



A systematic review of the indirect and social costs studies in fragility fractures

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Abstract

Fragility fractures (FF) are the main clinical consequence of osteoporosis. FF lead to a loss in quality of life (QL), increased dependency and higher costs due to loss of productivity. Despite this, very few studies have been performed about the indirect or social costs of FF. The objective of this review was to systematically synthesize published evidence regarding indirect costs of FF. We conducted a systematic literature review of empirical studies published as peer review papers between 1998 and 2019. A total of 295 papers were found about costs and osteoporosis. After an iterative process, only 16 papers fit the criteria of selection. Despite the important consequences for QL, only seven studies have included research of the issue and only one about dependency. Treatments are cost-effective, but adherence is low. Multiple fractures, older age and low socioeconomic profile imply higher costs. Most studies are performed using the human capital methodology. The main two variables are loss of productivity and absenteeism. Most of the people included in the samples are out of the active population. Those studies that include a follow-up period vary in a range between 3 months and 2 years. Depending on sample and methodology, the indirect costs (IC) are between 2 and 50%. The direct costs associated with FF generally far outweigh the IC. There is a lack of studies about the effects of treatments and adherence and about the dependency system. The changing role of women in coming generations will increase indirect costs.

Keywords Fragility fractures · Indirect costs · Osteoporosis · Social costs

Introduction

Osteoporosis is defined as “a systemic skeletal disease characterized by low bone mass and deterioration of the microarchitecture of bone tissue with a consequent increase in bone fragility and susceptibility to fracture” [1]. It is the most common bone disease in humans [2], with symptoms not presenting until the onset of complications, occurring mainly in older age groups [3]. Metabolic or hormonal problems, ageing, genetic predisposition, ethnicity, systemic inflammatory

response syndrome, low physical activity, smoking and vitamin D deficiency [4], among others, are identified as the main risk factors for its development.

Different studies place the prevalence of the disease in the world as one of the main challenges to public health. The work of Wade et al. (2014) [5] suggests that approximately 24 to 49 million people aged 50 and over in the USA, Canada, France, Germany, Italy, Spain, the UK, Japan and Australia had osteoporosis in 2010. In Europe, in 2010, it was estimated that 22 million women and 5.5 million men had osteoporosis [6].

Fragility fractures are the main clinical consequence of osteoporosis. Defined by the World Health Organization as “a fracture caused by an injury that would be insufficient to fracture a normal bone; the result of reduced resistance to compression and/or torsion of the bone” [7], currently, fragility fractures constitute the main reason for loss of quality of life for patients with osteoporosis. The scientific literature has focused mainly on fractures of the hip, spine and wrist [8–14], although fractures of the humerus, pelvis, rib, distal femur, tibia and clavicle are also analysed in relation to osteoporosis. The prevalence and incidence of fractures vary greatly

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depending on the geographic region of study [5, 15–17], and bone density does not always explain these differences [10]. For example, Cummings and Melton (2002) state that by 2050 there could be as many as 21 million people worldwide with hip fractures [18]. One of the main challenges at present is the prevention of secondary fractures [19, 20], as there is a considerably increased probability of new fractures immediately following the first fracture [21–23].

The increase in life expectancy in the world, and more particularly in developed countries, has made osteoporosis and associated fragility fractures of unusual economic interest. The costs are widely studied in the literature, and especially in the USA, where different studies were carried out in the 1980s and 1990s to evaluate the cost of osteoporosis [24–27]. Johnell’s work (1997) [28] estimated that by 1990 the cost of hip fractures worldwide amounted to 34,900 million dollars (34.9 US billion dollars), with an approximate cost per patient of 21,000 dollars for the first year, and projected worldwide costs of 131,500 million dollars (131.5 US billion dollars) for the year 2050. Burge et al. (2007) [29] estimated the costs of fragility fractures in 2005 for the USA to be 16,916 million dollars (16.91 US billion dollars), projecting expenditure would rise to 25,268 million dollars (25.26 US billion dollars) for the year 2025. In Europe, Ström et al. (2011) [30] carried out an extensive study of costs for Germany, France, Italy, Spain, the UK and Sweden for the year 2010, not only analysing the cost of fractures but also the value of lost QALYs, bringing the total cost for the six countries to 77,700 million Euros (77.7 US billion Euros). In line with the aforementioned study, but across the 27 countries in the European Union, Hernlund et al. (2013) [6], also for the year 2010, puts the figure for the whole of the European Union at 97,778 million Euros (97.77 US billion Euros), a figure which includes the value of QALYs and projects expenditure, by 2025, would reach 120,000 million Euros (120 US billion dollars) in Europe.

Depending on the methodology, each study addresses different costs of osteoporosis and fragility fractures in particular and can come to different consequences (see Table 1). It should be noted however that very few address the analysis of the indirect and/or social costs of the disease which are generally understood as those linked to absenteeism [31, 32] or productivity losses [33] due to injury, instead of those based essentially on direct costs.

The aim of this work is to review the scientific studies on the indirect and/or social costs of fragility fractures, through a review of the literature available on the main databases.

Method

A systematic review is based on the following [34, 35]: (a) the best scientific evidence, (b) rigour in the quality criteria of the

Table 1 Main methodologies used in studies on indirect or social costs in fragility fractures

Methodology	Short definition	Main variables	Pros	Cons
<i>Human capital</i>	Consists of an estimation of the lost of production, productivity or potential incomes of a person or company due to an illness or an accident in which consequences persist	Loss of production Potential incomes	Gives a good measurement of the social economic impact in terms of production and productivity	Costs tend to be reduced when people are outside active population (e.g. retired people, housewives, students) Measurements are estimated. There is no general consensus on values
<i>Friction costs</i>	Consists of an estimation of time (friction) equivalent to the time it takes to re-place the ill person	Cost of days off work	Includes an employer’s perspective	There is no general consensus of period of time. The results can vary widely depending on the values of time used Difficult to collect data from employers
<i>Opportunity Costs</i>	The costs or the benefits/profits an individual or business misses out on when choosing one alternative over another	Days/h dedicated to self-care or caring for others instead of working or using this time as leisure time	An easy measurement of time value	Valuation of leisure time, and/or hours of people out of the active population (e.g. retired people, students, unemployed) can be controversial. Generally accepted as 25% of the value of the working hours of someone with similar profile, but there is no general consensus
<i>Replacement cost</i>	The cost of the working hours of a person that substitutes the ill person	Cost of the working hours needed to replace the ill person	Provides a good image of the cost that it is saved by informal caregivers	Amount of hours needed by formal caregivers could be controversial (e.g. at night)

selected publications, (c) focusing on a delimited question that corresponds to a real problem and (d) being exhaustive; the aim is to locate as many studies on the subject as possible. The systematic method seeks to eliminate biases in the selection of articles.

In order to meet the above criteria, (a) only articles based on humans, published in journals, articles or reviews that follow the peer review procedure – peer reviewed – have been selected; (b) only articles based on empirical studies (or reviews thereof) published in English or Spanish have been selected; (c) only papers that clearly deal with indirect and/or social costs have been selected; and (d) the main databases have been reviewed with the most relevant search criteria and keywords, and those documents that do not meet the selection criteria, or were repeated in different searches within a database or on different databases (see Fig. 1), have been progressively eliminated.

In this case, the research question is: What are the indirect or social costs of fragility fractures in terms of their typology?

The sources of information and review were the most relevant bibliographic databases for literature on health economics: Cochrane, Scopus and Pubmed. No reviews were found in a Cochrane search. The selected search period is from 1998 to 2019. Searches were conducted from 1 to 22 June 2019.

Studies were selected in an iterative process (see Fig. 1). After the initial findings, and applying this selection criteria, works that were best suited to answer the research question were selected.

The keywords used for the first search (see Fig. 1, Phase I) were the following: “Fragility”, “Fragility Fracture”, “Indirect costs”, “Social Costs”, “Osteoporosis”, “Hip Fracture”, “Dependency” and “Burden”. The articles found the search threads, and the number of references found can be found in Tables 2 and 3. The Boolean operators used between keywords were always AND. In the case of “indirect costs” and “social costs,” it was always OR.

Phase I identified and obtained articles that had the search terms in their title, abstract or keywords. In phase II, all articles that were repeated in the different search sequences, or in more than one database, were eliminated so that only individual articles remained.

In phase III, the studies to be reviewed were determined. In phase IV, the titles and abstracts which refer to indirect cost studies were classified, although those dealing with direct costs were more numerous. Since the objective of the review focuses on studies of indirect or social costs, in phase V, those that did not include costs of this type were rejected.

In phase VI, a complete reading of the selected articles was performed. Those that did not meet the criteria of presenting a methodology of empirical studies, that focused on the cost analysis of a drug or intervention, that after review were considered not to be cost studies, did not clearly determine their

data source or did not determine how they had calculated indirect costs were discarded.

Finally, in phase VII, articles that were identified as answering the research question and had all the quality criteria that allowed their acceptance, were left and analysed.

Results

After a systematic review of the literature addressing indirect or social costs related to fragility fractures, it is notable that primarily most of them are focused essentially on osteoporosis fractures generically (62.5%), followed by those addressing multiple fractures and those focusing on hip fractures. Despite the quality of life consequences that these injuries cause, only in 7 of the 16 (43.75%) studies that meet the selection characteristics included analysis measurements on quality of life. Works that consider the population of the Mediterranean area are very scarce (if Portugal is included, because it is on the Iberian Peninsula, there is only one). Similarly, studies that include some measurements of dependence are very rare (see Table 4).

In 50% of the studies, the analysis of primary data was chosen, understood as data obtained by researchers through questionnaires or interviews directly with patients. This is followed by cases in which data was obtained from existing databases (31.25%). In two cases (12.5%), there is no empirical data. This is either because it is a simulation using a Markov model [41] or because it is based on data from other studies, carried out using the same projections [47].

Profile of the persons on whom the studies are carried out

The age group on which the studies are centred is, on the whole, over 50. The average risk at 50 years of age of an osteoporotic fracture has been estimated between 40 and 50% for women and 13 and 22% for men [51]; however, the majority of cases occurs between 65 years of age and older.

While in all studies both female and male populations are studied, injury occurrences are more prevalent in women. There is however a difference depending on the type of injury. In one of the included articles [52], in which a review of the literature was performed, it is stated that forearm injuries occur five times more in women, while vertebral injuries are also higher; they do not amount to twice as much in women in comparison with men.

There are not many studies that include socioeconomic factors; however, some authors point out the existence of a greater risk of fractures among people with low family incomes and high levels of comorbidity [32].

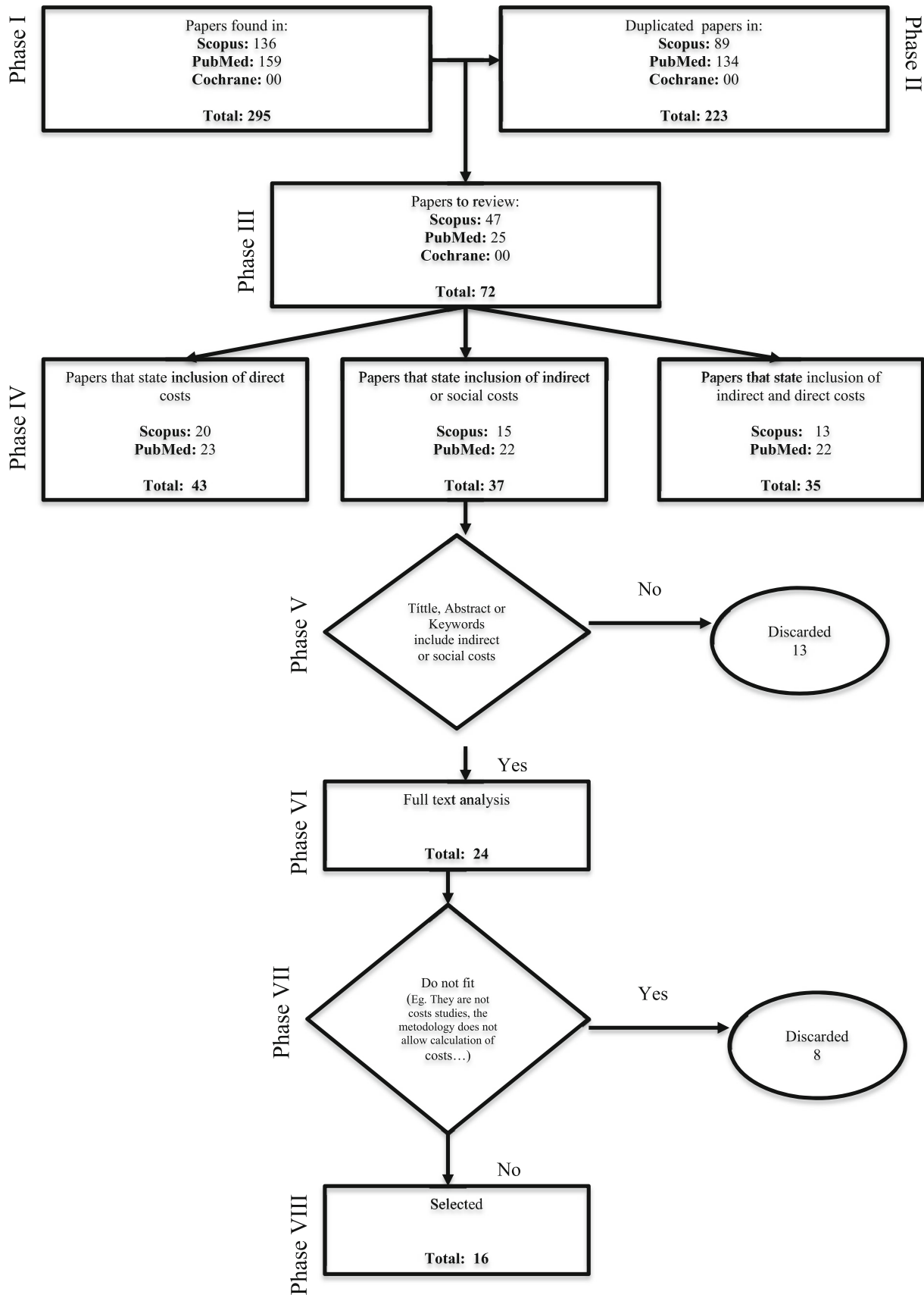


Fig. 1 Process for the selection of papers

Table 2 Keywords, search equations and references found in Scopus

Keywords	Keyword 1	Keyword 2	Keyword 3	Keyword	N° References
Keywords	Keyword 1	Keyword 2	Keyword 3	Keyword	N° References
Search equation	“Fragility Fracture”	“Indirect costs”	“Social Costs”		34
Keywords	Keyword 1	Keyword 2	Keyword 3	Keyword	N° References
Search equation	(TITLE-ABS-KEY (“Fragility fracture”) AND TITLE-ABS-KEY (“Indirect costs”) OR TITLE-ABS-KEY (“Social costs”)) AND (LIMIT-TO (DOCTYPE, “ar”) OR LIMIT-TO (DOCTYPE, “re”)) AND (LIMIT-TO (LANGUAGE, “English”) OR LIMIT-TO (LANGUAGE, “Spanish”))	“Osteoporosis”	“Indirect costs”	“Social Costs”	30
Keywords	Keyword 1	Keyword 2	Keyword 3	Keyword	N° References
Search equation	(TITLE-ABS-KEY (“Fragility fracture”) AND TITLE-ABS-KEY (“osteoporosis”) AND TITLE-ABS-KEY (“Indirect costs”) OR TITLE-ABS-KEY (“Social costs”)) AND (LIMIT-TO (DOCTYPE, “ar”) OR LIMIT-TO (DOCTYPE, “re”)) AND (LIMIT-TO (LANGUAGE, “English”) OR LIMIT-TO (LANGUAGE, “Spanish”))	Osteoporosis	“Indirect costs”	“Social Costs”	38
Keywords	Keyword 1	Keyword 2	Keyword 3	Keyword	N° References
Search equation	(TITLE-ABS-KEY (“hip fracture”) AND TITLE-ABS-KEY (osteoporosis) AND TITLE-ABS-KEY (“Indirect costs”) OR TITLE-ABS-KEY (“Social costs”)) AND (LIMIT-TO (DOCTYPE, “ar”) OR LIMIT-TO (DOCTYPE, “re”)) AND (LIMIT-TO (EXACTKEYWORD, “Human”) OR LIMIT-TO (EXACTKEYWORD, “Osteoporosis”) OR LIMIT-TO (EXACTKEYWORD, “Hip Fracture”) OR LIMIT-TO (EXACTKEYWORD, “Humans”) OR LIMIT-TO (EXACTKEYWORD, “Article”)) AND (LIMIT-TO (LANGUAGE, “English”) OR LIMIT-TO (LANGUAGE, “Spanish”))	Fragility	“Indirect Costs”	“Social Costs”	21
Keywords	Keyword 1	Keyword 2	Keyword 3	Keyword	N° References
Search equation	(TITLE-ABS-KEY (“Hip fracture”) AND TITLE-ABS-KEY (fragility) AND TITLE-ABS-KEY (“Indirect costs”) OR TITLE-ABS-KEY (“Social costs”)) AND (LIMIT-TO (DOCTYPE, “ar”) OR LIMIT-TO (DOCTYPE, “re”)) AND (LIMIT-TO (EXACTKEYWORD, “Human”) OR LIMIT-TO (EXACTKEYWORD, “Osteoporosis”) OR LIMIT-TO (EXACTKEYWORD, “Hip Fracture”) OR LIMIT-TO (EXACTKEYWORD, “Fragility Fracture”))	“Dependency”	“Indirect costs”	“Social costs”	0
Keywords	Keyword 1	Keyword 2	Keyword 3	Keyword	N° References
Search equation	(TITLE-ABS-KEY (“Fragility fractures”) AND TITLE-ABS-KEY (dependency) AND TITLE-ABS-KEY (“Indirect costs”) OR TITLE-ABS-KEY (“Social costs”))	“Fragility Fractures”	“Indirect costs”	“Social costs”	0
Keywords	Keyword 1	Keyword 2	Keyword 3	Keyword 4	N° References
Search equation	(TITLE-ABS-KEY (“Hip fractures”) AND TITLE-ABS-KEY (fragility) AND TITLE-ABS-KEY (burden) AND TITLE-ABS-KEY (“Indirect costs”) OR TITLE-ABS-KEY (“Social Costs”)) AND (LIMIT-TO (DOCTYPE, “ar”) OR LIMIT-TO (DOCTYPE, “re”)) AND (LIMIT-TO (LANGUAGE, “English”) OR LIMIT-TO (LANGUAGE, “Spanish”))	Fragility	Burden	Indirect cost OR Social cost	13

Table 3 (continued)

Keywords	Keyword 1	Keyword 2	Keyword 3	Keyword	N° References
	cost analysis"[All Fields] OR "costs"[All Fields]) OR (social[All Fields] AND ("costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields] OR "costs"[All Fields])) AND ((Journal Article[ptyp] OR Review[ptyp] OR systematic[sb]) AND "humans"[MeSH Terms] AND (English[lang] OR Spanish[lang]))				
Keywords					
Keyword 1	Keyword 2	Keyword 3	Keyword	N° References	
"Hip Fracture"	Fragility	"Indirect Costs"	"Social Costs"	15	
Search equation					
((("hip fractures"[MeSH Terms] OR ("hip"[All Fields] AND "fractures"[All Fields]) OR "hip fractures"[All Fields]) OR ("hip fracture"[All Fields]) AND fragility[All Fields]) AND ((indirect[All Fields] AND ("costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields]) OR "costs"[All Fields])) OR (social[All Fields] AND ("costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields]) OR "costs"[All Fields])) AND ((Journal Article[ptyp] OR Review[ptyp] OR systematic[sb]) AND "humans"[MeSH Terms] AND (English[lang] OR Spanish[lang])))					
Keywords					
Keyword 1	Keyword 2	Keyword 3	Keyword	N° References	
"Fragility Fractures"	"Dependency"	"Indirect costs"	"Social costs"	1	
Search equation					
((fragility[All Fields] AND ("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields]) OR "fracture"[All Fields]) AND ("dependency (psychology)"[MeSH Terms] OR ("dependency"[All Fields] AND "psychology"[All Fields]) OR "dependency (psychology)"[All Fields]) OR "dependency"[All Fields]) AND ((indirect[All Fields] AND ("costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields]) OR "costs"[All Fields]) OR (social[All Fields] AND ("costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields]) OR "costs"[All Fields])) AND ((Journal Article[ptyp] OR Review[ptyp] OR systematic[sb]) AND "humans"[MeSH Terms] AND (English[lang] OR Spanish[lang])))					
Keywords					
Keyword 1	Keyword 2	Keyword 3	Keyword	N° References	
"Hip Fracture"	Fragility	Burden	Indirect cost / Social cost	10	
Search equation					
((("hip fractures"[MeSH Terms] OR ("hip"[All Fields] AND "fractures"[All Fields]) OR "hip fractures"[All Fields]) OR ("hip fracture"[All Fields]) AND fragility[All Fields] AND burden fragility[All Fields] AND burden [All Fields]) AND ((indirect[All Fields] AND ("costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields]) OR (social[All Fields] AND ("costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields]) OR "costs"[All Fields])) AND ((Journal Article[ptyp] OR Review[ptyp] OR systematic[sb]) AND "humans"[MeSH Terms] AND (English[lang] OR Spanish[lang])))					

Table 4 Main characteristics of the studies of indirect or social cost of fragility fractures

Reference	Country	Type of fracture	Type of data	Source	Sample size	Does it analyse dependency?	Measures quality of life with
[32]	Japan	Osteoporosis	Secondary	The Japan National Health and Wellness Survey 2012–2014 database	1107	No	SF-6D
[36]	Singapore	Osteoporosis	Primary	Primary	67	No	No
[37]	Estonia	Waist	Primary	Primary	205	No	EuroQol-5D
[38]	Portugal	Osteoporosis	Primary	Primary	186	No	EuroQol-5D
[39]	China	Osteoporosis	Primary	Primary	938	No	No
[31]	Holland	Osteoporosis	Primary	Primary	116	No	No
[40]	Germany	Osteoporosis	Primary	Primary	Not specified	No	No
[41]	Germany	Osteoporosis	Not specified	Not specified	Not specified	No	EurQol-5D
[42]	Ethiopia	Osteoporosis	Secondary	Medical records	1169	No	No
[43]	Canada	Osteoporosis	Secondary	Five national administrative databases from the Canadian Institute for Health Information	Not specified	No	No
[44, 45]	Austria	Osteoporosis	Secondary	ICUROS	916	No	No
[46]	USA	Multiple fractures	Secondary	Not specified	53,500	No	No
[47]	Germany	Waist	Not specified	Not specified	Not specified	No	EurQol-5D
[48]	Sweden	Multiple fractures	Secondary	KOFOR	684	Yes	EurQol-5D
[49]	Slovenia	Multiple fractures	Primary	Primary	Not specified	No	No
[50]	Sweden	Multiple fractures	Primary	Primary	635	Yes	EurQol-5D

On the other hand, adherence to anti-osteoporotic treatments is indicated by some authors as low [32] despite studies indicating that the treatments are cost-effective [32, 52].

Multiple fractures

Some studies have specifically ruled out patients with multiple fractures [36, 37, 39, 48, 50] (more than two bone breaks), although most do not refer to this situation [31, 33, 38, 40–42, 44, 47, 49, 52]. Those that do consider the effects of multiple fractures concur that the increased risk that this implies in terms of mortality and morbidity [53], loss of quality of life and greater absenteeism [32], result in consequently higher costs [43, 46]. In the recent study by Fujiwara et al. (2019) [32], the older age of people suffering multiple fractures and their lower socioeconomic profile are additionally noted.

Factors considered to evaluate indirect or social costs

In general, studies on indirect costs are performed from the perspective or methodology of human capital, which essentially assesses the loss of production or potential income as a result of injury or illness. Thus, among the factors considered for the evaluation of indirect costs are those related to loss of productivity [38] and due to absenteeism [36, 41, 42, 45, 46, 49]. In this case, it should be pointed out that given that most of the people who suffer this type of injury are of non-working age, these costs are not usually high, except in a study carried out with the Ethiopian population [42] in which the affected population with ages around 50 was proportionally higher than usual. In other studies, they use the friction cost method [31, 40], which consists of estimating a time (friction) equivalent to the time it takes to replace the sick person with the fracture. Is employed instead of the human cost method. In the study by Eekman et al. (2014) [31], they estimate this period to be 22 weeks, although they do not justify clearly why they choose this period.

Some authors include costs related to informal care and the loss of leisure time in the calculation of indirect costs. In this case, they use the methodology calculating replacement costs, using as a reference the cost of home care [37, 42, 48, 50], or they use the method calculating opportunity costs [37, 42, 48, 50] (see Table 5).

Other works calculate indirect costs by estimating a net income plus taxes that are considered to be lost by the patient during the period in which they cannot work due to the fracture [37]. In some studies, mortality costs [47, 49] are added, i.e. the value of years lost due to premature deaths linked to fractures.

Table 5 Direct vs Indirect costs: Period of evaluation, variables and proportion of direct vs indirect costs

Reference	Country	Type of fractures	Indirect costs studied by	Period of cost evaluation	Variables used to evaluate indirect costs	% of direct vs indirect costs
[32]	Japan	Osteoporosis, without fracture, fractures	Human capital	Annual	Productivity losses	Without fracture: 58/42% One fracture: 65/35% More than one fracture: 80 vs 20%
[36]	Singapore	Osteoporosis, recently fractured and 1 year after the fracture	Human capital	Quarterly	Productivity losses and informal care	Recently fractured: 58 vs 42% More than 1 year: 83 vs 13%
[37]	Estonia	Waist	Human capital	18 months	Productivity losses and early retirement	92.4 vs 7.6%
[38]	Portugal	Waist	Human capital	Bi-annual	Productivity losses	First 12 months: 98.5 vs 1.5%
[39]	China	Different types of fractures	Human capital	Annual	Productivity losses, early retirement and loss of work	Months 13 to 24: 100 vs 0% Waist: 97.3 vs 2.7% Vertebra: 93.4 vs 6.6% Wrist: 92.2 vs 7.8%
[31]	Holland	Different types of fractures	Human capital	Annual	Productivity losses and loss of work	Vertebra: 10.9 vs 89.1% Waist: 79 vs 21% Humerus: 47.4 vs 52.6%
[40]	Germany	Different types of fractures	Human capital/friction costs	Projections	Productivity losses	Not specified
[41]	Germany	Different types of fractures	Human capital	Projections	Productivity losses (including early death)	66 vs 24%
[42]	Ethiopia	Different types of fractures	Human capital	Bi-annual	Productivity losses (only hospitalized days)	49.15 vs 50.85%
[43]	Canada	Different types of fractures	Human capital	Annual	Productivity losses and informal care	95 vs 5%
[44, 45]	Austria	Different types of fractures	Human capital	Annual	Productivity losses, early retirement and informal care	61.1 vs 38.9%
[46]	USA	Non vertebral fractures	Human capital	Annual	Productivity losses	71.8 vs 29.2%
[47]	Germany	Waist	Human capital	Annual	Productivity losses, early retirement and early death	91.3 vs 8.7%
[48]	Sweden	Different types of fractures	Human capital	6 months (month 13–18 after fracture)	Productivity losses and informal care	Waist: 100 vs 0% Vertebra: 100 vs 0% Wrist: 56.3 vs 42.7%
[49]	Slovenia	Osteoporosis and different types of fractures	Human capital	Annual	Productivity losses (including early death)	71 vs 29%
[50]	Sweden	Different types of fractures	Human capital	Annual	Productivity losses and informal care	Waist: 96.9 vs 3.1% Vertebra: 95.2 vs 4.8% Wrist: 90.9 vs 9.1%

Follow-up studies

Follow-up studies were performed at non-standardized periods. We find follow-ups at 3 [36]; at 4 and 12 [50]; at 4, 12 and 18 [37]; at 12 months [39] or in the second year after the fracture [38].

The costs figures

The cost figures vary considerably depending on the methodology used, although the results do tend to indicate a higher percentage of direct rather than indirect costs [36]. In a work on hip fractures, the proportion of indirect costs is between 5 and 8% of the total costs [37]. Other studies indicate that it is only at 2% in the first year after the fracture and is subsequently reduced [38]. In some cases, it is even stated that they have not found significant differences in indirect costs due to the type of fracture but on the basis of the number of fractures [32]. On the other hand, in other works, indirect costs are valued at around 24% [41], and in others indirect costs are evaluated to be around 44.7%, of which 30.2% are attributed to family care [44], or even 50% [42], rising to 81.9% of the costs in the case of spinal fractures [31] (see Table 5).

Some authors have performed a review on the social burden of osteoporosis fractures and have established the calculation of QALYs, from 5 dimensions of the perception of health, pain, mobility, self-care, independence in routine task and depression/anxiety, and posit that according to EU27 estimates, the QALYs lost in Europe by 2010 due to osteoporosis were estimated at 1.180,000 QALYs [52], a figure that other works put at 2.5 million QALYs [41] based on simulations using Markov models.

A relevant value taken into account for the calculation of costs in the human capital method is the number of days of absenteeism. The work of Tarride et al. (2012) [43] on the Canadian population estimates 3,123,298 days of absenteeism, of which 90% were days of hospitalization. However, other studies [36] stress that the cost of absenteeism is low given that most patients are over 65 years of age and are not in active employment.

Conclusions

Although the direct costs of osteoporosis and the associated fragility fractures have been analysed extensively in the scientific literature, the interest in indirect costs has not been subject to the same depth.

The works analysed in this study are sometimes different in their objectives; they do not all address the same fractures; they have been carried out at different times and with different timelines; some evaluate costs at 3, 6, 12, 18 months or biannually; and they are carried out in different countries, which in

many cases use different currencies. However, it can be concluded that the direct costs associated with fragility fractures generally far outweigh the indirect costs.

Apart from the few studies that incorporate indirect costs, we consider that this review allows us to draw a series of conclusions to be taken into account in future studies addressing the aforementioned cost dimension:

There is no one-size-fits-all approach to indirect costs. The different studies analysed do not allow a direct comparison because although they all include lost labour productivity as the main cost associated with indirect costs, many of the studies include informal care, early retirement, loss of the job, loss of productivity from voluntary work and premature death. On the other hand, some studies only take into account work days lost due to hospital stays and do not include productivity loss due to outpatient care or treatment. Undoubtedly, the availability of data and the ease with which patients can be followed may be the reason behind why some studies cover more concepts than others.

There is a predominance of focus on the human capital approach. The study of indirect costs can be carried out using different methodological approaches (human capital, opportunity costs, friction costs, replacement costs), although the predominant approach seems to be that of human capital, followed to a lesser extent by that of the friction cost. Following the review of the work, only one [40] included both approaches. Obviously, the friction cost analysis, which takes into account the employer's perspective, will represent lower indirect costs. On the other hand, the difficulty of collecting information from employers discourages the use of such an approach, but perhaps in an environment of serious labour market imperfections and high unemployment, the friction cost approach could be considered an interesting alternative.

Generational change, gender perspective and retirement age need to be considered. Given that indirect costs are predominantly composed of labour productivity, the labour situation and the retirement age of the sick person greatly determine the amount to which they can rise. In this context, most of the work is carried out in developed countries, focusing on postmenopausal women over 50 (when osteoporosis is most prevalent), many of them housewives who have never entered the labour market or have only done so partially, meaning that the indirect costs estimated by these studies are often low. In the current context, with a clear increase in population and life expectancy, in a climate of generational change that brings with it a female population more participative in the labour market, and with a possible increase in retirement age, it is normal that if there is no correct prevention and treatment of osteoporosis, indirect costs will become very important in the very near future.

Studies in developing countries are lacking. In relation to generational change, gender perspective and retirement age, and taking into account the improvement in life expectancy in developing countries, it would be interesting to carry out more

studies that address the indirect costs of osteoporosis in these countries, especially in those in which income distribution and labour market conditions are more similar to the developed world.

It is interesting to study the impact of indirect costs of second and successive fractures. One of the main challenges in osteoporosis is the prevention of a second fracture. With the exception of one of the studies, carried out in Japan [32], no study in which different treatments that would make it viable to analyse the possible indirect cost savings that could be made by avoiding second fragility fractures have been found. Taking this into account would make it possible to address this challenge with even more arguments. The timeline of the studies and the number of patients may be hindering this analysis, but we believe it is interesting to tackle it in order to evaluate the cost of the different treatments that can prevent these second episodes.

It would be necessary to consider the dependency costs. None of the studies reviewed include estimates of costs related to the system of dependency care that some states offer.

Studies on treatments and indirect costs are lacking. Finally, it should be pointed out that the scarcity of studies that have linked indirect or social costs with the effects of treatments and adherence to them is striking, more so when some studies [48, 50] emphasize the positive cost-effectiveness ratio of existing treatments.

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Compliance with ethical standards

Conflict of interest Manuel Ruiz-Adame and Manuel Correa declare that they have no conflict of interest.

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