



# A systematic review of the Irish osteoporotic vertebral fracture literature

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## Abstract

**Introduction** Vertebral fractures (VF) are the most common osteoporotic fracture. They are associated with significant morbidity and mortality and are an important predictor of future fractures. The epidemiology of VF in Ireland is limited and a greater understanding of their scale and impact is needed. Therefore, we conducted a systematic review of publications on osteoporotic VF in Ireland.

**Methods** Systematic searches were conducted using PubMed, Medline, Embase, Scopus and Cochrane electronic databases to identify eligible publications from Ireland addressing osteoporotic VF.

**Results** Twenty studies met the inclusion criteria out of 1558 citations. All studies were published since 2000. Data was obtained on 182,771 patients with fractures. Nine studies included more than 100 subjects and three included more than 1000. Females accounted for 70% with an overall mean age of 65.2 years (30–94). There was significant heterogeneity in study design, methods and outcome measures including the following: use of administrative claims data on public hospital admissions, surgical and medical interventions, the impact of a fracture liaison service and the osteoporosis economic burden. The prevalence of VF was difficult to ascertain due to definitions used and differences in the study populations. Only two studies systematically reviewed spine imaging using blinded assessors and validated diagnostic criteria to assess the prevalence of fractures in patient cohorts.

**Conclusions** Several studies show that VF are common when addressed systematically and the prevalence may be rising. However, there is a deficit of large studies systematically addressing the epidemiology and their importance in Ireland.

**Keywords** Vertebral fracture · Osteoporosis · Spine · Epidemiology · Systematic review

## Background

Osteoporosis is a significant global public health issue. One in three post-menopausal women and one in five men over the age of 50 will sustain an osteoporotic fracture in their lifetime equating to 9 million fractures per year worldwide [1, 2].

Treatment to prevent fractures in those with low bone mineral density and a prior fragility fracture is particularly effective. Unfortunately, the majority of individuals who sustain fractures are never diagnosed with osteoporosis or receive treatment for their underlying bone disease [3]. A recent world report suggests Ireland has the sixth highest rate of hip fractures worldwide, while data on other fracture types are less common [4]. Others have shown a continuous increase in the absolute numbers of major osteoporotic fractures in Ireland requiring hospitalisation, with an increase of 30% between 2000 and 2014 and a 43% increase in number of bed days. If age-standardised fracture rates remain stable, hospitalisations for osteoporotic fractures are projected to increase by 150% to 31,605 admissions in 2046 [5].

The spine is the most common osteoporotic fracture site. All vertebral fractures (VF) are associated with significant morbidity, particularly clinical fractures [6]. There is up to an eightfold increased risk in mortality following the fracture

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which appears to be independent of age, sex and comorbidities [7, 8]. Left untreated, VF can progress to involve multiple levels of the thoracolumbar spine with potential for spinal instability, disabling pain and polypharmacy. Kyphotic deformities may be complicated by a loss of equilibrium, a predisposition to future falls, restrictive lung disease, dysphagia and loss of independence and result in a significant financial burden [9]. VF are an important predictor of future fractures and should trigger assessment for secondary prevention [10]. However, only one-third are diagnosed at the time of occurrence and thus, many opportunities for intervention are missed [11].

Recent reviews of the global epidemiology of VF show considerable variation between gender, ages and regions [11, 12]. The prevalence and incidence of VF varies considerably between studies, ranging from 5 to 64% [13, 14]. Data from the USA shows that VF account for more than 18% of hospital fragility fracture admissions which is second only to hip fracture and length of hospital stay is similar to hip fractures [15]. In Ireland, published studies that have used national public hospital administrative claims data have suggested that VF only account for 5% of hospitalised fragility fractures and 6% of outpatient fractures which contrasts with other epidemiological studies [5, 14–16].

Empirical evidence from our institution shows many spine fractures are under-reported, not coded as a diagnosis in hospital discharge summaries, and follow-up is sporadic. A greater understanding of the scale and impact is needed to guide future resource management in a financially constrained health care system. Therefore, we conducted a systematic review of published literature on osteoporotic VF in Ireland to gain a better understanding of the epidemiology, impact and cost.

## Methods

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [17].

### Selection criteria

We performed a systematic literature search to identify all interventional and observational studies addressing osteoporotic VF pertaining to Ireland and Northern Ireland. We restricted the eligible studies to full-text original articles, i.e. excluding review articles, case reports, letters and editorials. We excluded non-human data, paediatric data, non-Irish data, non-osteoporotic fractures and studies that only included bone mineral density data (rather than data on VF). No language limitations were imposed. We included multi-centre studies that included Irish data.

## Search strategy

Systematic searches using PubMed, Medline, Embase, Scopus and Cochrane databases were carried out from inception to November 2018. In addition, we hand searched references from eligible studies to identify further studies for inclusion. The search strategy is outlined in Table 1. The Medical Subject Headings (MeSH) and keywords included (“vertebra\*” OR “spine” OR “spinal” OR “lumbar” OR “thoracic” OR “thoracolumbar” OR “cervical”) AND (“fracture” OR “fractures”) AND (“osteoporosis” OR “fragility” OR “osteopenia”) AND (“Ireland” OR “Northern Ireland” OR “Irish”).

## Data abstraction

The results generated from the search were screened for inclusion by title and abstract. The full text was assessed if required to make the decision (see Fig. 1 for flow chart for eligible studies). Any disagreements were resolved by discussion or upon consultation with the senior author if necessary. Data was extracted independently by the authors. The items for extraction included the following study characteristics: study design and duration, number of participants, age, sex, number with VF, diagnostic criteria for VF (clinical or morphometric), number prescribed anti-osteoporotic treatment, number who underwent surgical intervention for VF, reported comorbidities, hospitalisation rates and economic analysis carried out (Table 2).

## Results

### Characteristics of included studies

Using the search strategy as outlined in Table 1, we obtained 1558 citations, 20 of which met our inclusion criteria. All were observational research published since 2000. There was significant heterogeneity in terms of design and reported outcomes, thereby rendering a meta-analysis inappropriate. Descriptive characteristics of included studies are summarised in Table 3, with a summary of interventions and outcomes included in Table 4.

### Patient characteristics

Data was obtained on 182,771 patients with fractures. Nine studies included more than 100 subjects and three studies included more than 1000 subjects. Seventy percent of participants were female with an overall mean age of 65.2 years (30–94). Fractures were defined morphometrically in nine studies and clinically (according to ICD-10, self-reported or not described) in eleven. There was a wide variation in the

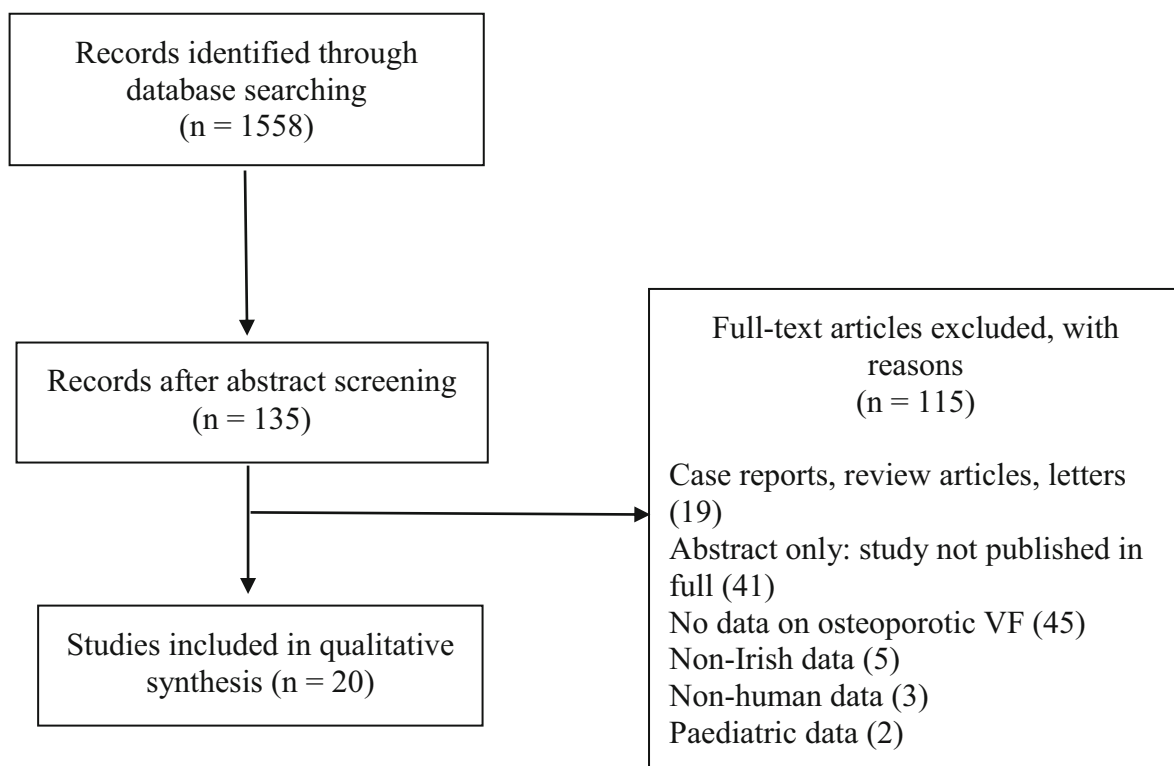
**Table 1** Example of search strategy using PubMed

Spine	“spine” [MeSH Terms] OR “spine” [All Fields]
Thoracic	“thorax” [MeSH Terms] OR “thorax” [All Fields] OR “thoracic” [All Fields]
Lumbar	“lumbosacral region” [MeSH Terms] OR (“lumbosacral” [All Fields] AND “region” [All Fields]) OR “lumbosacral region” [All Fields] OR “lumbar” [All Fields]
Cervical	“neck” [MeSH Terms] OR “neck” [All Fields] OR “cervical” [All Fields]
Fracture	“fractures, bone” [MeSH Terms] OR (“fractures” [All Fields] AND “bone” [All Fields]) OR “bone fractures” [All Fields] OR “fracture” [All Fields]
Ireland	“ireland” [MeSH Terms] OR “ireland” [All Fields]
Northern Ireland	“northern ireland” [MeSH Terms] OR (“northern” [All Fields] AND “ireland” [All Fields]) OR “northern ireland” [All Fields]
Osteoporosis	“osteoporosis, postmenopausal” [MeSH Terms] OR (“osteoporosis” [All Fields] AND “postmenopausal” [All Fields]) OR “postmenopausal osteoporosis” [All Fields] OR “osteoporosis” [All Fields] OR “osteoporosis” [MeSH Terms]
Humans [Mesh]	“humans” [MeSH Terms]

reported prevalence of VF ranging from 2.7 to 87% due to differences in included participants and ascertainment methods. Generally, the prevalence appeared to significantly increase after 60 years and peak after 70 years amongst patients presenting to osteoporosis services [18]. For the studies that provided information on fragility fracture subtype proportions ( $n = 181,050$ ), spine fractures accounted for 5.5%, hip fractures 34.5%, radial fractures 18%, humerus 5.5% and others accounted for 36.5% [2, 5, 19–21].

Three studies provided descriptive information on patients ( $n = 385$ ) assessed by osteoporosis/fracture liaison

services and discussed potential benefits these services provide [18–20]. Identified risk factors in the patient cohorts include the following: a history of previous fracture (11–50%), vitamin D deficiency (49–66%), smoking history (25–37%), excess alcohol intake (4–30%), glucocorticoid intake (7–19%), history of falls (8–13%), previous hysterectomy (7%), anti-epileptic medication intake (7%) and a diagnosis of rheumatoid arthritis (4%). One author included information on further laboratory investigations for 37 male patients showing 14% (5) had positive coeliac antibody screens, 14% (5) had elevated parathyroid

**Fig. 1** PRISMA flow diagram

**Table 2** Osteoporotic fracture proportions in Ireland

Fracture site	Inpatients (%) (administrative claims data from Hospital In-patient Enquiry System) [37]	Outpatients (%) (fracture liaison service data) [16]
Radiographic spine	5	6
Clinical spine	5	6
Hip	36	10
Radius	17	39
Humerus	8	11
Other	34	34

hormone levels and 27% (10) had low testosterone results [20].

Mohammed et al. showed a VF prevalence of 13% (77/603) amongst a cohort of patients with rheumatoid arthritis (RA) aged 40 years and older assessed by vertebral fracture assessment (VFA) imaging [22]. The majority of these fractures were classified as moderate-severe by blinded trained musculoskeletal radiologists. Forty percent of these patients did not meet *T*-score criteria for osteoporosis on DXA. Significant associations included older age, duration of RA, ACPA positivity, elevated markers of disease activity and a DXA classification of osteoporosis [22].

### Diagnostic imaging for vertebral fractures

Two studies systematically examined VF using VFA images of patients attending osteoporosis and rheumatology services using blinded assessors and validated diagnostic criteria (Genant semi-quantitative method) to assess the prevalence of fractures [22, 23]. McGuinness et al. compared the use of lateral vertebral assessment (LVA) to diagnose VF with standard lateral spine radiographs amongst patients attending an osteoporosis clinic who had symptoms suggestive of a recent vertebral fracture including new back pain, height loss or a recent fall. A total of 95 participants were included, all of whom had *T*-scores less than  $-2.5$ . The prevalence of VF amongst this pre-selected cohort was 87% (83/95), ranging from 0 to 9 fractures, 82% of which were grade 2 or 3. Overall agreement between the two methods was acceptable (weighted kappa 0.82, 95% CI 0.72, 0.92). There were no false positives with (LVA); however, 20 fractures on radiographs could not be visualised on LVA. Mohammed reported the prevalence of VF amongst a cohort of RA patients with using LVA imaging, as noted above [22]. Forty-one percent of this cohort had *T*-scores less than or equal to  $-2.5$ . Twenty-seven percent of subjects had two or more fractures, and the majority were located in the lumbar spine (68%). Fracture severity was mild (grade 1) in 31%, moderate (grade 2) in 55% and severe (grade 3) in 14%.

### Osteoporosis medication prescribing and adherence

Data from the National Primary Care Reimbursement Services (PCRS) scheme show prescribing of pharmacological therapy for osteoporosis increased significantly between 2001 and 2011, in particular following hospitalisation for osteoporotic fracture [2, 24]. The proportion of Irish adults who were on treatment has increased prior to fracture (3 to 11%) while post-hospitalisation for fracture, it has increased from 11 to 47% [25]. In this study, less than 5% of patients had VF, and prescription of medication did not differ between fracture types. However, a treatment gap still exists, estimated to be between 20 and 26% for those at high fracture risk [2]. Adherence rates to osteoporosis medication are less than 50% at 1 year [24].

### Surgical management of osteoporotic vertebral fractures

Four case series studies addressing surgical interventions, i.e. kyphoplasty [26, 27] and vertebroplasty [28, 29], for VF were identified. They included patients with VF secondary to osteoporosis and other causes, e.g. malignancy and trauma. The kyphoplasty studies solely examined the impact of patient positioning on restoring vertebral height by showing a significant improvement in mean anterior vertebral height differences and Cobb angle. The vertebroplasty studies examined the impact of the procedure on pain levels and mobility showing a significant reduction of pain, a cessation or reduction of opioid use [29] and improved self-reported mobility outcomes following vertebroplasty [28]. Details were limited, the sample sizes were small (range 8–149) and no control groups were included.

### Economic evaluation of the osteoporotic burden

Multiple country-specific reports on the economic burden of osteoporosis were published by the International Osteoporosis Foundation in 2013 [2]. The report on Ireland described the clinical and economic burden of osteoporosis in 2010 by incorporating available data on fracture incidence and

**Table 3** Study characteristics

Author	Year	Study design	Region	Sample size	% participants with osteoporotic VF	Mean age (years)	% female	Study duration	VF diagnosis
Ahmed [19]	2012	Cross-sectional	South Tipperary General Hospital	124	3.2	68.3 (46–94) in females; 69.6 (50–92) in males	81	2009–2011	Clinical
Beringer [21]	2006	Cohort	Royal Victoria Hospital, Musgrave, Belfast	86	40.7	65.3 (34–82)	70	2001–2005	Clinical
Cawley [26]	2011	Case series	Galway University Hospitals	31	50	59 ( $\pm$ 19)	65	2006–2010	Morphometric
Hilgsmann [37]	2012	Economic analysis	Rep. of Ireland	-	-	-	-	2006–2009	Clinical
Kelly [5]	2018	Cohort	Rep. of Ireland	161,735	4.4	Age-standardised rates reported	72	2000–2014	Clinical
Kevane [29]	2009	Case series	Cork University Hospital	21	80	65.1 (SD not reported)	52	2003–2007	Morphometric
Kim [38]	2014	Economic	Rep. of Ireland	-	-	-	-	2013	Clinical
McDonnell [32]	2009	Experimental	National University of Ireland, Galway	-	-	-	-	Not reported	Morphometric
McDonnell [31]	2010	Experimental	National University of Ireland, Galway	-	-	-	-	Not reported	Morphometric
McGowan [30]	2013	Cohort	Rep. of Ireland	102,053	4.2	Age-standardised rates reported	72	2000–2009	Clinical
McGowan [24]	2013	Cohort	Sligo General Hospital, St James's Hospital, Dublin	744	Not reported	78.1 ( $\pm$ 8.5)	76	2005–2008	Clinical
McGowan [18]	2012	Cohort	St James's Hospital, Dublin	224	33	68 ( $\pm$ 14.3)	88	2006–2007	Morphometric
McGowan [25]	2011	Cohort	St James's Hospital, Dublin	821	4.6	78.1 ( $\pm$ 9.53)	77	2004–2009	Clinical
McGuinness [23]	2009	Cohort	Queen's University Belfast	95	87	65.9 ( $\pm$ 11.3) in females; 59.5 ( $\pm$ 14.2) in males	74	Not reported	Morphometric
McNeilly [39]	2013	Cohort	Musgrave Park Hospital, Belfast	138	Mean number of VF	74 (46–90)	94	2007–2011	Clinical
Mohammad [22]	2014	Cross-sectional	Galway University Hospitals	603	13	56.5 ( $\pm$ 11.82)	72	2011–2012	Morphometric
Ng [27]	2016	Case series	Galway University Hospitals	20	19	54.5 (27–90)	67	2007–2014	Morphometric
O'Brien [28]	2006	Case series	Cappagh National Orthopaedic Hospital, Mater Misericordiae Hospital, Dublin	8	75	62 (SD not reported)	88	2000–2003	Morphometric
Svedbom [2]	2013	Epidemiological	Rep. of Ireland (national)	18,084	14.8	Age-standardised rates reported	67	2010	Clinical
Wright [20]	2007	Cross-sectional	Northern Ireland (national)	37	2.7	54 (30–71)	0	2000–2001	Clinical

**Table 4** Summary of interventions and outcomes included in studies

Descriptor	Inclusion rate (%)
Pre-fracture status (function, residence)	5
Post-fracture functional outcome	20
Discharge location (home, nursing home, rehabilitation)	0
Co-morbidities	20
Hospital length of stay	15
Inpatient mortality	0
1-year mortality	5
Osteoporosis diagnosis	70
Osteoporosis treatment	50
Fall prevention	10
Re-admissions	0
Interventions (FLS, balloon kyphoplasty, vertebroplasty)	35
Economic	20
Basic science	10

associated costs into a model in conjunction with the European Federation of Pharmaceutical Industry Associations. The investigators defined the population at risk as being those aged 50 years or older who met the World Health Organization diagnostic criteria (*T*-score less than  $-2.5$ ) for osteoporosis equating to 170,000 individuals during 2010. They estimated 18,000 incident fractures occurred in Ireland during this period, including 2700 VF (15%), accounting for an expenditure of €223 million and 6100 in lost quality-adjusted life years (QALYs). When osteoporosis expenditure was combined with the value for QALY lost ( $2 \times$  gross domestic product), osteoporosis costs totalled to €650 million in Ireland in 2010. Direct “first-year costs” following fracture amounted to €125 million, subsequent-year costs amounted to €62 million and preventative osteoporosis treatment costs equated to €35 million. Interestingly, expenditure on osteoporosis pharmacotherapy treatment only amounted to 15.8% of the overall total costs. Hip fractures were the most expensive fragility fractures (€105 million), followed by “other” fractures (€72 million), spine (€8 million) and forearm fractures (€3 million) [2].

Data from Irish Public Hospitals has shown that there is an average of 478 VF hospital admissions per year, equating to 3674 bed days based on data from 2000 to 2014. However, there has been over a 150% increase in the number of women hospitalised with VF in 2014 compared with 2000 and a 20% increase in male admissions. The mean duration of hospital admission for VF has increased from 12 days for women and 11 days for men to 17 and 19 days respectively over this time period. Assuming the mean cost for VF admissions from 2003 to 2008, then the mean cost in 2014 was €2.1 million for men and €3.5 million for women accounting for longer admission durations. Overall, we know that hospitalisations for fragility fractures are on the rise. By 2046, expenditure is projected to

increase to €304 million compared with €118 million in 2014 and 58% of the affected patients are anticipated to be 80 years or older [5, 30].

### Other studies

Two studies from the Department of Mechanical and Biomedical Engineering at NUI Galway examined vertebral trabecular bone loss using simulation models [31, 32]. McDonnell et al. show vertebral trabecular bone is at greater risk of loss from wedge action loading (combination of compression and flexure loading) compared with uni-axial compression loading [31], and horizontal trabeculae may be at greatest risk of damage from strain adaptive resorption [32].

### Discussion

This is the first systematic review that examined the literature on osteoporotic spine fractures in Ireland. Overall, they appear to be increasing in incidence and cost but it is probable that many remain undiagnosed and are not being captured and their importance is under-recognised. We found that there is a lack of studies addressing this area and the available data is heterogeneous which limits the inferences that can be made. More formal studies are needed to better understand the incidence, prevalence, effect on patients and their long-term outcome and cost to patients and society. The deficit in data reflects the current situation of osteoporotic spine care in Ireland where streamlined multi-disciplinary care for investigation and management of VF or a national database does not exist. This is in contrast to hip fractures despite spine accounting for a higher proportion of total fragility fractures and their near-equal significance [11, 33]. The National Hip Fracture

Care Pathway introduced by the Health Service Executive (HSE) in tandem with the establishment of the Irish Hip Fracture Database (IHFD) has significantly improved patient care for thousands of individuals admitted with hip fractures in Ireland per year [34]. A similar care pathway is greatly needed for vertebral fractures to highlight their significance and to address the confusion that often arises around investigations, management and service access.

We had a clear objective prior to conducting this systematic review and used appropriate pre-defined inclusion and exclusion criteria with a reproducible protocol. We searched multiple different electronic databases and reference lists of relevant articles in order to identify studies that would be potentially eligible for inclusion, but it is possible we did not identify all eligible studies. Due to the limited number of studies that met our inclusion criteria and their heterogeneity, we were unable to perform a meta-analysis and a robust quantitative analysis.

We found a wide range of vertebral fracture prevalence in Ireland, from less than 5% amongst hospitalised populations to almost 90% in older patients with low BMD in whom a fracture was suspected. VF tend to be under-recognised compared with other fragility fractures for several reasons. Firstly, many are asymptomatic and studies suggest only one in three present clinically [11]. However, others have shown even “radiographic” fractures are associated with morbidity, are important for predicting future fracture and are associated with mortality which exceeds hip fracture [6–8, 35]. Multi-national studies show the majority do not occur following a fall, unlike non-vertebral fractures [36]. Patients presenting with suggestive symptoms are sometimes dismissed and not imaged, or may delay or not seek medical attention. Fractures often go unreported on imaging performed for other reasons, possibly due to inattentive blindness [37]. When fractures are recognised, reports may contain ambiguous terminology such as “wedging”, “loss of height” and “end-plate depression”, and consequently, the referring clinician may not realise there is an actual fracture. Finally, the only large sample data for Ireland contains data reported from public hospital admissions. This data is a conservative estimate for two main reasons: (a) only 59% of recorded emergency admissions have a discharge diagnosis and our own audits show that under-reporting is a significant problem and (b) this data does not include patients seen and managed in other facilities or in outpatient clinics [38].

Despite the limited availability of data, we found evidence that the overall number of VF may be increasing and is particularly high in some populations and the numbers are greater when imaging is formally scrutinised for fractures using agreed criteria. The evidence suggests that VF are more common in older Irish adults, those with low BMD or those with co-morbidities such as rheumatoid arthritis. There appears to be a trend for greater prescription

use amongst people deemed high risk for fracture or following hospitalisation for fragility fracture. However, there is very limited data on medication adherence and compliance. In addition, we do not have clear evidence of the true rates of osteoporosis diagnosis and treatment rates specifically following VF. We did not find observational studies specifically addressing the incidence of VF, patients’ pre-morbid status, mortality or long-term outcomes including patient perceptions and quality of life. There is limited data addressing the overall economic cost for Irish people with VF but the estimates are concerning and are probably a significant underestimation. While we know the overall osteoporosis poses a high economic burden in this jurisdiction, we have not been able to fully address the true impact and importance of VF in this study.

## Conclusion

In summary, there is a large deficit of large studies addressing the epidemiology of osteoporotic fractures in Ireland, in particular vertebral. Several studies show that VF are common when addressed systematically and the prevalence may be rising. Published studies are heterogeneous making inferences difficult. This deficit must be rectified to improve our understanding of the burden of VF in Ireland and enable more effective service planning for fracture prevention and management.

## Compliance with ethical standards

**Conflicts of interest** JJC has received speaker fees from Eli Lilly, Amgen, UCB, Pfizer, Hospira and Celtrion. He has received travel support from Roche, Amgen, Eli Lilly, MSD and UCB and grant and educational support from Amgen, UCB, Eli Lilly, Abbvie, MSD and the Irish Society for Rheumatology. He has served on several committees for and is past-President of the International Society for Clinical Densitometry, is a member of the Committee for Scientific affairs for the International Osteoporosis Foundation and is a founding member of and current president of the Irish DXA Society. EMC, AI, RS, MK, CA, FH and DB, JPMC declare that they have no conflict of interest to disclose.

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