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ORIGINAL ARTICLE

The burden and undertreatment of fragility fractures among senior women

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Abstract

Summary Using a large population database, we showed that fragility fractures were highly prevalent in senior women and were associated with significant physical disability. However, treatment rates were low because osteoporosis treatment was not prescribed or not agreed to by the majority of women with prevalent fragility fractures.

Purpose The purpose of the study is to estimate prevalence of fragility fractures (FF), risk factors, and treatment rates in senior women and to assess impact of FF on physical function and quality of life.

Methods Women aged 65 years and older from the EpiReumaPt study (2011–2013) were evaluated. Rheumatologists collected data regarding FF, clinical risk factors for fractures, and osteoporosis (OP) treatment. Health-related quality of life (EQ5D) and physical function (HAQ) were analyzed. Peripheral dual-energy X-ray absorptiometry was performed. FF was defined as any self-reported low-impact fracture that occurred after 40 years of age. Prevalence estimates of FF were calculated.

Results Among 3877 subjects evaluated in EpiReumaPt, 884 were senior women. The estimated prevalence of FF was 20.7%. Lower leg was the most frequent fracture site reported (37.8%) followed by wrist (18.6%). Only 7.1% of the senior women reporting a prevalent FF were under treatment for OP, and 13.9% never had treatment. OP treatment was not prescribed in 47.7% of FF women, and 23.4% refused treatment. Age (OR = 2.46, 95% CI 1.11–5.47), obesity (OR = 2.05, 95% CI 1.14–3.70), and low wrist BMD (OR = 2.29; 95% CI 1.20, 4.35; $p = 0.012$) were positively associated with prevalent FF. A significantly higher proportion of women in the lowest quintile of wrist bone mineral density reported FF (OR = 2.29, 95% CI 1.20–4.35). FF were associated with greater physical disability ($\beta = 0.33$, 95% CI 0.13–0.51) independent of other comorbidities.

Conclusion FF was frequently reported among senior women as an important cause of physical disability. However, the prevalence of OP treatment was low, which constitutes a public health problem in this vulnerable group.

Keywords Fragility fractures · Osteoporosis treatment · Epidemiology · Women

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Introduction

Osteoporosis is a metabolic skeletal disease characterized by low bone mass and microarchitecture deterioration [1]. Clinically, osteoporosis manifests as the occurrence of fragility fractures, which represents a public health problem and results in increased mortality and morbidity. Fragility fractures are also a major and growing economic burden on healthcare systems worldwide [2].

Fragility fractures are defined by any low trauma fracture (those resulting from a fall from standing height or less) and are associated with low bone mineral density (BMD) and higher subsequent fracture risk [3, 4]. The most common fragility fractures occur in the wrist, spine, hip, humerus, pelvis, and ribs [5–7]. In Europe, more than 3.5 million fragility fractures are observed each year, accounting for 37 billion euros in healthcare costs. One percent of the disability-adjusted life year (DALY) attributable to non-communicable diseases is due to fragility fractures [8, 9].

With the increase in worldwide life expectancy, the number of individuals who will have a fragility fracture is expected to increase [10, 11]. In fact, the individual lifetime risk for sustaining a fragility fracture from the age of 50 years is estimated to be one in two for women, and one in five for men. Indeed, postmenopausal women are at particularly high risk for fragility fractures due to the sudden estrogen drop in menopause, which leads to bone loss and microarchitectural deterioration [12, 13].

To identify individuals at high risk for fragility fractures, clinical risk factors such as BMD, age, body mass index, and prior fractures must be considered. Accordingly, algorithms to predict individual fracture risk should include several risk factors. A number of algorithms for fragility fracture prediction have been validated, with FRAX algorithm being the most widely used [14]. The identification of the most frequent modifiable fracture risk factors in a certain population is important for public health policymakers. It is still unknown exactly what the risk factors are in some European countries, including Portugal. Moreover, considering the effectiveness of available therapeutic options in decreasing fracture risk [15], it is of paramount importance to understand if osteoporosis treatments are appropriately provided to high-risk patients, such as those who have sustained a previous fragility fracture.

EpiReumaPt is a population-based study performed in Portugal in 2011–2013 to assess rheumatic diseases including osteoporosis. From this survey, the estimated prevalence of osteoporosis among the Portuguese adult population was determined to be 10.2% [16]. As part of this study, we looked specifically at the high-risk population of senior women (65 years and older) and estimated the prevalence of fragility fractures, risk factors for fragility fractures, and treatment rates. We also assessed the impact of prevalent fragility fractures on physical function and quality of life.

Material and methods

Data source

This study was developed under the scope of EpiReumaPt, a national cross-sectional study conducted in Portugal from September 2011 to December 2013. The main objective of EpiReumaPt was to estimate the prevalence of 12 rheumatic and musculoskeletal diseases (RMDs), including osteoporosis [17]. In EpiReumaPt, a representative sample of the adult Portuguese population (10,661 participants) was assessed to capture and characterize all cases of RMDs [18]. The study included non-institutionalized adults (≥ 18 years old) living in private households in the Portuguese Mainland and Islands (Madeira and Azores). The study sample was stratified by administrative territorial units [(NUTS II) (Norte, Centro, Lisboa and Vale do Tejo, Alentejo, Algarve, Açores Islands (Azores) and Madeira Islands (Madeira)], and the size of the population within each locality (< 2000; 2000–9999; 10,000–19,999; 20,000–99,999; and ≥ 100,000 inhabitants, respectively). Of the 28,502 households we attempted to contact, 8041 refused to participate in the study, and 10,661 completed interviews. The EpiReumaPt population was similar to the Portuguese population (CENSUS 2011) in age strata, gender, and NUTII distribution [16].

We followed the EpiReumaPt methodology as previously described, which consisted of a three-phase approach [18]. In the first phase, a survey was administered through a face-to-face interview of households (10,661 participants) random selected by route methodology to screen for RMDs. This study assessed health-related quality of life and physical function. In the second phase, all subjects who screened positive for at least one RMD during the first phase, as well as 20% of randomly selected individuals without rheumatic complaints, were examined by rheumatologists. The selected phase 1 participants were invited to bring current medication, imaging, and medical records for the clinical appointment. The rheumatologists assessed second-phase participants ($n = 3877$) in a structured evaluation that included standardized physical examination, and laboratory and imaging tests (when needed) at a mobile unit to establish RMD diagnosis and evaluate disease-related information. The rheumatologists were blind for all health-related information and screening result collected in EpiReumaPt first phase. The second phase occurred a maximum of 1 month after the face-to-face interview conducted in the first phase. Finally, in the third phase, a team of three experienced rheumatologists reviewed all clinical, laboratory,

and imaging data and confirmed the diagnoses according to validated criteria for the different RMDs [15].

Study population

The population of interest for the present study was defined as all women 65 years and older who participated in the second phase of EpiReumaPt (Fig. 1).

Case definition

Fragility fracture was defined as any self-reported low-impact fracture (fractures that resulted from a fall from a standing height or less, or that occurred in the absence of trauma) in individuals older than 40 years [19, 20]. Fractures of the face, skull, foot, fingers, and toes were excluded. The accuracy of self-reported fragility fracture was previously shown to be acceptable [21–23]. We analyzed the overlap of self-reported previous fragility fractures captured in the first phase of EpiReumaPt and previous fractures as diagnosed by the rheumatologist in the second phase. Using this data, we computed Cohen's kappa (overall agreement was 82.68% with a kappa coefficient of 0.51). The overall sensitivity of the self-reported previous fragility fracture was 61.2% with a specificity of 89.2%. The positive predictive value was 63.2%, and the negative predictive value was 88.4%.

Measurement, assessment, and instruments

Sociodemographic and economic data (age, gender, ethnicity, education, marital status, household income, and composition), anthropometric data (self-reported weight and height), and self-reported chronic diseases (high cholesterol, high blood pressure, gastrointestinal disease, cardiac disease, diabetes, thyroid and parathyroid disease, pulmonary disease, hyperuricemia, cancer, neurologic disease, and hypogonadism) were collected during the first phase of EpiReumaPt. Anxiety and depression symptoms were assessed by the Portuguese-validated version of the Hospital Anxiety and Depression Scale (HADS). HADS is divided into an Anxiety subscale (HADS-A) and a Depression subscale (HADS-D), both containing seven related considerations (in both subscales, a score ≥ 11 translates into the presence of symptoms of anxiety or depression) [24]. Clinical risk factors (CRFs) for fractures, other than the risk factor of age, also were collected: body mass index (BMI) [categorized as underweight (BMI < 18.5 kg/m^2), normal weight (BMI between 18.5 and 24.9 kg/m^2), overweight (BMI between 25 and 29.9 kg/m^2), and obese (BMI ≥ 30 kg/m^2)], parental history of hip fracture, long-term use of oral glucocorticoids (≥ 3 months), rheumatoid arthritis, current smoking, alcohol intake (≥ 3 units/day), and the presence of other secondary causes of osteoporosis. The 10-year probability of major fractures and hip fractures was calculated using the FRAX tool available online [25], without using axial dual-energy X-ray absorptiometry (DXA) information. The

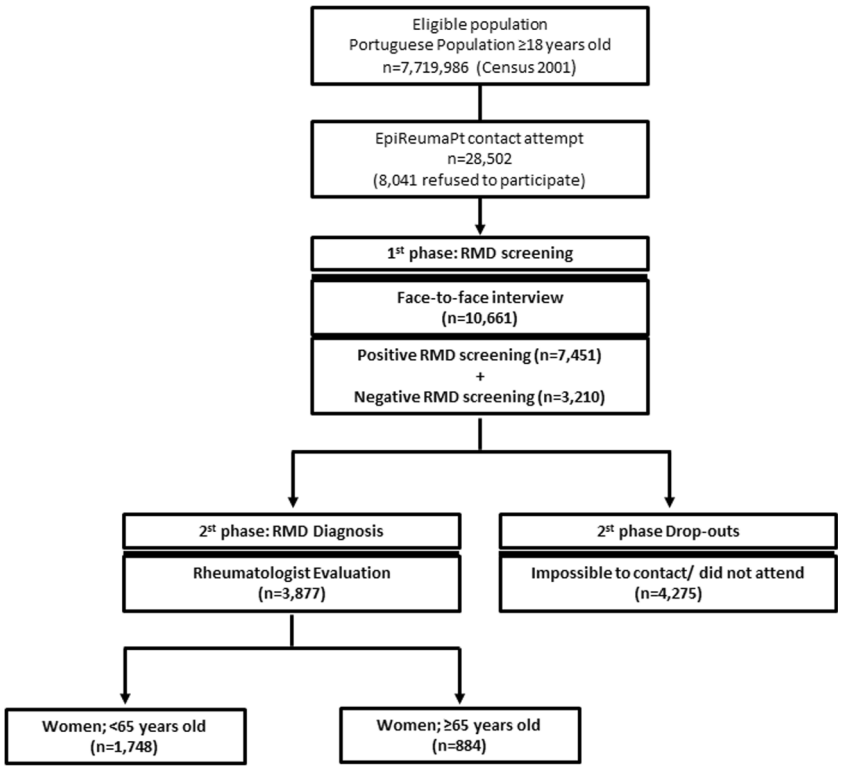

Fig. 1 Flow chart of study design. *RMD* rheumatic and musculoskeletal diseases

appropriateness of the osteoporosis treatment decision was judged according to the 2016 Multidisciplinary Portuguese Recommendations on DXA Request and Indication to Treat in the Prevention of Fragility Fractures (10-year risk probability of major fracture ≥ 11% or 10-year risk probability of hip fracture ≥ 3%) [26].

To evaluate generic health-related quality of life (HRQoL), a Portuguese-validated version of the European Quality of Life questionnaire, with five dimensions and three levels (EQ-5D-3L) [27, 28], was applied. Physical function was assessed by the Health Assessment Questionnaire (HAQ) [29]. Information regarding pharmacological therapies was also collected.

Fragility fractures and current medications were assessed by rheumatologists in the second phase of EpiReumaPt [18]. Fragility fracture diagnosis made by rheumatologists was based on a structured interview, physical examination, and medical and imaging record when it was available. Osteoporosis diagnosis was based on the presence of at least one of the following: previous self-reported fragility fractures, previous osteoporosis diagnosis, current osteoporosis treatment, or fulfillment of the World Health Organization criteria, when DXA was available. The presence of inflammatory rheumatic diseases was assessed in this stage (rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, and polymyalgia rheumatica).

To reduce recall bias, pharmacological treatment for osteoporosis was reassessed via a phone call questionnaire specifically designed for this purpose. The questionnaire was used for all women 65 years and older who underwent the second phase of the EpiReumaPt study, which was performed no more than 3 months after the physical examination performed in the second phase. Trained interviewers asked questions regarding present and past pharmacological treatment (bisphosphonates, strontium ranelate, selective estrogen receptor modulators, denozumab, and teriparatide), treatment duration, and adverse events.

Peripheral DXA procedures

All participants who participated in the second phase of the study had a wrist DXA on a Lunar PIXI™ device (a peripheral instantaneous X-ray imager; GE Medical Systems, Florence, SC, USA) at the mobile unit. This procedure provided assessment of distal BMD at 0.2-mm pixels of image resolution.

Biochemical assessment

Blood samples were collected during the second phase of the EpiReumaPt study and were sent to a central lab [24]. Levels of bone remodeling markers, 25-hydroxyvitamin D3 (vitamin D), and creatinine were determined using fresh serum samples in all women 65 years and older. Laboratory parameters were measured according to the manufacturers' instructions. Serum levels of creatinine were measured by rate-blanked creatinine method on a Dimension Vista System (Siemens, Lisbon, Portugal) with Siemens reagents, and an estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [30].

Serum levels of intact parathyroid hormone (iPTH), osteocalcin, cross-linked C-telopeptide of type I collagen (CTX-I), and serum amino-terminal propeptides of type I procollagen (P1NP) were measured on fully automated Immulite 2000® electrochemiluminescent immunoassay analyzers (Siemens). Serum levels of vitamin D were measured using the LIAISON competitive immunoassay (DiaSorin, Sallugia, Italy).

Statistical analysis

Prevalence estimates for fragility fractures, osteoporosis, and fracture sites were computed as weighted proportions taking sampling design into account as described elsewhere[18]. In fact, the second-phase sub-sample inclusion probabilities were calculated considering NUTII region, size of locality, gender age stratum, and the different proportion of participants with positive screening for RMD (80%) and negative screening for RMD (20%) according to sampling design (stratified two-stage cluster sampling). Second-phase weight was also calibrated to account differences between second-phase participants and non-responders. Second-phase participants did not differ the second-phase non-responders except for the presence of positive screening for RMD, age group, gender, and residence region according to the NUTS II [18].

Subjects were divided in two groups, with and without prevalent fragility fractures. The characterization of sociodemographic, non-communicable chronic diseases, and risk factors for fractures, quality of life, and physical function were performed for the study population, and for the two groups as described. All categorical variables are presented as counts and proportions, while continuous variables are presented as means and standard deviations. Comparisons between groups were also weighted according to study design. Weighted treatment rates were computed in accordance with the existence of a prevalent fragility fracture, fracture site, and individual 10-year fracture risk (using the FRAX algorithm).

To evaluate risk factors associated with prevalent fragility fractures, univariable logistic regression analysis was first performed to assess differences between the groups with and without prevalent fragility fracture. Then, the association was assessed using multivariable analysis with variables selected in the previous step and according to the study design. For the majority of the risk factors, the adjustment was made

for age, NUTSII (Nomenclature of Territorial Units for Statistics), peripheral BMD (wrist), and categorical BMI. This was not the case for categorical age (≥ 65 to 69 as reference, categories from 70 to 79, and > 80 years old), dichotomous BMI (obesity vs other categories), and peripheral BMD (wrist). The adjustment for vitamin D also included the season of the year.

To assure a better clinical interpretation, some variables were subjected to categorical transformation. For chronic renal insufficiency, a new dichotomous variable was created with the cutoff set at moderate to severe loss of kidney function (30 ml/min/1.73 m^2) (yes/no). Vitamin D was categorized as vitamin D insufficiency (< 30 ng/ml), vitamin D deficiency (10 ng/ml) (yes/no), and normal levels of vitamin D (> 30 ng/ml). For peripheral BMD, the variable was categorized according to quintiles (the lower category vs. the four higher quintiles grouped as one category). Lastly, for all serum markers of bone fragility (CTX, P1NP, and osteocalcin) and PTH, the variables were categorized as terciles (the lower tercile vs. the two higher terciles).

To assess the independent relationship between prevalent fragility fracture, HRQoL (EQ5D), and physical function (HAQ), linear multivariable regression models were constructed (continuous outcomes), adjusted for age, NUTSII, years of education, married status [dichotomized by married/consensual union and single/widow(er)/divorced], cardiac disease, and categorical BMI.

The cutoff value for significance was at $p < 0.05$. All analyses were weighted and performed using Stata IC version 12 (StataCorp. 2011 Stata Statistical Software: Release 12, College Station, TX, USA).

Ethical issues

EpiReumaPt study was approved by the Ethics Committee of NOVA Medical School and by the Portuguese Data Protection Authority (*Comissão Nacional de Proteção de Dados*). Written informed consent, in accordance with the principles established by the Declaration of Helsinki, was obtained from all participants. Further details of ethical issues of EpiReumaPt were previously described [31].

Results

Among the 3877 subjects evaluated clinically in EpiReumaPt, 884 were women older than 65 years of age (Fig. 1). In this age stratum, the estimated prevalence of fragility fractures was 20.7% and the prevalence of osteoporosis was 49.5%. The average time since the last fragility fracture was 10.2 ± 12 years, and only 5.15% of women who reported a fragility fracture reported its occurrence in the previous year. Prevalent fragility fractures increased significantly with age. In fact, 33.6% of women 80 years and older had at least one fragility fracture, and 58.2% were diagnosed with osteoporosis by a rheumatologist (Fig. 2a). Non-vertebral, non-hip fractures (lower leg, wrist, elbow, humerus, clavicle, or rib) were the most prevalent fracture sites (Table 1). When considering only women with a prevalent fragility fracture, the lower leg was the most frequently reported fracture site (37.8%), followed by the wrist (18.6%), elbow (17.5%), and humerus (16.8%). Hip fractures were reported in 6.6% of women with fragility fractures, and clinical vertebral fractures were reported in 5.3% (Fig. 2b). Of note, the combined frequency of lower leg, and/or wrist, and/or elbow, and/or humerus, and/or clavicle, and/or rib fractures among women with fragility fractures was 85.4%.

Regarding the prevalent fragility fractures, 56.3% of women reported one prevalent fragility fracture, 27.3% reported two prevalent fragility fractures, and 16.4% reported three or more prevalent fragility fractures. We verified that only 7.1% of the women with prevalent fragility fractures were currently being treated for osteoporosis, and only 13.9% had previously been under osteoporosis treatment for a mean duration of 130.23 ± 171.76 months. When considering women who had a prevalent fragility fracture and had never had osteoporosis treatment, the treatment was not prescribed in 54.7% and treatment was prescribed but not used in 23.4%. Treatment rates were low regardless of the fracture site reported (Fig. 2b). Finally, the individual risk of a new fragility fracture was calculated for women with a prior prevalent fragility fracture using the FRAX algorithm. We verified that 54.4% had a 10-year risk of major osteoporosis ≥ 11% and 64.4% had a 10-year risk of hip fracture ≥ 3%, which are the cutoff standards for osteoporosis treatment decision according to the 2016 Multidisciplinary Portuguese Recommendations on DXA Request and Indication to Treat in the Prevention of Fragility Fractures [26] (Fig. 2c). Of interest, treatment rates among women without prevalent fragility fractures were lower, and 10-year risk of a fragility fracture was higher (16.0%) than in women with a previous fragility fracture.

Table 2 summarizes the sociodemographic, economic, and health characteristics of participants according to the existence of a prevalent fragility fracture. The majority of Portuguese senior women have low literacy, have low household income per month, and have a high prevalence of chronic non-communicable diseases, namely high blood pressure, diabetes, and high cholesterol level. Women who had a prevalent fragility fracture were more frequently older and widows. Low prevalence of inflammatory rheumatic diseases was found among senior women. Regarding lifestyles, the majority of Portuguese senior women (with and without a prevalent fragility fractures) do not smoke, do not have alcohol intake above 3 units per day but are physical inactive (81.3%).

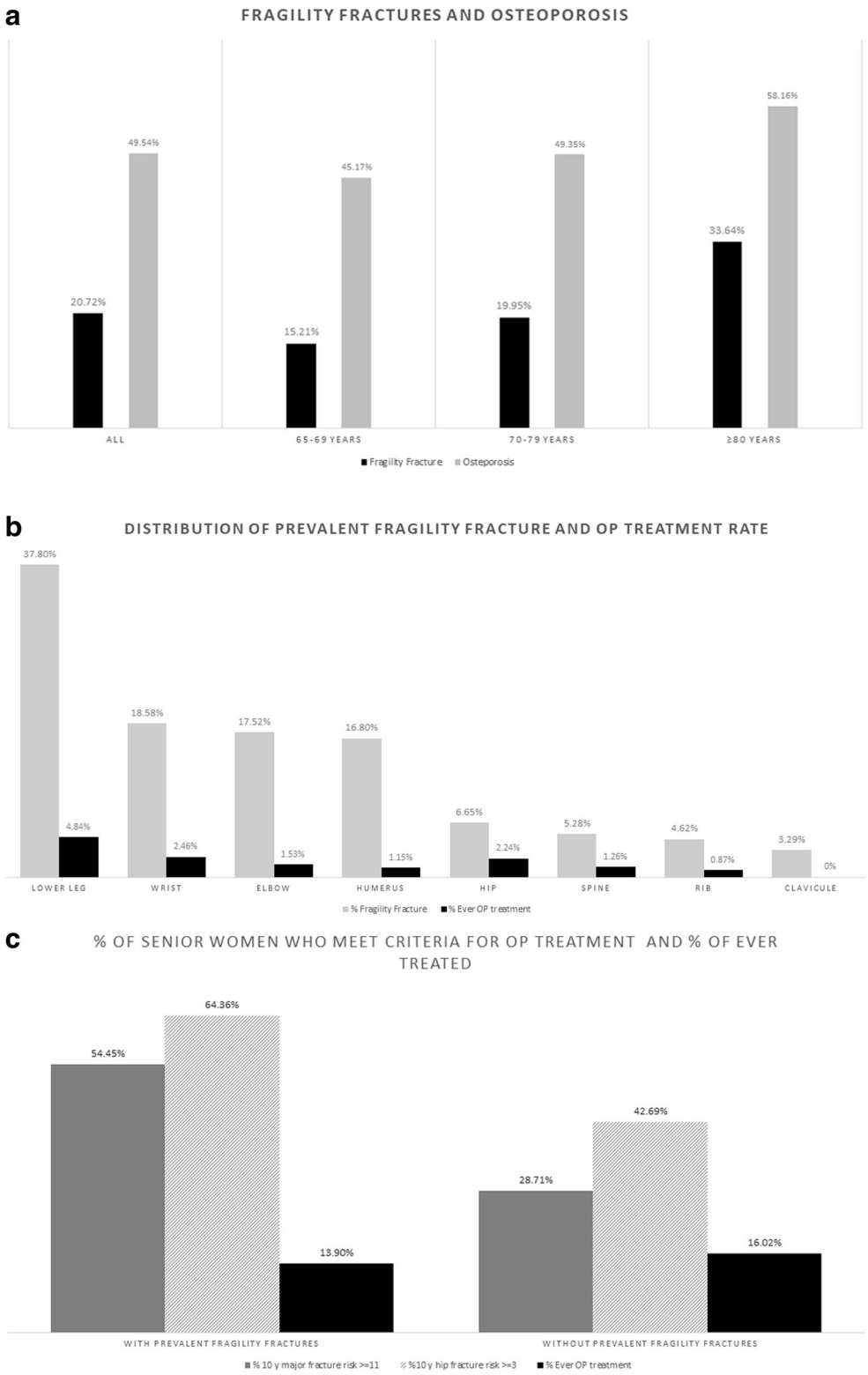

Fig. 2 Fragility fractures, fracture site, and treatment rates in women + 65 years old. **a** Fragility fractures and osteoporosis by age group. **b** Distribution of prevalent fragility fractures and OP treatment rate. **c** Proportion of senior women who met criteria for OP treatment and proportion of ever-treated subjects

Risk factors of fragility fractures among senior women

The clinical risk factors for fractures that were significantly and independently associated with prevalent fragility fracture were age (OR = 2.46, 95% CI 1.11, 5.47; $p = 0.027$) and obesity (OR = 2.05, 95% CI 1.14, 3.70; $p = 0.017$) (Table 3). No other clinical risk factors were found significantly different between women with and without prevalent fragility fractures. Regarding distal BMD, a significantly higher proportion of women in the lowest quintile of wrist BMD reported a fragility fracture (OR = 2.29; 95% CI 1.20, 4.35; $p = 0.012$) (Table 3).

No independent association was verified between prevalent fragility fractures and serum levels of vitamin D (Table 3). The prevalence of vitamin D insufficiency (< 30 ng/ml) was found in 32.5% of the patient cohort. Of women who reported a prevalent fragility fracture, 34.3% had vitamin D insufficiency. A similar result was found among women who did not report prevalent fragility fractures (35.1%). No independent association was found with serum markers of bone turnover (CTX, P1NP, and osteocalcin) and prevalent fragility fracture either (Table 3).

Association of fragility fractures, quality of life, physical disability

To address the burden of fragility fractures, we studied the association between fragility fractures and physical function and quality of life. Women with a prevalent fragility fractures reported greater physical disability than those without prevalent fragility fractures (HAQ score 1.04 ± 1.19 vs 0.74 ± 0.99) (Table 2). In fact, prevalent fragility fractures among elderly women was associated with greater physical disability in general ($\beta =$ 0.33, 95% CI 0.13, 0.51; $p \leq 0.001$) after adjustment for age, NUTSII, years of education, marital status, cardiac disease, and BMI (Table 4). Further, we performed a sensitivity analysis and tested for interaction between the independent association between prevalent fragility fracture and HAQ score, and we found that time since the last fragility fracture is indeed an effect modifier and the association between fragility fractures and HAQ score is higher among the ones with lower time since last fracture (data not showed).

Regarding HRQoL, although women with prevalent fragility fractures reported lower quality of life compared to those with no prevalent fragility fractures (Table 2), this result was not statistically significant after adjustment for confounders (Table 4).

Discussion

In this large population-based study through EpiReumaPt, reported fragility fractures (20.7%) and diagnoses of osteoporosis (49.5%) were both highly prevalent among senior women. However, the high prevalence of these conditions was in stark contrast with the low rates of OP treatment (13.9%). Non-hip, non-vertebral (NHNV), lower leg, wrist, humerus, rib, clavicle, and elbow fractures accounted for the majority of fragility fractures. Moreover, the clinical risk factors independently significantly associated with prevalent fragility fractures were increased age, obesity, and lower distal BMD.

We have characterized all prevalent fragility fractures and included clinical vertebral, hip, and NHNV fractures, because of recent evidence showing that all fragility fractures, including NHNV, are associated with an increased risk of subsequent fracture, and higher morbidity and mortality. The most prevalent sites of self-reported fragility fracture among women older than 65 years were NHNV fractures. These results are in line with other studies reporting that NHNV fractures

Table 1 Estimates of the prevalence of fragility fracture site by age group

Fragility fracture site		Age group		
	All, *n* (%)	65–69 y.o., *n* (%)	70–79 y.o., *n* (%)	> 80 y.o., *n* (%)
Lower leg	55 (6.06%)	19 (7.55%)	24 (4.57%)	12 (7.90%)
Wrist	39 (3.85%)	9 (2.09%)	21 (4.33%)	9 (5.87%)
Elbow	38 (3.42%)	10 (2.70%)	18 (3.28%)	10 (5.18%)
Humerus	38 (3.28%)	6 (1.55%)	22 (3.64%)	10 (5.39%)
Hip	11 (1.38%)	3 (0.80%)	3 (1.23%)	5 (2.92%)
Spine	11 (1.09%)	3 (1.10%)	5 (0.99%)	3 (1.36%)
Rib	9 (0.90%)	2 (0.71%)	6 (1.12%)	1 (0.60%)
Clavicle	7 (0.64%)	0 (0%)	4 (0.66%)	3 (1.79%)

y.o. years old, % percentage

Table 2 Crude analysis of sociodemographic, economic characteristics, risk factors for fractures, and health status of the Portuguese women 65 years and older with and without prevalent fragility fracture

	Women ≥ 65 y.o. ($n = 884$) *n* (%)	Women with prevalent fragility fractures ($n = 189$) *n* (%)	Women without prevalent fragility fractures ($n = 654$) *n* (%)	*p* value
Sociodemographic				
Age				
65–69 y.o.	295 (31.52%)	53 (24.34%)	239 (36.46%)	0.017*
70–79 y.o	443 (51.40%)	94 (47.91%)	319 (50.23%)	
> 80 y.o	146 (17.08%)	42 (27.75%)	96 (14.31%)	
NUTS II				
Norte	235 (33.82%)	54 (31.61%)	162 (32.50%)	0.642
Centro	201 (22.81%)	37 (21.85%)	151 (22.87%)	
Lisboa	150 (25.60%)	36 (29.30%)	108 (25.56%)	
Alentejo	71 (8.45%)	17 (9.31%)	54 (8.88%)	
Algarve	46 (5.36%)	8 (3.81%)	37 (6.02%)	
Azores	88 (1.46%)	12 (1.01%)	74 (1.65%)	
Madeira	93 (2.50%)	25 (3.12%)	68 (2.53%)	
Ethnicity/race				
Caucasian	851 (99.12%)	165 (99.43%)	646 (99.13%)	0.294
Black	3 (0.33%)	0 (0%)	3 (0.43%)	
Other	2 (0.23%)	0 (0%)	2 (0.31%)	
Did not know/ did not answer	3 (0.32%)	1 (0.57%)	1 (0.13%)	
Education level (years)				
> 12	46 (7.35%)	9 (4.42%)	33 (7.49%)	0.176
10–12	32 (5.89%)	5 (2.62%)	25 (6.80%)	
5–9	69 (8.20%)	18 (13.19%)	47 (7.00%)	
0–4	719 (78.57%)	149 (79.77%)	541 (78.71%)	
Marital status				
Single	46 (5.99%)	7 (3.66%)	36 (6.54%)	0.011*
Married	425 (47.94%)	73 (39.95%)	332 (49.57%)	
Divorced	46 (7.38%)	6 (2.76%)	37 (8.58%)	
Widow(er)	341 (38.66%)	80 (53.63%)	246 (35.27%)	
Consensual union	1 (0.03%)	0 (0%)	1 (0.0.4%)	
Household income per month				
< 500€	285 (38.67%)	66 (36.03%)	211 (39.12%)	0.264
501€ to 750€	186 (25.72%)	39 (30.68%)	142 (24.33%)	
751€ to 1000€	73 (9.74%)	17 (12.15%)	53 (8.82%)	
1001€ to 1500€	62 (12.83%)	16 (15.72%)	44 (12.33%)	
1501€ to 2000€	35 (7.44%)	5 (3.71%)	30 (8.69%)	
2001€ to 2500€	11 (3.85%)	1 (0.69%)	10 (4.81%)	
2501€ to 3000€	7 (0.91%)	2 (1.03%)	4 (0.82%)	
3001€ to 4000€	4 (0.55%)	0 (0%)	4 (0.71%)	
> 4000€	2 (0.29%)	0 (0%)	2 (0.37%)	
Non-communicable chronic diseases (self-reported)				
High blood pressure	554 (59.38%)	127 (64.12%)	407 (58.77%)	0.425
Diabetes	199 (20.99%)	43 (27.21%)	150 (20.24%)	0.162
High cholesterol level	512 (56.15%)	104 (51.52%)	380 (56.63%)	0.412
Pulmonary disease	97 (10.57%)	25 (14.03%)	66 (9.59%)	0.156
Cardiac disease	282 (32.79%)	68 (43.03%)	194 (29.90%)	0.032*
Gastrointestinal disease	305 (35.86%)	72 (42.03%)	219 (34.85%)	0.242
Neurologic disease	68 (7.20%)	14 (7.94%)	50 (7.06%)	0.713

Table 2 (continued)

	Women ≥ 65 y.o. ($n = 884$) n (%)	Women with prevalent fragility fractures ($n = 189$) n (%)	Women without prevalent fragility fractures ($n = 654$) n (%)	p value
Neoplastic disease	74 (8.06%)	16 (8.66%)	53 (7.71%)	0.722
Thyroid and parathyroid disease	166 (19.86%)	42 (25.30%)	116 (17.55%)	0.094
Hypogonadism	11 (1.58%)	4 (1.98%)	6 (0.89%)	0.269
Mental disease				
Anxiety symptoms (HADS score ≥ 11)	182 (17.90%)	43 (21.74%)	127 (16.47%)	0.158
Depression symptoms (HADS score ≥ 11)	174 (19.31%)	42 (25.71%)	121 (16.80%)	0.089
Inflammatory rheumatic diseases				
Rheumatoid arthritis	22 (2.00%)	6 (1.87%)	15 (2.04%)	0.886
Spondyloarthritis	9 (0.95%)	1 (0.62%)	8 (1.11%)	0.590
Systemic lupus erythematosus	1 (0.12%)	1 (0.60%)	0 (0%)	NA
Polymyalgia rheumatica	4 (0.55%)	0 (0%)	4 (0.74%)	NA
Secondary osteoporosis				
Yes	29 (2.79%)	6 (2.98%)	22 (2.77%)	0.899
No	854 (97.21%)	183 (97.02%)	631 (97.23%)	
Glucocorticoid intake				
Yes	35 (3.79%)	6 (3.05%)	26 (3.81%)	0.658
No	848 (96.21%)	183 (96.95%)	627 (96.19%)	
Parent hip fracture				
Yes	55 (7.10%)	13 (6.87%)	36 (6.79%)	0.976
No	828 (92.90%)	176 (93.13%)	617 (93.21%)	
Anthropometric data				
Body mass index (kg/m^2)				
Underweight	7 (0.81%)	3 (1.61%)	4 (0.67%)	0.110
Normal weight	228 (28.69%)	50 (29.42%)	161 (27.33%)	
Overweight	379 (47.82%)	78 (39.71%)	287 (51.05%)	
Obese	251 (22.68%)	53 (29.26%)	189 (20.94%)	
Lifestyle habits				
Current smoking				
Yes	17 (1.81%)	2 (1.17%)	13 (1.76%)	0.602
No	866 (98.19%)	187 (98.83%)	640 (98.24%)	
Alcohol (3 or more units/day)				
Yes	15 (1.96%)	3 (1.58%)	11 (1.54%)	0.975
No	868 (98.04%)	186 (98.42%)	642 (98.46%)	
Physical activity				
Inactive	524 (81.30%)	110 (86.67%)	390 (81.02%)	0.473
Moderate	24 (4.33%)	4 (2.80%)	17 (3.66%)	
Active	69 (14.37%)	12 (10.53%)	55 (15.32%)	
FRAX				
FRAX Major (mean ± sd)	9.96 ± 9.51	13.56 ± 11.61	8.71 ± 7.67	< 0.001*
FRAX Hip (mean ± sd)	4.42 ± 7.26	6.26 ± 8.81	3.67 ± 5.63	0.004*
Peripheral BMD (g/cm^2)				
Distal (mean ± sd)	0.36 ± 0.12	0.35 ± 0.12	0.37 ± 0.12	0.117
Biochemical assessment				
Vitamin D (nmol/ml)				
< 10	19 (2.03%)	5 (3.26%)	14 (1.87%)	0.607
≥ 10 and < 20	73 (8.52%)	17 (10.14%)	51 (7.76%)	
≥ 20 and < 30	150 (24.03%)	25 (20.85%)	118 (25.55%)	
Normal (≥ 30)	402 (65.42%)	83 (65.74%)	300 (64.82%)	

Table 2 (continued)

	Women ≥ 65 y.o. ($n = 884$) n (%)	Women with prevalent fragility fractures ($n = 189$) n (%)	Women without prevalent fragility fractures ($n = 654$) n (%)	p value
Chronic renal insufficiency (ml/min/1.73 m^2)				
eGFR < 15	7 (0.93%)	1 (0.77%)	6 (1.04%)	0.380
≥ 15 and < 30	9 (1.18%)	3 (2.00%)	6 (1.05%)	
≥ 30 and < 60	194 (27.57%)	37 (26.50%)	148 (27.73%)	
≥ 60 and < 90	360 (56.50%)	86 (62.43%)	260 (55.30%)	
≥ 90	102 (13.82%)	15 (8.30%)	79 (14.87%)	
PTH (pg/ml) (mean ± sd)	50.92 ± 54.62	50.76 ± 5.07	50.67 ± 55.62	0.987
CTX (ng/ml) (mean ± sd)	0.24 ± 0.25	0.26 ± 0.22	0.23 ± 0.27	0.452
P1NP (ng/ml) (mean ± sd)	37.97 ± 30.84	33.03 ± 26.79	39.20 ± 33.12	0.282
Osteocalcin (ng/ml) (mean ± sd)	3.80 ± 3.71	3.56 ± 3.27	3.68 ± 3.80	0.794
Quality of life and physical function				
EQ5D score (mean ± sd)	0.63 ± 0.40	0.55 ± 0.42	0.66 ± 0.40	0.002*
HAQ score (0–3) (mean ± sd)	0.81 ± 1.04	1.04 ± 1.19	0.74 ± 0.99	0.001*

Sample size is not constant due to the following:

Post-menopausal women—ethnicity ($n = 859$), education level ($n = 866$), marital status ($n = 859$), household income ($n = 665$), high blood pressure ($n = 873$), diabetes ($n = 872$), high cholesterol level ($n = 870$), pulmonary disease ($n = 874$), cardiac disease ($n = 866$), gastrointestinal disease (=873), neurologic disease ($n = 875$), neoplastic disease ($n = 879$), thyroid and parathyroid disease ($n = 869$), hypogonadism ($n = 852$), secondary osteoporosis ($n = 883$), glucocorticoids ($n = 883$), parent hip fracture ($n = 883$), body mass index ($n = 865$), current smoking ($n = 883$), alcohol ($n = 883$), physical activity ($n = 617$), N. falls previous 12 months ($n = 840$), FRAX major ($n = 876$), FRAX minor ($n = 876$), bone mineral density wrist ($n = 759$), vitamin D ($n = 644$), eGFR ($n = 672$), PTH ($n = 626$), CTX ($n = 307$), P1NP ($n = 305$), osteocalcin ($n = 308$), EQ5D score ($n = 874$).

With any self-reported fragility fracture—ethnicity ($n = 166$), education level ($n = 181$), marital status ($n = 166$), household income ($n = 146$), high blood pressure ($n = 185$), diabetes ($n = 184$), high cholesterol level ($n = 183$), pulmonary disease ($n = 186$), cardiac disease ($n = 178$), gastrointestinal disease (=185), neurologic disease ($n = 185$), neoplastic disease ($n = 187$), thyroid and parathyroid disease ($n = 185$), hypogonadism ($n = 179$), body mass index ($n = 184$), physical activity ($n = 126$), N. falls previous 12 months ($n = 182$), FRAX major ($n = 187$), FRAX minor ($n = 187$), bone mineral density wrist ($n = 160$), vitamin D ($n = 130$), eGFR ($n = 142$), PTH ($n = 125$), CTX ($n = 65$), P1NP ($n = 64$), osteocalcin ($n = 64$), EQ5D score ($n = 186$).

Without any self-reported fragility fracture—ethnicity ($n = 652$), education level ($n = 646$), marital status ($n = 652$), household income ($n = 500$), high blood pressure ($n = 648$), diabetes ($n = 648$), high cholesterol level ($n = 647$), pulmonary disease ($n = 648$), cardiac disease ($n = 647$), gastrointestinal disease ($n = 648$), neurologic disease ($n = 650$), neoplastic disease ($n = 652$), thyroid and parathyroid disease ($n = 644$), hypogonadism ($n = 634$), secondary osteoporosis ($n = 653$), glucocorticoids ($n = 653$), parent hip fracture ($n = 653$), body mass index ($n = 641$), current smoking ($n = 653$), alcohol ($n = 653$), physical activity ($n = 462$), N. falls previous 12 months ($n = 645$), FRAX major ($n = 649$), FRAX minor ($n = 649$), bone mineral density wrist ($n = 565$), vitamin D ($n = 483$), eGFR ($n = 499$), PTH ($n = 471$), CTX ($n = 224$), P1NP ($n = 223$), osteocalcin ($n = 226$), EQ5D score ($n = 649$)

y.o. years old, % percentage, *sd* standard deviation, *NUTS II* Nomenclature of Territorial Units for Statistics (Norte, Centro, Alentejo, Algarve, Lisboa, Madeira, and the Azores), *EQ5D* European Quality of Life questionnaire five dimensions three levels, *HAQ* Health Assessment Questionnaire, *HADS* Hospital Anxiety and Depression Scale, *eGFR* glomerular filtration rate, *PTH* parathyroid hormone, *CTX*-I cross-linked C-telopeptide of type I collagen, *P1NP* serum amino-terminal pro-peptides of type I procollagen, *BMD* bone mineral density, *ml* milliliters, *ng* nanogram

*p value < 0.05

accounted for more than two thirds of all fragility fractures [5, 6, 32]. The prevalence of fragility fracture found among women older than 65 years in Portugal was lower than in other countries of Northern Europe [33–35], Australia [36], and the USA, but similar to other countries in the Mediterranean region [8].

Regarding treatment rates, we found that a significantly low proportion of senior women who had sustained a fragility fracture were or had ever been treated for osteoporosis. Even when we queried for those that sustained a major osteoporotic fracture (hip, spine, wrist, or humerus), where guidelines [26] recommend osteoporosis treatment, regardless of BMD information and other risk factors, the treatment rates were still low. When we calculated the 10-year risk of a subsequent fragility fracture using the FRAX algorithm without BMD, we found that few women who were eligible for osteoporosis treatment according to Portuguese guidelines [26] were undergoing treatment for osteoporosis. These results highlight the importance of developing strategies to increase the implementation of the osteoporosis treatment guidelines in clinical practice. Moreover, 23.4% of women who had fragility fractures decided not to take prescribed osteoporosis therapeutics, which underscores the need for development of effective osteoporosis and fragility fracture campaigns to increase public awareness and treatment adherence. These awareness campaigns for osteoporosis treatment must take into account the socioeconomic

Table 3 Crude and adjusted analysis for the association between risk factors for fracture and prevalent fragility fracture among Portuguese women 65 years and older

			Self-reported any fragility fractures			
Age	Crude analysis OR [95% CI]	*p* value	Global *p* value	Adjusted[a] analysis OR [95% CI]	Adjusted[a] *p* value	Adjusted global *p* value
70–79 y.o. vs 65–69 y.o.	1.39 [0.81; 2.38]	0.230	0.017*	1.27 [0.68; 2.35]	0.452	0.073
> 80 y.o. vs 65–69 y.o.	2.82 [1.38; 5.79]	0.005*		2.46 [1.11; 5.47]	0.027*	
Body mass index (kg/m^2)						
Obese vs underweight/normal/overweight	1.56 [0.94; 2.61]	0.088		2.05 [1.14; 3.70]	0.017*	
Parent hip fracture (yes vs no)	1.01 [0.45; 2.26]	0.976		1.22 [0.49; 3.04]	0.669	
Current smoking (yes vs no)	0.66 [0.14; 3.10]	0.602		0.65 [0.08; 5.36]	0.691	
Alcohol (3 or more units/day) (yes vs no)	1.02 [0.27; 3.80]	0.975		1.45 [0.34; 6.11]	0.615	
Physical activity (inactive vs active)	1.52 [0.78; 2.99]	0.222		1.23 [0.55; 2.75]	0.619	
Glucocorticoids (yes vs no)	0.79 [0.29; 2.20]	0.658		1.00 [0.34; 2.88]	0.933	
Rheumatoid arthritis (yes vs no)	0.92 [0.28; 3.04]	0.886		1.44 [0.38; 5.45]	0.589	
Spondyloarthritis (yes vs no)	0.56 [0.07; 4.62]	0.590		1.09 [0.12; 10.04]	0.937	
Systemic lupus erythematosus (yes vs no)	NA	NA		NA	NA	
Polymyalgia rheumatica (yes vs no)	NA	NA		NA	NA	
Secondary osteoporosis (yes vs no)	1.08 [0.33; 3.48]	0.899		0.58 [0.13; 2.56]	0.474	
Chronic renal insufficiency						
eGFR < 30 vs eGFR ≥ 30 ml/min/1.73 m^2	1.33 [0.41; 4.34]	0.637		0.98 [0.23; 4.14]	0.976	
Peripheral bone mineral density (g/cm^2)						
Wrist Q1 (< 0.311) vs Q2/Q3/Q4/Q5 (≥ 0.311)	1.96 [1.02; 3.75]	0.044*		2.29 [1.20; 4.35]	0.012*	
Serum markers of bone fragility						
Vitamin D (nmol/ml) (deficiency (< 10) vs normal (≥ 10))	1.77 [0.58; 5.38]	0.315		1.09 [0.14; 8.45]	0.937	
PTH (pg/ml)						
Q2 (between 33.2 and 51.2) vs Q1 (< 33.2)	0.65 [0.32; 1.33]	0.242	0.496	0.60 [0.26; 1.38]	0.225	0.478
Q3 (≥ 51.2) vs Q1 (< 33.2)	0.71 [0.34; 1.48]	0.360		0.66 [0.28; 1.58]	0.355	
CTX (ng/ml)						
Q2 (between 0.167 and 0.26) vs Q1 (< 0.167)	1.55 [0.42; 5.69]	0.511	0.780	2.04 [0.52; 7.95]	0.305	0.568
Q3 (≥ 0.26) vs Q1 (< 0.167)	1.27 [0.50; 3.26]	0.614		1.07 [0.31; 3.66]	0.913	
P1NP (ng/ml)						
Q2 (between 30.3 and 44) vs Q1 (< 30.3)	0.84 [0.26; 2.70]	0.771	0.475	0.54 [0.14; 2.00]	0.354	0.380
Q3 (≥ 44) vs Q1 (< 30.3)	0.55 [0.18; 1.65]	0.284		0.33 [0.07; 1.59]	0.169	
Osteocalcin (ng/ml)						
Q2 (between 2.1 and 3.8) vs Q1 (< 2.1)	0.57 [0.09; 3.47]	0.541	0.697	0.64 [0.11; 3.84]	0.626	0.870
Q3 (≥ 3.8) vs Q1 (< 2.1)	0.77 [0.12; 4.82]	0.778		0.72 [0.09; 5.59]	0.756	

y.o. years old, *%* percentage, *sd* standard deviation, *vs* versus, *eGFR* glomerular filtration rate, *PTH* parathyroid hormone, CTX-I cross-linked C-telopeptide of type I collagen, *P1NP* serum amino-terminal pro-peptides of type I procollagen, *BMD* bone mineral density, *ml* milliliters, *ng* nanogram

[a] Adjusted for age, NUTII (Nomenclature of Territorial Units for Statistics), peripheral bone mineral density (wrist), and body mass index

Except in

Age: NUTII (Nomenclature of Territorial Units for Statistics), peripheral bone mineral density (wrist), and BMI

BMI: Age, NUTII (Nomenclature of Territorial Units for Statistics), and peripheral bone mineral density (wrist)

Peripheral bone mineral density (wrist): NUTII (Nomenclature of Territorial Units for Statistics, and BMI

Vitamin D: Age, season of the year, BMI, and peripheral bone mineral density (wrist)

PTH: Age, peripheral bone mineral density (wrist), and BMI

CTX: Age, peripheral bone mineral density (wrist), and BMI

P1NP: Age, peripheral bone mineral density (wrist), and BMI

Osteocalcin: Age, peripheral bone mineral density (wrist), and BMI

*p value < 0.05

Table 4 Multivariable models for the association between prevalent fragility fracture and quality of life and physical function among Portuguese women 65 years and older

Quality of life and physical function (dependent variables)	Prevalent fragility fracture			
	Crude analysis β [95% CI]	p value	Adjusted[a] analysis β [95% CI]	Adjusted[a] p value
EQ5D	− 0.10 [− 0.17; − 0.04]	0.002*	− 0.06 [− 0.13; 0.01]	0.118
HAQ	0.30 [0.11; 0.49]	0.002*	0.33 [0.13; 0.52]	0.001*

EQ5D European Quality of Life questionnaire five dimensions three levels, *HAQ* Health Assessment Questionnaire

[a] Adjusted for age, NUTSII (Nomenclature of Territorial Units for Statistics), years of education, married/consensual union vs single/widow(er)/divorced, cardiac disease, and categorical BMI

*p value < 0.05

conditions of this population group namely the low literacy and low household income.

Low osteoporosis treatment rates and compliance in high-risk populations are a reality worldwide [37, 38]. There is a large gap between the number of women who are treated compared to the proportion of women eligible for treatment [39]. Hernlund et al. [8] showed that the treatment gap varies between European countries. The largest treatment gaps are described in Bulgaria and the Baltic states, where less than 15% of the population eligible receives osteoporosis treatment; the lowest treatment gap was found in Spain where 75% of the eligible women are potentially undergoing osteoporosis therapy. Moreover, even in patients who sustain a fragility fracture, less than 20% receive treatment in the year following the fracture. Finally, as in our study, it was found that a large number of low-risk women were undergoing osteoporosis treatment.

Considering the risk factors for fracture, we found that in our population, higher age, obesity, and lower distal BMD were independently associated with a prevalent fragility fracture. Age and low distal BMD are known risk factors for fragility fractures, and even for NHNV fractures [35, 40]. It is also well established that low body weight is a risk factor for hip and spine fractures, while obesity is not protective [41, 42]. Recently, obesity was shown as a risk factor for fracture, particularly for NHNV fractures [36, 43], which is in accordance with our data. Indeed, visceral obesity is associated with low BMD, probably due to higher levels of inflammatory cytokines, lower levels of leptin, and higher levels of adiponectin [44]. Moreover, obese people have higher risk of fall and protective response impairment [45].

We did not find any independent association between fragility fractures and other clinical risk factors, namely secondary osteoporosis, smoking, and alcohol intake, probably because very few Portuguese elderly have these risk factors.

Our results show that a prevalent fragility fracture is associated with greater physical disability in Portuguese women older than 65 years of age, which clearly shows that any fragility fracture that occurs after 40 years of age leads to significant disability. Surprisingly, we did not find an independent association between a prevalent fragility fracture and HRQoL. A cross-sectional analysis of the Canadian Multicentre Osteoporosis Study (CaMos) showed that in women, a previous fracture of the hip, sub-clinical spine, or lower body, but not other fragility fracture sites, was negatively associated with HRQoL [6]. These different findings can be explained by the fact that the CaMos study used a different instrument to measure HRQoL than we did in our study. Additionally, the CaMos divided fragility fractures according to facture site, while we analyzed all fragility fractures together. In addition, Roux et al., using the Global Longitudinal Study of Osteoporosis in Women (GLOW) [5], showed that spine, hip, and NHNV fractures had a detrimental effect on women's HRQoL, with the effect greater in the spine and hip. Moreover, they verified that the detrimental effect of the NHNV and spine fractures specifically affected the patients' mobility. This observation is in accordance with our findings that show that a prevalent fragility fracture is associated with greater physical disability.

This study has some important limitations. Considering the cross-sectional nature of the data, it was not possible to establish causal associations between a fragility fracture and risk factors for fracture. Fragility fractures were self-reported, which has been shown as less accurate for clinical vertebral fractures and an underestimation of their prevalence [46]; however, the overall performance of self-reported fragility fractures is acceptable [21–23], which we also demonstrated in this study. Other limitation of our study was the absence of vitamin D supplementation information.

Several important strengths of this current should be acknowledged. Our data came from a large, nationally representative sample of the Portuguese adult population. Our participants were examined by rheumatologists. Different fragility

fractures and health-related measurements were captured, providing relevant information about risk factors, treatment rates, and their impact in Portuguese senior women.

In conclusion, our study demonstrates that fragility fractures are frequently reported among Portuguese senior women and are an important cause of physical disability. The most important risk factors for fractures identified were older age, obesity, and low wrist BMD. The use of osteoporosis treatment in this high-risk group was low due to both underprescribing therapeutics and to patients' non-compliance. This study highlights the need to increase awareness regarding fragility fractures and osteoporosis treatment, targeted not only to healthcare professionals but also to the high-risk population stratum for fragility fractures.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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