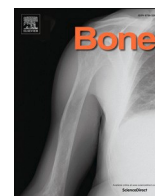




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Trends in hip and distal femoral fracture rates in Italy from 2007 to 2017

Brigid Unim^{a,*,1}, Giada Minelli^{b,1}, Roberto Da Cas^c, Valerio Manno^b, Francesco Trotta^d,
Luigi Palmieri^a, Lucia Galluzzo^a, Stefania Maggi^e, Graziano Onder^a^a Department of Cardiovascular, Endocrine-metabolic Diseases and Aging, Istituto Superiore di Sanità, Rome, Italy^b Service of Statistics, Istituto Superiore di Sanità, Rome, Italy^c National Centre for Drug Research and Evaluation, Istituto Superiore di Sanità, Rome, Italy^d Italian Medicines Agency, Rome, Italy^e Neuroscience Institute, Aging Branch, CNR, Padua, Italy

ARTICLE INFO

Keywords:

Osteoporosis

Hip fractures

Distal femoral fractures

Elderly

Anti-osteoporosis drugs

ABSTRACT

Osteoporosis-related fractures are a growing public health concern worldwide due to high societal and economic burden. The study aims to assess trends in incidence rates of hip and distal femoral fractures and in the use of anti-osteoporosis drugs in Italy between 2007 and 2017. Patients with hip and distal femoral fractures (ICD-9-CM codes 820.x and 821.x) were identified in the Italian National Hospital Discharge Database while anti-osteoporosis medication data were retrieved from the National Observatory on the Use of Medicines Database. A joinpoint regression analysis was performed to identify the years where the trends in incidence rates of hip and distal femoral fractures changed significantly; the average annual percentage change for the period of observation was estimated. Hospitalizations for femoral fractures were 991,059, of which 91.4% were hip fractures and 76.5% occurred in women. Age-standardized hip fractures rate per 100,000 person-years decreased both in women (−8.7%; from 789.9 in 2007 to 721.5 in 2017) and in men (−4.3%; from 423.9 to 405.6), while the rate of distal femoral fractures increased by 23.9% in women (from 67.78 to 83.95) and 22.7% in men (from 27.76 to 34.06). These changes were associated with an increment in the use of anti-osteoporosis drugs from 2007 to 2011 (from 9.1 to 12.4 DDD/1000 inhabitants/day), followed by a plateau in the period 2012–2017. The use of bisphosphonates increased progressively from 2007 to 2010 (from 8.2 to 10.5 DDD/1000 inhabitants/day), followed by a plateau and then decreased from 2015 onwards. The decreasing trend of hip fractures could be related to a major intake of anti-osteoporosis medications while the increment of distal femoral fractures might be due to population aging and to the use of bisphosphonates and denosumab. Further research is needed to identify and implement interventions to prevent hip and distal femoral fractures.

1. Introduction

Osteoporosis is characterized by low bone mass and qualitative skeletal changes that predispose to bone fragility and to fractures even from low-trauma events. Although more frequent in postmenopausal women [1], osteoporosis is also a relevant health issue in men. It is responsible for over 9 million fractures per year worldwide, of which 39% occur in men [2]. In Western European countries, the prevalence of osteoporosis ranges from 21.8% in the UK to 23.1% in Italy for women, and from 6.7% in Germany to 7.0% in Italy for men [3]. In North America, this condition affects 1.5 million Canadians aged 40 or older

[4] and 10.2 million Americans aged 50 or older [5].

One of the most common consequence of osteoporosis is represented by fracture of the proximal end of the hip. This condition has a relevant impact on disability, mortality, quality of life and cost of treatment [1] and in Italy its socio-economic burden is comparable to that of acute myocardial infarction and stroke [6]. The trend of hip fracture rates in recent years is stable in some western countries (e.g., Germany, the Netherlands, and the UK) and in decline in others (e.g. Canada, Denmark, Finland, Sweden and Norway) [7–12]. This might relate to the positive effects of osteoporosis medications [9], including bisphosphonates, denosumab and parathyroid hormone (PTH) analogues.

* Corresponding author at: Department of Cardiovascular, Endocrine-metabolic Diseases and Aging, Istituto Superiore di Sanità, Via Giano della Bella 34, 00162 Rome, Italy.

E-mail address: brigid.unim@iss.it (B. Unim).

¹ Co-first authors. Equally contributed to this work.

<https://doi.org/10.1016/j.bone.2020.115752>

Received 29 July 2020; Received in revised form 20 October 2020; Accepted 9 November 2020

Available online 12 November 2020

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Atypical subtrochanteric and diaphyseal (distal) femoral fractures are rare conditions and their occurrence has been associated with long term use of bisphosphonates and denosumab [13–15]. This condition has been associated with increased morbidity and mortality and several studies suggested that its incidence has increased progressively in the last 20 years [13].

This study aims to assess trends in incidence rates of hip and distal femoral fractures (including subtrochanteric and diaphyseal fractures) and in the use of anti-osteoporosis drugs in Italy between 2007 and 2017.

2. Materials and methods

2.1. Source of data

Records from the Italian National Hospital Discharge Database were used to identify patients with hip and distal femoral fractures. The National Hospital Discharge Database collects data of all patients discharged from any Italian hospital after an urgent or planned (diagnostic or interventional) admission. For each patient, demographic data (e.g., sex, date of birth) as well as the primary diagnosis and up to five secondary discharge diagnoses are recorded, and diagnoses are codified according to the World Health Organization (WHO) International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

2.2. Hip and distal femoral fracture definition

For the purposes of this study, patients diagnosed with ICD-9-CM code 820.x reported as primary discharge diagnosis, were considered as hip fracture cases and those diagnosed with ICD-9-CM code 821.x as primary diagnosis were considered as distal femoral fracture cases. Each Hospital Discharge Record (HDR) reports a main diagnosis and up to five secondary diagnoses; we chose to examine only the main diagnosis, opting for the so-called “conservative choice” which could lead to an underestimation of cases, but which minimizes false positives. For instance, hip fractures as main diagnosis and femur fractures as secondary diagnoses were considered as hip fractures. Italian studies that have compared the medical records with HDRs in order to assess their accuracy and completeness have shown the satisfactory accuracy level of the main diagnosis compared to the secondary diagnoses that can be sometimes incomplete. Further, Italian and International studies have shown that measures based only on the main diagnosis are more specific (less false positives), whereas measures that take into account all diagnoses are more sensitive (less false negatives) [16,17].

The annual number of hip and distal femoral fractures was tabulated for the study period (2007 to 2017) and stratified by sex and age groups (5-year intervals). For the aim of the study and in consideration of the increasing prevalence of hip fractures with increasing age, we assessed fractures occurring in the population 65 or older.

The validity of the national hospital discharge data, including fracture outcomes used in the present study, is established at the Ministry of Health by the New Health Information System (Nuovo Sistema Informativo Sanitario-NSIS), which is responsible of the quality control and validity of all health data [18].

2.3. Medication data

Data on drug prescriptions in Italy between January 1, 2007 and December 31, 2017 were collected from the National Observatory on the Use of Medicines Database (OsMed). This database collects data regarding the medications dispensed by community pharmacies and reimbursed by the Italian National Health Care Service, as well as those provided directly from health facilities, excluding in-hospital and out-of-pocket drug use. OsMed is responsible for the development and validation of data collection methods, quality control, analysis and

interpretation of data on drug utilization in Italy, including those for osteoporosis [19].

The pharmaceutical categories have been identified according to the Anatomical Therapeutic Chemical (ATC) classification established by the WHO Collaborating Centre (WHOC) for Drug Statistics Methodology [20] as bisphosphonates (M05BA-BB), raloxifene (G03XC01), PTH analogues (H05AA), strontium ranelate (M05BX03), and denosumab (M05BX04).

Drug utilization data was presented as number of Defined Daily Dose (DDD) prescribed and dispensed to the population, which represents the maintenance dose per day of therapy, in adult subjects, related to the main therapeutic indication of the substance [21]; the number of DDD refers to 1000 inhabitants for each day of the year. Drug utilization data presented in DDDs is a rough estimate of consumption and not an exact picture of actual use. DDDs are assigned by the WHO Collaborating Centre in Oslo for medicines given an ATC codes and only one DDD is assigned per ATC code and route of administration [22]. Individual data on DDD was not available for the study and this information is provided as the overall estimate of drug prescription and consumption at the national level.

2.4. Statistical analysis

Age-standardized rates were obtained through the direct standardization method, using the 2013 European population as the standard population. The European standard population 2013 is the revised version of the 1976 population standard and is based on the 2011–2030 population projections of the unweighted average age structure of the of EU-27, including the European Free Trade Association (i.e., Iceland, Liechtenstein, Norway, and Switzerland). This revised version is the most recent comparison population and is representative of the current age structure of EU countries, including Italy, with a higher rate of individuals aged 65 years or older and a lower proportion of children and young adults [23,24]. Incidence rates and age-standardized rates were sex-adjusted.

A joinpoint regression analysis was performed to identify the year(s) where the trends in incidence rates of hip and distal femoral fractures changed significantly; the average annual percentage change (AAPC) for the whole period of observation was then estimated. The analysis was performed using the Joinpoint Regression Program (version 4.8.0.1 released April 22, 2020) of the US National Cancer Institute [25].

3. Results

We identified 991,059 hospitalizations for femoral fractures in Italy from 2007 to 2017 reported as a primary diagnosis in the discharge note, of which 906,111 (91.4%) were hip fractures and 758,740 (76.5%) occurred in women. As shown in Figs. 1 and 2, over the 11-year period, the hip fractures rates increased by 14.3% in women (from 58,525 in 2007 to 66,902 in 2017) and 29.4% in men (from 17,089 to 22,111). The crude hip fracture rate per 100,000 person-years also increased by 1.5% in women (from 855.3 to 868.4) and 8.4% in men (from 346.7 to 375.9). When the rate of hip fractures per 100,000 person-years was age-standardized, a reduction over time was observed both in women (−8.7%; from 789.9 to 721.5) and in men (−4.3%; from 423.9 to 405.6).

The annual number, crude and age-standardized rates of distal femoral fractures showed an increasing trend in both men and women (Figs. 3 and 4). In particular, the number of events increased by 54% in women (from 4947 in 2007 to 7616 in 2017) and 55.7% in men (from 1218 to 1896). The crude rate increased by 36.7% (from 72.30 to 98.86) in women and 37.8% (from 24.71 to 34.06) in men, while the age-standardized rate increased by 23.9% in women (from 67.78 to 83.95) and 22.7% in men (from 27.76 to 34.06).

When different age groups were examined separately (Supplementary Material-Table 1), the age-specific hip fracture rates per 100,000 person-years decreased within each age group, except for the 65–69 age

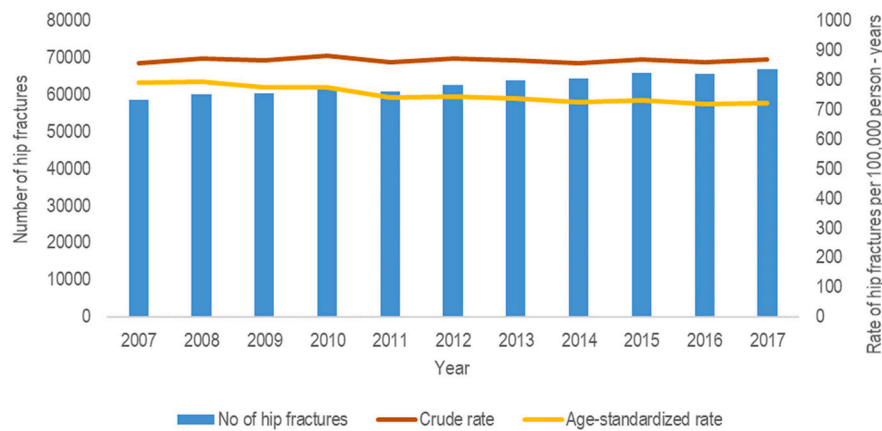


Fig. 1. Annual number, crude rates, and age-standardized rate of hip fractures in women.

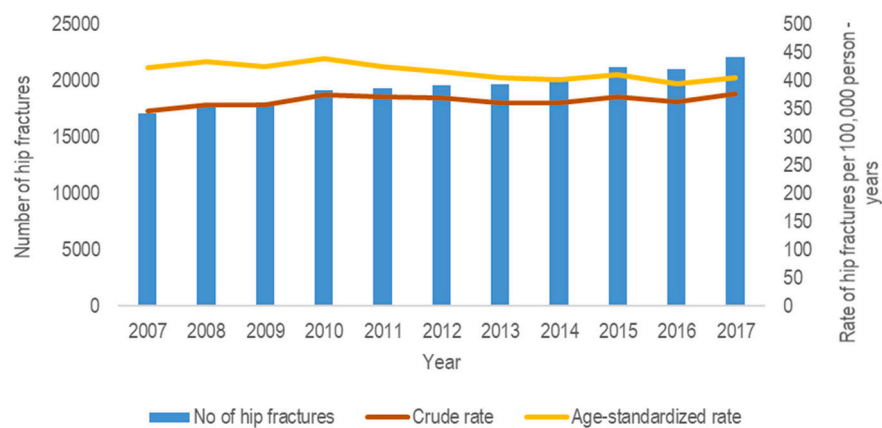


Fig. 2. Annual number, crude rates, and age-standardized rate of hip fractures in men.

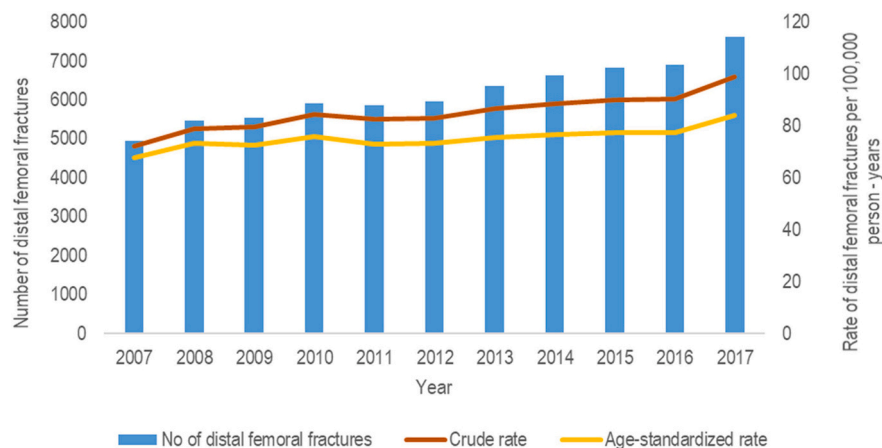


Fig. 3. Annual number, crude rates, and age-standardized rate of distal femoral fractures in women.

group presenting a slight increase of 0.6%. The largest decline was observed in the 80–84 age group (–14.6%), followed by the 75–79 age group (–13.3%). Considering distal femoral fractures in both men and women (Supplementary Material-Table 2), the age-specific rates increased within all age groups. The highest increment was observed in individuals aged 90–94 years (48.5%), followed by those aged 85–89 years (36.9%).

The joinpoint regression analysis, performed to evaluate if the change in age-standardized femoral fracture rates in both genders was

constant across the study period, underlined a decline in age-standardized rate of hip fractures in both genders with an average annual percentage change (AAPC) of –1.1 in women (Fig. 5A) and –0.9 in men (Fig. 5B). The joinpoint regression analysis also confirmed the increment in age-standardized rate of distal femoral fractures with an AAPC of 1.4 in women (Fig. 5C) and 1.8 in men (Fig. 5D).

As shown in Fig. 6, the use of any anti-osteoporosis drug in Italy in the study period showed a steady increment from 2007 to 2011 (from 9.1 to 12.4 DDD/1000 inhabitants/day), followed by a plateau in the

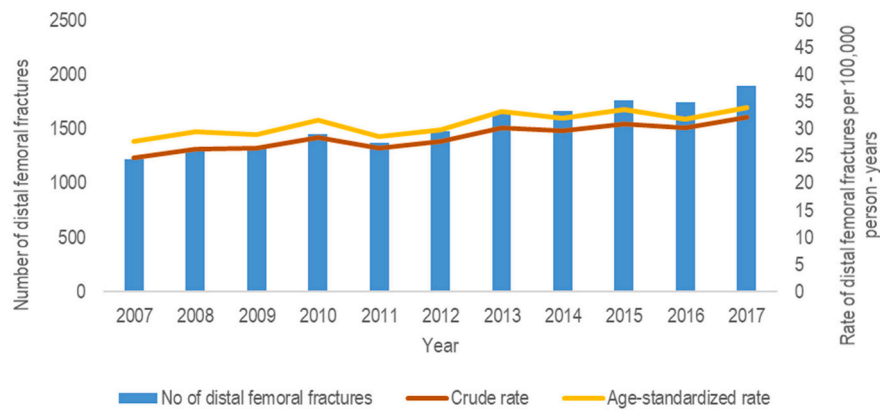


Fig. 4. Annual number, crude rates, and age-standardized rate of distal femoral fractures in men.

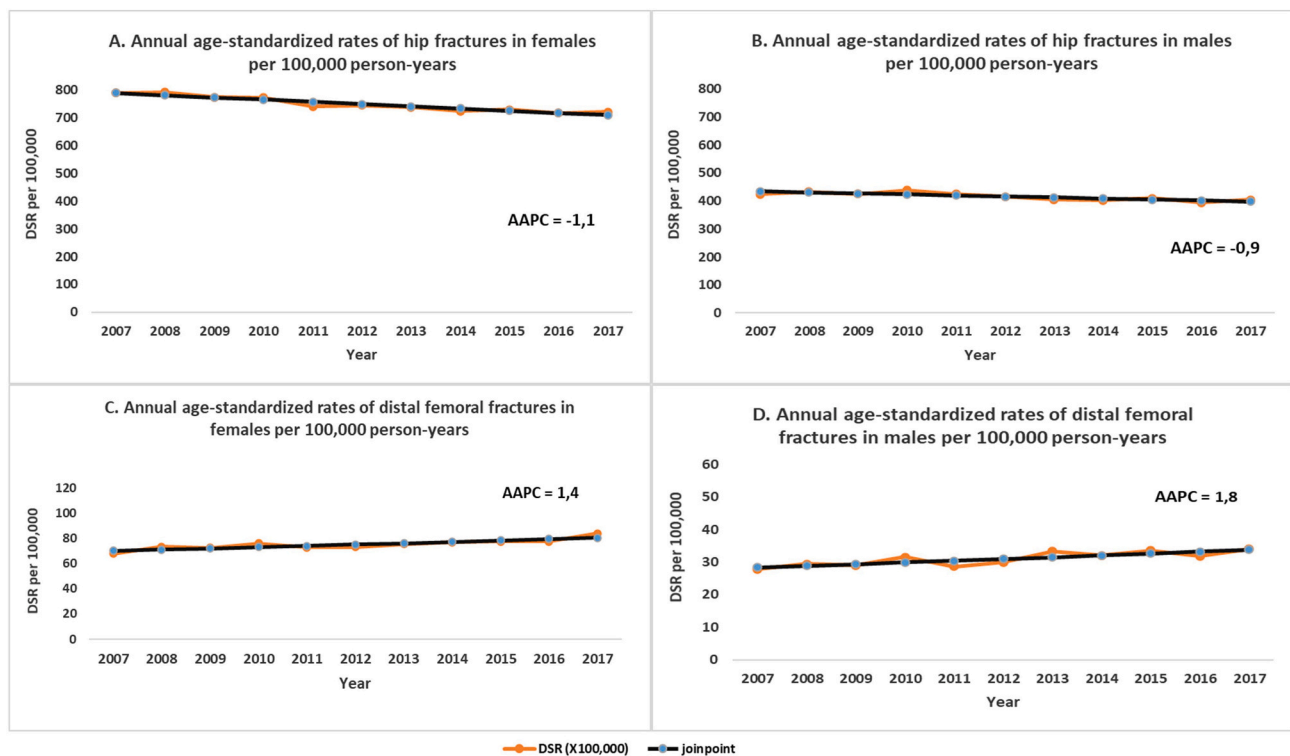


Fig. 5. Trend in hip and distal femoral fractures by gender according to join points. AAPC = average annual percentage change; DSR = directly standardized rates.

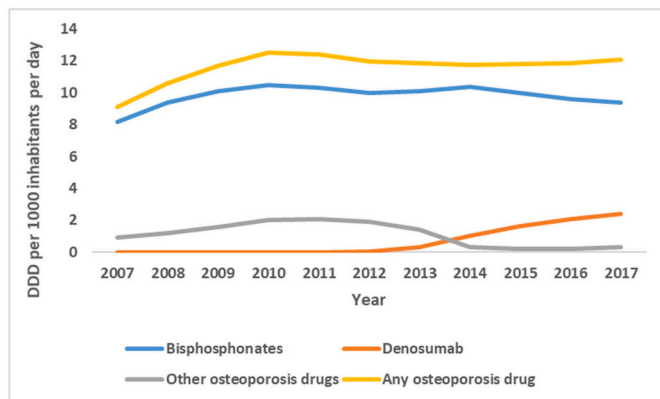


Fig. 6. Annual use of anti-osteoporosis drugs in Italy from 2007 to 2017. DDD = Defined Daily Doses.

period 2012–2017. The population exposure to bisphosphonates increased progressively from 2007 to 2010 (from 8.2 to 10.5 DDD/1000 inhabitants/day), followed by a period of relative stability and then decreased from 2015 onwards. The use of denosumab was observed from 2012 (0.05 DDD/1000 inhabitants/day) and increased progressively over years (2.4 DDD/1000 inhabitants/day in 2017). The intake of other anti-osteoporosis drugs (i.e., raloxifene, PTH analogues, and strontium) increased steadily from 0.9 DDD/1000 inhabitants/day in 2007 to 2.1 DDD/1000 inhabitants/day in 2011 and declined from 2012 onwards.

4. Discussion

The present study reports the trends in incidence rates of hip and distal femoral fractures, as well as in the use of anti-osteoporosis drugs in Italy from 2007 to 2017. Although the age-standardized hip fractures rates decreased in both genders, as well as the age-specific rate for

individuals ≥ 70 years, the crude rate of hip fractures increased with age in the same period. This is attributable to the constant growth of the elderly population, who have higher fracture risk due to deterioration of bone architecture and bone quality. It should be noted that Italy has the oldest population in Europe; individuals aged 65 or older in 2017 were 22.3% of the Italian population [26] as opposed to the average of 19.2% in EU28 [27]. A study conducted in Italy [28] also found a decline in hip fracture rates from 2006 to 2014, though only in individuals aged 65–74 years. In regard to other western countries, a decreasing trend of age-standardized hip fracture rates in both genders was observed in Canada [7], with 1.2% decrease per year in 1985–1996 and 2.4% per year after 1996. Likewise, in Denmark there was a decrease by 1.2% in both genders per year after 1993 and 30% during 2005–2015 [8,9]. In Finland, the decline was 1% per year in men and 1.9% per year in women during 1997–2010 [10]. Similar trends were observed in Sweden (1996–2002) [11] and Norway (1999–2008) [12].

The decreasing trend in age-specific hip fracture rate has been attributed to the use of anti-osteoporotic agents and, in particular, oral bisphosphonates [29,30]. It should be noted that prescriptions of anti-osteoporosis drugs, bisphosphonates in particular, declined in the UK [31,32] and in the USA following the US Food and Drug Administration's (FDA) announcements about the potential risks of bisphosphonates, namely atrial fibrillation in 2007 and atypical hip fracture in 2010 [33]. In addition, a stagnating rate in the use of anti-osteoporotic medications was observed in Denmark from 2014. The Danish study found that approximately 80% of the decline is not related to anti-osteoporosis medications, but to a temporary decrease in population risk level which is expected to increase due to aging population [9]. Hence, the decreasing trend in hip fractures in Western Europe and in the USA cannot be totally ascribed to the use or prescriptions of anti-osteoporosis drugs.

In Italy, the decreasing trend of hip fractures could be related to the increased prescribing rates of any anti-osteoporotic medication observed in 2007–2011. The prescription of bisphosphonates in Italy decreased slightly from 2015 onwards and was substituted with other anti-osteoporosis drugs (i.e., raloxifene, PTH analogues, strontium, and denosumab). This finding could be related to the FDA's warnings and the opinion of the Committee for Medicinal Products for Human Use [34] about the potential adverse events of bisphosphonates, including atrial fibrillation, atypical hip fracture and osteonecrosis of the jaw. Enhancement of bone mineral density has been indicated as a major contributing factor in the decreasing trend observed in western countries, for instance in Canada [35], Sweden [11] and in Portugal [36]. A similar event could be hypothesized for Italy, as suggested by the association between BMD and functional recovery after hip fracture [37]. Other contributing factors could be balanced diet, including higher calcium and vitamin D intake, and regular physical activity. Infact, musculoskeletal diseases have received great attention in recent years with active promotion of lifestyle and dietary measures that can limit bone loss in the elderly [38,39].

Distal femoral fractures are less common, accounting for 3–6% of all femoral fractures [40], and are also less studied compared to hip fractures [41]. The current study confirmed the increment in the incidence rates of distal femoral fractures reported in the literature. This increment might be due to the rapid growth of the elderly population and the increasing number of knee injuries [40,42]. A further potential contributor for the observed increases in these fractures over the study period could be the increased immigration to Italy of populations at higher risk of atypical femoral fractures, such as immigration fluxes from Asia [43]. In addition, anti-osteoporosis medications, namely bisphosphonates and denosumab can have a role in reducing bone turnover, leading to an increment in these fractures [13–15] Indeed, the age-standardized rate, crude rate and annual number of distal femoral fractures increased in all age groups and in both genders over the 11-year observational period and, in parallel, an overall increment in the use of bisphosphonates was shown. There is also a possibility that due to

increased awareness of distal femoral fractures as a potential adverse effect of bisphosphonate use, fractures occurring in the femoral shaft -near but not within the hip- may have been differentially recorded in the medical record over time, with early events coded as hip fractures, and later events coded as femoral shaft fractures.

In accordance with our results, a study conducted in the US for fractures that occurred between 1984 and 2007 [44] reported an increase in age-specific rates of distal femoral fractures, mostly in women over-90 years old. Comparable data were also found in a study performed in the UK [41] indicating that distal femoral fractures prevail in elderly women in western countries, mostly in those over-85 years of age.

A limitation of the current study is the lack of data on ethnicity in the database; thus, we could not explore the trends under analysis in other ethnic groups and the results of the study may not be applicable to other populations. However, the observed trends in incidents rates of femoral fractures in Italy are comparable to those reported in Europe and North America. In addition, we could not evaluate whether non-pharmacological factors may have influenced the decreasing trend in hip fracture rates in Italy. Given that osteoporosis is a multifactorial disorder, the changes in hip fracture rates could be related to modifications of several factors influencing BMD (e.g., family history of fragility fractures, age of menopause, physical activity, smoking habits, alcohol consumption, the presence of comorbidities, and so on). Moreover, several factors that influence BMD may have changed over time in this population and there could be some major events that may have induced potentially lifetime effects of musculoskeletal health (e.g., living during the world war II, living in rural areas, and so on). Lastly, we did not quantify the amount and/or provide information on the number of fractures with trauma indicators. Considering that the views about the treatment of and inclusion of traumatic vs. non-traumatic fractures have changed over time, this aspect should be explored in future research.

The strength of the current study is the use of hospital discharge records representative at the national level for the identification of hip fractures. To our knowledge, there are no validation studies of the Italian HDRs considering femoral fractures. Although validation studies of the Italian HDRs considering femoral fractures are lacking, the main diagnosis is used to assess the value of diagnosis-related groups (DRGs) [28], which are used to identify hospital reimbursements. Therefore, the main diagnosis is considered to be an accurate choice for the identification of femoral fractures from HDRs and has been used in similar studies [45–47]. Conversely, the identification of chronic conditions (including osteoporosis chronic conditions) and associated medications using Italian automated pharmacy data has been validated in 2005 [48]. The study demonstrated that use of pharmacy data is a valuable strategy to estimate the extent to which large populations are affected by chronic conditions, the associated pharmaceutical utilization and cost.

4.1. Conclusion

In conclusion, our findings are in line with studies reporting the decline in age-standardized hip fracture rates albeit the stagnation in prescriptions of anti-osteoporosis drugs in Italy. On the other hand, the crude rate of hip fractures and the age-standardized distal femoral fractures continue to increase due to rapid population aging. Great attention has been given to research and treatment of elderly patients with hip fractures and less to those with distal femoral fractures. More research and preventive strategies are required to avoid high economic and societal burden of these conditions.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bone.2020.115752>.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Brigid Unim: Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing. **Giada Minelli:** Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing. **Roberto Da Cas:** Methodology, Data curation, Formal analysis, Writing - review & editing. **Valerio Manno:** Data curation, Formal analysis, Writing - review & editing. **Francesco Trotta:** Data curation, Formal analysis, Writing - review & editing. **Luigi Palmieri:** Visualization, Writing - review & editing. **Lucia Galluzzo:** Visualization, Writing - review & editing. **Stefania Maggi:** Supervision, Writing - review & editing. **Graziano Onder:** Conceptualization, Methodology, Project administration, Writing - original draft, Writing - review & editing.

Declaration of competing interest

All authors state that they have no conflicts of interest.

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