–2.00)	1.42 (1.35–1.49)	2.09 (1.43–3.05)	1.30 (1.19–1.43)
Neurologic disease	1.33 (1.02–1.74)	1.15 (0.97–1.37)	1.66 (1.04–2.66)	1.23 (0.91–1.67)
Hyperthyroidism	1.00 (0.58–1.72)	0.89 (0.72–1.10)	1.69 (0.76–3.78)	1.21 (0.87–1.69)
Gastrointestinal disease	1.13 (1.02–1.27)	1.17 (1.10–1.25)	1.11 (0.89–1.38)	1.13 (1.00–1.29)
Chronic hepatic disease	1.49 (1.27–1.73)	1.33 (1.19–1.48)	1.92 (1.45–2.54)	1.38 (1.13–1.68)
Depression	1.17 (0.95–1.44)	1.24 (1.14–1.35)	1.51 (1.05–2.16)	1.36 (1.17–1.57)
Asthma	1.09 (0.87–1.37)	1.08 (0.96–1.20)	0.82 (0.48–1.39)	1.13 (0.92–1.39)
COPD	1.24 (1.09–1.40)	1.22 (1.10–1.34)	1.19 (0.96–1.49)	1.24 (1.04–1.46)
<i>Pharmacotherapy</i>				
Anticonvulsants	1.57 (1.27–1.95)	1.49 (1.32–1.70)	2.07 (1.45–2.96)	1.61 (1.28–2.01)
<i>Number of concurrent medications</i>				
0	1	1	1	1
1	1.22 (1.12–1.33)	1.22 (1.16–1.29)	1.12 (0.94–1.33)	1.09 (0.99–1.21)
2+	1.23 (1.13–1.33)	1.18 (1.12–1.25)	1.25 (1.06–1.47)	1.15 (1.04–1.26)

COPD: Chronic Obstructive Pulmonary Diseases, BMI: Body Mass Index.

^a Incidence rate ratio and 95% CI.

^b BMI: patients with a BMI measurement within 3 years before the Index date.

aged 70 years than lower sixties. Furthermore, a significant increased risk was here reported for the same characteristics related to the overall fractures, with some exceptions. In fact, rheumatoid arthritis, a diagnosis of osteoporosis, depression and COPD did not show any association with hip fracture occurrence.

Instead, among men, the predictors significantly associated with any osteoporotic fracture comprised advanced age, history of fracture, BMI <= 20, a diagnosis of osteoporosis, chronic hepatic disease and COPD as well as the use of anticonvulsants and the increasing number of coexistent medications. Increased age, previous fractures (FRAX® component), a diagnosis of osteoporosis, chronic hepatic disease, use of anticonvulsants and the increasing number of concurrent medications were significantly associated with the risk of hip fracture.

The concurrent prevalence of one or more risk factors significantly affected the results (Fig. 3). The risk of either overall or hip fracture ranged from 8.2 (95% C.I. 8.03 to 8.31) to 2.2 (95% C.I. 2.10 to 2.25)

per 1000 person years among patients with no risk factor to 20.5 (95% C.I. 17.61 to 23.77) and 7.0 among patients (95% C.I. 5.47 to 9.03) with 2 or more risk factors, respectively.

Discussion

The present study provides the basis for the assessment of 5-year probability fracture risk in men and women in a large specific Italian population. The use of primary care data, derived from the HSD, has allowed the examinations of the general relationship which each predictor of osteoporotic fractures by gender and duration of follow-up. In general, a higher incidence of osteoporotic fractures was observed among females when compared with males, as well as in the older population strata. This result was confirmed when analysis was restricted to hip fractures. Additionally, we identified predictors which were those expected by FRAX® algorithm and identified in some previous surveys.

In keeping with current medical literature, females showed a higher incidence of osteoporotic fractures than males. When compared with ours, Hippisley-Cox and coworkers [11] reported analogue rates for both genders; Barrett-Connor et al. [27] retrieved a similar incidence of approximately 4 cases per 1000 person-years among male elders; Cooper and Cheng [28,29] showed secular and geographical trends of osteoporotic fractures, whose estimates were coherent with ours.

As expected, an increasing trend of fractures occurrence was positively related to the increasing patients' age. The rate appeared higher among females across all age groups, and a wider gap has been observed from the 65–69 years group and forward. Yet, our findings agree with other surveys [2,4,16,27–32], where the more evident difference was estimated after 60–65 years. As per Cummings [2], Hippisley-Cox [11] and Piscitelli et al. [4], hip and vertebral fractures should be mainly responsible of this trend.

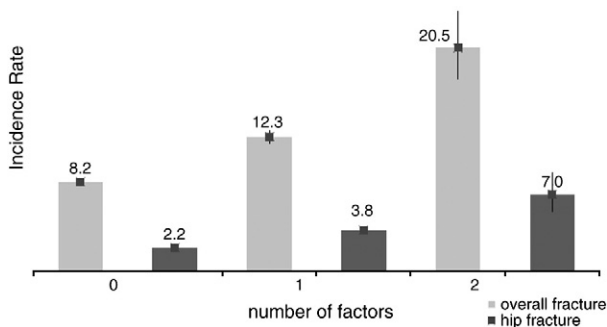


Fig. 3. Incidence rates of fracture (per 1000 person-years) according to the number of risk factors.

Consistently, our estimates were reproducible with previous findings when the analysis was focused on the hip site [2,4,11]. A sharp increase was achieved among older males and females until the age group of 80–85 years. Between genders, as also reported by Piscitelli et al. [4], no relevant differences has been recorded up to 60–65 years of age, while they strictly diverge moving towards the older age groups. The plausible explanation to these results could be due to bone loss associated with menopause, which is generally more common after 55–60 years of age [2,28,29,31,32].

Also the other determinants of osteoporotic fractures here reported were somewhat in line with other studies [2,4,16,27,30]. Nevertheless, smoking habits and asthma were not supported by our results. Some explanations could address the differences. The fact that a 10-year cohort was adopted by some previous surveys [11,30] implies a higher number of cases, and an increased cumulative effect of risk factors over time [18]. Herein, some clinical features could be missed by our analysis. Furthermore, a study from UK [11] enrolled patients at 30 years of age, whereas we selected patients aged 50+ years to preserve a clinical plausibility between fractures and osteoporosis. Along this line, while asthma is a risk factor in previous investigations [11], the presence of COPD in our predictors could be suggestive of a related respiratory impairment which is more common among elderly than in younger asthmatic patients. Concerning smoking habits, although it was proportionally coherent with the participants' age and selection (oncologic patients were excluded) when compared with the general Italian population [33], its lacking association with fracture occurrence could be due to social desirable answers [34].

Rheumatoid arthritis did not result a risk factor as well. Such an explanation, it could be due to the fact that this disorder is self-reported by patients, who generally misclassify rheumatoid arthritis, osteoarthritis or arthralgia [18].

Concerning both overall and hip fractures, Hippisley-Cox et al. [11] reported the use of tricyclic antidepressants as a predictor. Partly in keeping with them but fully in agreement with other surveys [30], our data report depression as a risk factor. We examined the disease instead of its pharmacological treatment to overcome the possibility of confounding by indication [35]. On the contrary, anticonvulsants were expectedly associated to fracture occurrence also taking into account their indication of use [23,24,36].

In any case, although not-significant, most of the patient's features (e.g. use of steroids among males) inspected by us, were not so far to exclude unit from their CIs.

From a clinical perspective, the history and combination of one or more risk factors could be profitably adopted by the PCP to evaluate the predictability of osteoporotic fractures. FRAX® score is currently proposed by WHO and its use could be part of clinical activity to overcome BMD insensitivity. To this purpose, each predictor here discussed is part of FRAX® [37,38], so demonstrating its or certain variants usefulness for the PCPs [18].

This study has some limitations. Firstly, no validation study has been formally carried out to test the accuracy of the fractures diagnosis. However, the incidence rates here reported are consistently in line with current literature, either between genders or among age categories [2,4,11,16,17,19,27,31,32].

Secondly, absence of information on certain features (e.g. history of falls, alcohol intake, fracture family history [9,37]) could have missed other possible risk factors. Indeed, HSD database does not supply with accurate measures of some covariates. For instance, alcohol abuse it is difficult to measure because of social desirable answers albeit its causal association with osteoporotic fractures is not still exhaustively demonstrated [18]. In the same way, history of falls might be inaccurately recorded in the database, because the PCP does not collect radiographs for most patients [18]. Thus, it appears difficult to record severe falls that are plausibly related to fractures. Consistently, the fracture family history appeared

not analytically usable when the PCPs' standard quality requirements [12] were verified.

Finally, the possibility of competing rates with mortality could partly explain the lacking association between some covariates, such as smoking habits, and the risk of fracture. Nevertheless, it is more plausible that a relatively short follow-up (5 years instead of 10) could not have permitted an exhaustive analysis of certain variables.

Conclusions

This survey provides a model for the assessment of 5-year probability fracture risk in men and women in a large specific Italian population. The use of primary care data confirms, in fact, a higher incidence of osteoporotic fractures among females when compared with males, as well as in the older population strata. In addition, predictors of osteoporotic fractures were those expected to be identified by the FRAX® algorithm in a general practice setting as well.

In the light of the clinical utility of a simple risk score for the assessment of absolute fracture risk among osteoporotic patients, its assessment and validation in the Italian HSD could potentially provide an applicable prediction tool in primary care.

Conflict of interest

No disclosures.

Acknowledgments

We are very grateful to all PCPs who continue to collect data and update HSD.

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