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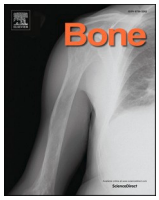

Full Length Article

Healthcare costs associated with opportunistically identifiable vertebral fractures

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ABSTRACT

Purpose: Vertebral fractures (VFs) are often available on radiological imaging undertaken during daily clinical work, yet the healthcare cost burden of these opportunistically identifiable fractures has not previously been reported. In this study, we examine the direct healthcare costs of subjects with vertebral fractures available for identification on routine CT scans.

Methods: Thoracolumbar vertebral fractures were identified from 2000 routine CT scans. Subjects with VF on the scan were matched 1:2 against subjects with no VF on the scan, and similarly in a 1:3-ratio against a general population cohort. We excluded those subjects who received treatment with osteoporosis medication(s) in the year prior to baseline. Direct healthcare costs, identified from the national Danish registers, were accrued over up to 6 years of follow-up, and reported per day at risk and per year.

Results: In subjects undergoing a CT scan, costs were initially high, yet declined over time. Comparing subjects with prevalent vertebral fracture (n = 321) against those subjects with no vertebral fracture (n = 606), mean total healthcare costs per day at risk was numerically higher in the first three years after baseline, while healthcare costs per year were similar between the cohorts. No differences reached statistical significance. When compared to the general population cohort, costs were significantly higher in the vertebral fracture cohort.

Conclusion: Subjects with vertebral fractures available for identification on routine CT scans incur substantially higher healthcare costs than matched subjects representing the general population, and numerically, albeit non-significantly, higher healthcare costs per day at risk in the short term, as compared to subjects with no visible VF on the CT scan.

1. Introduction

Geographically diverse studies have shown that vertebral fractures (VFs) are a frequent finding in older men and women [1]. The incidence is high, with global estimates suggesting a staggering 8.6 million VF cases in 2019; an increase from 6.2 million in 1990 [2]. As VF incidence rates increases with age [2], and with an increasing life expectancy and growing elderly population foreseen in coming years [3], a further surge in VF incidence could well be expected [4].

Vertebral fractures are clinically important, as they are associated with death [5,6], future fractures [7–9], and other comorbidities and medical complications [10,11]. Of patients hospitalized with osteoporotic clinical VFs, 34–50 % are discharged to a care facility and 1-year mortality is 20–26.9 % [12]. In accordance with these findings, patients with clinical VFs incur substantially higher post-fracture healthcare costs as compared to non-fracture controls [13–17], often driven by the cost of hospitalizations [13,15,17]. However, most VFs observed on radiographs have not been clinically diagnosed [18], and only few

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studies using radiological imaging to identify all VFs have assessed healthcare utilization and costs. Comparing subjects with vs without prevalent VF, one study found a 21 % higher risk of any hospitalization over a 5-year follow-up period [19]. Furthermore, a non-recent study found that both pre- and postfracture total incremental healthcare costs were numerically but non-significantly higher in 42 subjects with incident radiographic VF vs matched controls [20].

When performing radiological imaging including all or part of the trunk, VFs are frequently visible, yet despite of their clinical importance they often remain unreported [21–24]. We and others have previously shown that patients with VFs available for identification on routine CT scans are at increased risk of future major osteoporotic fractures, hip fractures, and death [25–28]. No studies have reported the observed healthcare costs of opportunistically identifiable VFs. To further explore the rationale for improved reporting of opportunistically identifiable VFs, the aim of this study was to evaluate the direct healthcare costs of subjects with VFs available for identification on CT scans performed as part of routine clinical practice, and not treated for osteoporosis at the time of the scan.

2. Materials and methods

This paper presents the healthcare costs of subjects with VFs available on routine CT scans, based on an observational cohort study previously described in detail [27,28]. Approval of this study was obtained from the Danish Patient Safety Authority (3-3013-2687/1), Statistics Denmark (707480), and the Danish Data Protection Agency (granted through Region Zealand [REG-101-2018]). In brief, we used the Holbæk Hospital radiology database to identify the first 2000 individuals, aged 50 years or older, with a CT scan including the chest and/or abdomen. First eligible date of CT scan was 1st January 2010. These CT scans were reevaluated to diagnose thoracolumbar VFs according to the Genant Semiquantitative classification [29], as described in detail in a prior publication [27], with six radiologists contributing to the final diagnosis and grading ($\kappa = 0.78$ for vertebra-level inter-reader agreement, based on re-examination of 50 CT scans blinded to the initial results [report on file]). We linked these findings to the national Danish registers, and used data therefrom to form two distinct populations for analyses: 1) the *analysis population*, including subjects with VF on the CT scan matched 1:2 on age group and sex against subjects with no VF on the CT scan; 2) the *scaling analysis population*, consisting of subjects with VF on the CT scan matched 1:3 on age group and sex against general population subjects sampled through the Danish registers. Subjects with conflicting (<0.1 % of the subjects from the general population sample) or no registry data were excluded, and as were subjects with less than one year of registry data available prior to baseline (date of CT scan; for the general population cohort the baseline date was transferred from the matched case), and those receiving treatment with an osteoporosis medication (OM) in the year prior to baseline or emigrated prior to baseline. From the general population sample we also excluded those who were dead or <50 years old at baseline.

2.1. Outcomes

The primary outcome was the mean total healthcare costs per day at risk in subjects with VF on the CT scan as compared to subjects with no VF on the CT scan. This was evaluated from baseline until end of follow-up, operationalized as the time of death, migration out of Denmark, or at 6 years after baseline. Total healthcare costs incorporate the cost of admissions, outpatient visits, and prescription medication costs. Primary healthcare sector costs were not included in this outcome. The costs were first annualized according to year of follow-up, based on date of admission, date of outpatient clinic visit, and date of prescription redemption, respectively. To obtain the individual-level average costs per day, annualized costs were divided by the number of days at risk in that given year of follow-up for each individual. We report the mean average costs per day at risk per year of follow-up, and in the year prior to baseline (*baseline year*). Individuals only contribute to the analyses in the years they were considered at risk (i.e., contributing to the analyses on the first day in that given year), and thus not after the end of their follow-up. Taking time at risk into account may be important, as we have previously shown – for the cohorts examined in this report – a substantially higher mortality in subjects with VF on the CT scan as compared to subjects with no visible VF and even more pronounced when compared to the general population cohort [28]. Thus, cost accrual time (time at risk) is likely to be different between the cohorts.

We also evaluated the mean total healthcare costs per year of follow-up, which was similar to the primary outcome, except days at risk in the given years were not taken into account. Using these results, we also pooled the individual-level total costs for years 1 to 3 and 4 to 6, respectively, and report the proportion of subjects in each of four purposively selected cost categories for each time period.

Finally, primary healthcare sector costs – including, for example, general practitioners and dentists – were evaluated separately, and treated as an exploratory endpoint, as the time of service delivery is less granular than for the registers used in the above-mentioned analyses. Thus, instead of reporting the actual date(s) of service delivery – as is done for the cost variables described above – the primary healthcare sector costs are reported according to the week number and year in which they are invoiced by the healthcare professional to the public sector. Furthermore, each invoice may aggregate several similar services over time for a single individual.[1] These conditions makes it impossible to accurately ascertain the time of service delivery, and therefore, to avoid miscategorizing costs in terms of time of follow-up, costs were allocated and reported according to calendar year. Therefore, for these analyses, the baseline year is the calendar year of the CT scan (or the CT scan of the matched case for the general population cohort), year 1 is the first calendar year after the year of the CT scan, and so forth. Subjects contribute until the year in which they are censored.

We identified the healthcare costs in the Danish registers, using the Danish National Patient Register to identify somatic admission and outpatient visit costs, the Danish National Health Service Register for primary healthcare sector costs, and the Danish National Prescription Register for prescription medication costs (excl. VAT). Medications administered in hospitals and outpatient clinics are included in the costs derived from the National Patient Register. Hospital costs, as given in the registers, are based on the Diagnosis Related Groups (DRG) system, which assigns a tariff to each contact [30]. For Danish citizens, healthcare services are provided for free, while co-payment policies are implemented for prescription medications [31]. Additional primary healthcare sector services covered by private health insurance or out-of-pocket are available, but these are not included in the Danish National Health Service Register. Over-the-counter medications are not included in the registers [30].

2.2. Other covariates and data sources

Individual-level data used to inform the baseline analyses as well as delineate follow-up (using the date of death or date of emigration) were identified in the Danish registers, using the Civil Registration System, the National Patient Register, the National Prescription Register, and the Register of Causes of Death. Detailed information on applied codes and methods are available in Skjødt et al (JBMR Plus, 2023) [27]. Beyond this, the Income Register was used to obtain socioeconomic status [32].

[1] Details on primary healthcare sector costs obtained from Statistics Denmark, accessed 28th January 2023; https://www.dst.dk/extranet/ForskningVariabellister/SSSY%20-%20Sygesikring%20(6-cifret).html.

2.3. Statistical analyses

Baseline characteristics are presented descriptively by number and proportion for categorical variables, and median with interquartile range for continuous variables. For baseline characteristics and total healthcare (admission, outpatient and medication) costs, the baseline date is the date of the CT scan. For primary healthcare costs, baseline is the calendar year of the CT scan. For the general population cohort, this is the date and year, respectively, of the CT scan of the matched case.

Costs are adjusted for inflation using index estimates for January of each respective year, scaled to January 2022 estimates (using Statistics Denmark price index estimates for the respective healthcare sectors: www.statbank.dk) and presented descriptively in US dollars (USD) using a conversion rate of 7.168 DKr to 1 USD (official exchange rate per 25 November 2022, using the Danish National Bank exchange rates: www.nationalbanken.dk/Valutakurser).

To evaluate the differences between the cohorts in terms of healthcare costs, we fitted linear mixed-effect models separately for each outcome (mean total healthcare costs per day at risk, mean total healthcare costs per year, and primary healthcare sector costs per year). We used the Stata code "*mixed*", and modelled random intercepts by matching group and subject, respectively, to account for clustering of the data. Adding age and sex to the models only marginally affected parameter estimates and significance tests, thus we chose to report the simpler model without age and sex. To meet model assumptions, the dependent variable (costs) was transformed in all six models. For each separate model, we chose the transformation which fitted best with model assumptions. Across all six models, this was either log-transformation (1 added to costs before log-transformation to avoid taking the log of 0) or cube root-transformation. The models were used to assess statistical significance of the cost differences between the cohorts, *not* to predict individual-level costs.

Analyses were performed using STATA 16/17 (StataCorp, Texas, USA).

3. Results

The assessment of the 2000 CT scans showed one or more VFs in 423 (21.2 %) subjects. Subsequent to exclusion and matching, as previously described [27,28], the *analysis population* was composed of 321 subjects in the VF cohort and 606 subjects in the no VF cohort (VF subjects were omitted if no matched comparators had been assigned following the matching process, leading to differences in number of subjects in the VF cohort across the *analysis* and *scaling analysis* populations). Similarly for the *scaling analysis population*, the VF cohort consisted of 332 subjects and the general population cohort of 996 subjects.

3.1. Baseline characteristics

Baseline characteristics are shown in Table 1. The age- and sex-distributions were balanced within the *analysis* and *scaling analysis populations*, respectively, as expected given the matching process. Almost all subjects were of Danish descendance.

For the *analysis population*, the socioeconomic status was overall comparable between the VF and no VF cohorts, with the majority of the subjects being retired. Medical history showed that more subjects in the VF cohort had a history of fractures, and more subjects fell into the Charlson Comorbidity Index (CCI) score categories of 2 and 3+. As previously reported, the worst VF available on the baseline CT scan was mild in 31.2 % of the subjects in the VF cohort, moderate in 36.4 %, and severe in 32.4 % [27].

Baseline characteristics for the *scaling analysis population* showed that a larger proportion of subjects in the VF cohort were retired as compared to the general population cohort who, on the other hand, were more

Table 1
Baseline characteristics.

	Analysis population		Scaling analysis population	
	VF on CT scan (N = 321)	No VF on CT scan (N = 606)	VF on CT scan (N = 332)	General population (N = 996)
Sex, male; n (%)[a]	172 (53.6 %)	322 (53.1 %)	181 (54.5 %)	543 (54.5 %)
Age, years; median (IQR)[a]	73 (65–79)	73 (65–79)	73 (65–79)	73 (65–80)
Country of origin, Denmark; n (%)[a,b]	312 (97.2 %)	592 (97.7 %)	323 (97.3 %)	967 (97.1 %)
Socioeconomic status; n (%)[c]				
Self-employed	5 (1.6 %)	9 (1.5 %)	5 (1.5 %)	21 (2.1 %)
Employed	24 (7.5 %)	75 (12.4 %)	24 (7.2 %)	157 (15.8 %)
Unemployed	n < 5	n < 5	n < 5	6 (0.6 %)
Retired	286 (89.1 %)	515 (85.0 %)	297 (89.5 %)	802 (80.5 %)
CCI-score; n (%)[d]				
0	100 (31.2 %)	258 (42.6 %)	103 (31.0 %)	723 (72.6 %)
1	37 (11.5 %)	65 (10.7 %)	39 (11.7 %)	77 (7.7 %)
2	97 (30.2 %)	149 (24.6 %)	98 (29.5 %)	134 (13.5 %)
3+	87 (27.1 %)	134 (22.1 %)	92 (27.7 %)	62 (6.2 %)
Prior fractures; n (%)[a]				
Any fracture[e]	112 (34.9 %)	142 (23.4 %)	115 (34.6 %)	208 (20.9 %)
Major osteoporotic fracture[f]	70 (21.8 %)	71 (11.7 %)	72 (21.7 %)	116 (11.6 %)

This table shows the baseline characteristics of the *analysis population* (subjects with VF on CT scan vs subjects with no VF on CT scan) and the *scaling analysis population* (subjects with VF on CT scan vs general population sample).
CCI, Charlson Comorbidity Index; CT, computed tomography; IQR, interquartile range; VF, vertebral fracture.
[a] Adapted from Skjødt et al. (JBMR Plus, 2023) [27].
[b] Denotes that at least one parent is born in Denmark and is Danish citizen. If parents unknown, this is based on the subject.
[c] Derived from the Statistics Denmark classification of socioeconomic status, based on the last calendar year before the year of the index date. The category "self-employed" is pooled across subgroups based on number of employees; the category "retired" is pooled across early retirement, voluntary early retirement, and retirement. Numbers does not add up to 100 %, as categories with n < 5 in all cohorts have been removed together with a "not available" category.
[d] Charlson Comorbidity Index score based on the updated weights suggested by Quan et al. (American Journal of Epidemiology, 2011) [27,34].
[e] Any prior fracture, excluding fractures of the face, skull, and fingers.
[f] Major osteoporotic fractures include hip fractures, non-cervical vertebral fractures, distal forearm fractures and humerus fractures.

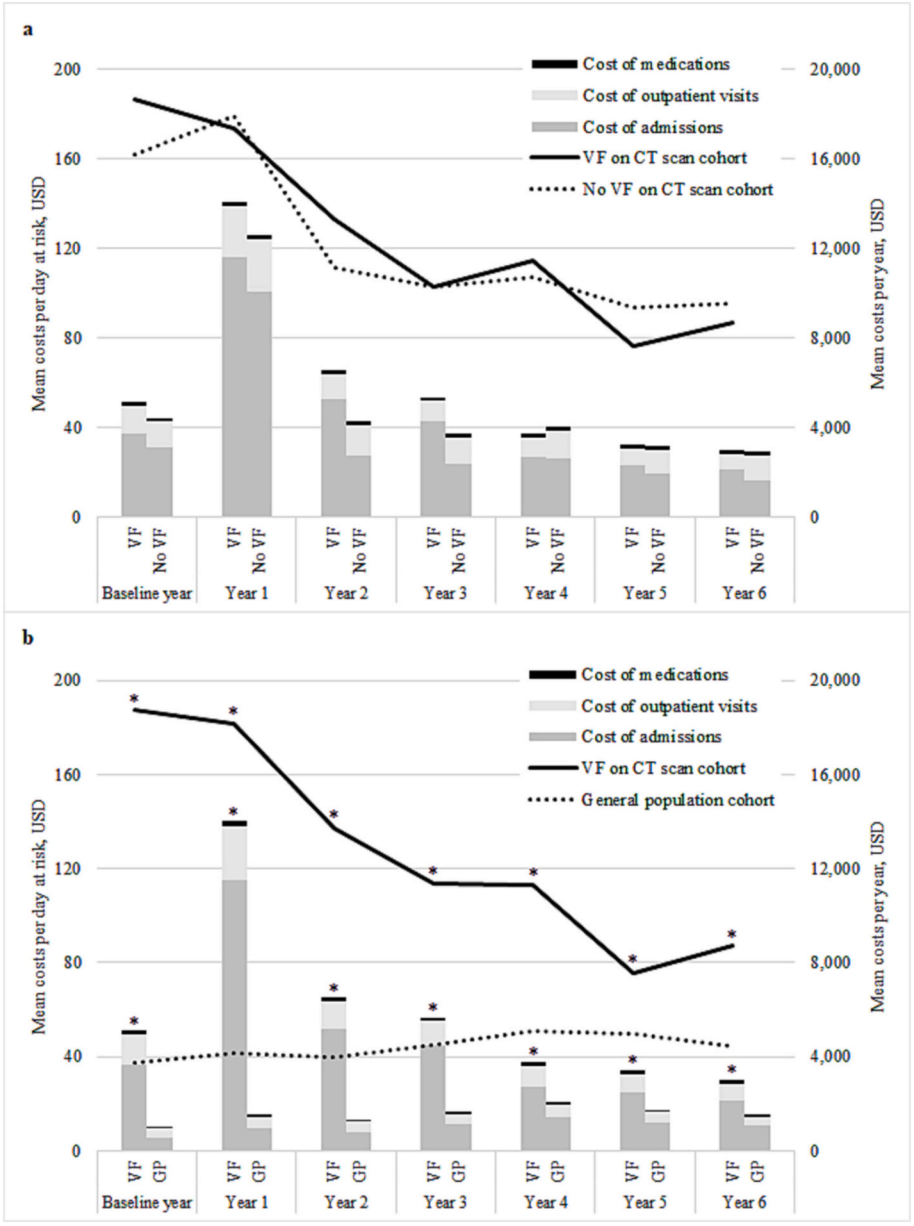

Fig. 1. Healthcare costs per year of follow-up.
The figure shows the healthcare costs per year of follow-up for subjects with VF on the CT scan vs subjects with no VF on the CT scan (*analysis population*; panel a) and for subjects with VF on the CT scan vs the general population cohort (*scaling analysis population*; panel b).
The stacked bars show the mean costs per day at risk per year of follow-up (values on primary – left – Y-axis), split into the cost of admissions (dark grey bars), the cost of outpatient visits (light grey bars) and the cost of medications (black bars).
The lines show the mean total costs per year of follow-up (values on secondary – right – Y-axis) for subjects in the VF on CT scan cohort (full line) vs subjects in the comparator cohort (dotted lines).
Only subjects alive on the first day of the respective year of follow-up contribute to the analyses of that year.
We assessed the statistical difference between the cohorts in terms of the mean total costs per day at risk and the mean total costs per year, respectively. There were no statistically significant differences between the cohorts in the *analysis population* (panel a). In the *scaling analysis population* (panel b) there were significant differences: *$p < 0.001$.
Costs are indexed to January 2022, and given in US dollars.
CT, computed tomography; GP, general population; USD, US dollars; VF, vertebral fracture.

often actively working. Substantially larger proportions in the VF cohort fell into the 2 and 3+ CCI-score subgroups.

3.2. Healthcare costs in subjects with VF vs without VF on the CT scan (analysis population)

In the *analysis population* (subjects undergoing a CT scan), the mean total healthcare costs per subject per year were high at baseline in both the VF and the no VF cohorts (Fig. 1a, black lines; additional details available in Table 2). Overall, these costs decreased over time in both cohorts. While this metric does not reflect differences in time at risk, this was, however, observed in the mean costs per day at risk (Fig. 1a, stacked bars; additional details available in Table 2). This showed a steep increase from baseline to year 1 in both cohorts, followed by a decline over time. Costs were driven by the cost of admissions, followed by the cost of outpatient visits.

The mean total costs per day at risk was numerically higher in the VF cohort as compared to the no VF cohort at baseline, which persisted up to year 3 after baseline. After that, costs were similar in the two cohorts. The mean total costs per year was again numerically higher at baseline, but beyond that generally similar throughout the study. The year-by-year differences between the cohorts in mean total healthcare costs – both per day at risk and per year – did not reach statistical significance. Similarly, the overall differences between the cohorts across the entire follow-up were not statistically significant (mean costs per day at risk: $p = 0.51$; mean costs per year: $p = 0.17$).

The distribution of subjects according to total costs during year 1 to 3 and year 4 to 6, respectively, is shown in Fig. 2a and b. There were only minor differences between the cohorts in these distributions. Approximately 15–16 % of the cohorts had a total cost above 60,000 USD during the first triennium, which fell to approximately 9–11 % during the second triennium.

3.3. Healthcare costs in subjects with VF on the CT scan vs the general population cohort (scaling analysis population)

Within the *scaling analysis population* (Fig. 1b; additional details available in Table 3), the VF cohort – similar to what has been described

Table 2
Mean healthcare costs (USD) in the *analysis population*.

		Mean costs (SD) per day at risk		Mean costs (SD) per year	
		VF on CT scan	No VF on CT scan	VF on CT scan	No VF on CT scan
Baseline year	Cost of admissions	37.0 (52.5)	30.8 (48.9)	13,499.6 (19,169.6)	11,263.4 (17,858.7)
	Cost of outpatient visits	12.5 (28.9)	11.9 (33.5)	4573.1 (10,553.7)	4353.4 (12,246.3)
	Cost of medications	1.7 (2.1)	1.5 (2.2)	604.9 (778.4)	558.8 (792.4)
	Total costs	**51.1 (64.1)**	**44.3 (64.3)**	**18,677.7 (23,424.8)**	**16,175.5 (23,490.4)**
Year 1	N at risk at start of the year	321 (100.0 %)	606 (100.0 %)	321 (100.0 %)	606 (100.0 %)
	Cost of admissions	116.1 (318.2)	100.5 (489.3)	12,333.7 (19,777.9)	11,114.4 (17,619.3)
	Cost of outpatient visits	22.4 (50.2)	23.5 (50.5)	4498.4 (10,156.9)	6277.9 (13,938.5)
	Cost of medications	2.3 (3.3)	1.9 (2.8)	503.0 (757.0)	491.8 (673.2)
	Total costs	**140.7 (325.1)**	**125.8 (491.7)**	**17,335.1 (24,302.0)**	**17,884.0 (24,336.2)**
Year 2	N at risk at start of the year	182 (56.7 %)	425 (70.1 %)	182 (56.7 %)	425 (70.1 %)
	Cost of admissions	52.8 (266.6)	27.6 (81.4)	9343.6 (22,306.7)	6148.1 (13,731.9)
	Cost of outpatient visits	10.6 (25.3)	13.5 (34.4)	3356.5 (7683.7)	4422.4 (11,791.4)
	Cost of medications	1.9 (2.7)	1.7 (2.3)	593.8 (805.5)	554.9 (705.1)
	Total costs	**65.2 (270.2)**	**42.9 (91.8)**	**13,294.0 (26,729.7)**	**11,125.5 (19,365.7)**
Year 3	N at risk at start of the year	150 (46.7 %)	378 (62.4 %)	150 (46.7 %)	378 (62.4 %)
	Cost of admissions	42.7 (184.9)	23.4 (104.1)	6889.0 (12,710.3)	5812.5 (14,113.0)
	Cost of outpatient visits	9.0 (23.6)	11.8 (33.4)	2819.7 (7811.7)	3891.3 (11,570.3)
	Cost of medications	1.7 (2.3)	1.8 (2.4)	580.3 (826.1)	581.2 (692.3)
	Total costs	**53.4 (193.2)**	**37.0 (113.2)**	**10,289.0 (17,195.5)**	**10,285.0 (20,332.3)**
Year 4	N at risk at start of the year	132 (41.1 %)	350 (57.8 %)	132 (41.1 %)	350 (57.8 %)
	Cost of admissions	26.5 (57.2)	25.9 (70.0)	7910.5 (15,479.0)	6449.4 (14,278.0)
	Cost of outpatient visits	8.9 (28.4)	12.5 (35.5)	2934.5 (9839.7)	3645.1 (9487.5)
	Cost of medications	1.9 (2.3)	1.7 (2.1)	625.2 (811.8)	584.1 (747.7)
	Total costs	**37.3 (71.1)**	**40.1 (87.3)**	**11,470.2 (21,098.7)**	**10,678.6 (19,827.6)**
Year 5	N at risk at start of the year	110 (34.3 %)	313 (51.7 %)	110 (34.3 %)	313 (51.7 %)
	Cost of admissions	22.9 (51.0)	19.3 (47.0)	5112.8 (11,278.0)	5284.0 (11,281.1)
	Cost of outpatient visits	7.4 (18.0)	10.3 (29.6)	1914.8 (3560.6)	3479.7 (10,412.1)
	Cost of medications	1.9 (2.3)	1.8 (2.1)	577.6 (702.5)	598.6 (710.3)
	Total costs	**32.2 (63.2)**	**31.3 (62.2)**	**7605.3 (13,709.3)**	**9362.4 (17,628.0)**
Year 6	N at risk at start of the year	89 (27.7 %)	282 (46.5 %)	89 (27.7 %)	282 (46.5 %)
	Cost of admissions	20.9 (53.0)	16.3 (38.8)	5658.7 (12,795.5)	5134.9 (12,182.6)
	Cost of outpatient visits	7.1 (12.8)	10.8 (31.1)	2442.7 (4620.1)	3749.1 (10,955.2)
	Cost of medications	1.7 (2.1)	1.9 (2.4)	602.1 (780.1)	646.3 (811.8)
	Total costs	**29.7 (57.7)**	**28.9 (55.9)**	**8703.6 (14,550.0)**	**9530.4 (18,715.6)**

The table shows the mean (standard deviation) costs of admissions, outpatient visits, medications, and in total for subjects with VF on the CT scan vs subjects with no VF on the CT scan. Also shown is the number of subjects at risk at the beginning of each year of follow-up. Data are stratified according to year of follow-up (baseline year is the last full year before the date of the CT scan). Costs are shown as 1) mean costs per day at risk (left column), where individual-level costs have been split across the number of days at risk in the respective year; 2) mean costs per year for subjects alive at the beginning of the respective year, irrespective of the number of days at risk (right column). Costs are indexed to January 2022, and given in US dollars.
Differences between the cohorts in mean total costs – per day at risk and per year, respectively – evaluated by linear mixed-effects models. We found no statistically significant differences (at the $p < 0.05$-level) between the cohorts.
CT, computed tomography: SD, standard deviation; USD, US dollars; VF, vertebral fracture.

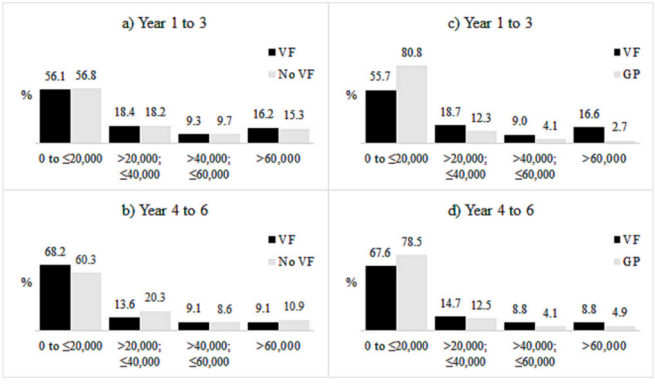

Fig. 2. Cost groups.
The figure shows the proportion of subjects (%) according to total healthcare costs (including admissions, outpatient visits, and prescription medications) during year 1 to 3 of follow-up and year 4 to 6 of follow-up, respectively. Panels a and b are the *analysis population* (subjects with VF on the CT scan vs subjects with no VF on the CT scan), while panels c and d are the *scaling analysis population* (subjects with VF on the CT scan vs the general population cohort).
Costs are indexed to January 2022, and given in US dollars.
GP, general population; VF, vertebral fracture.

above – showed high mean total costs per year at baseline, which generally decreased over time. The mean total costs per day at risk showed an initial steep increase from baseline to year 1, and then also decreased over time. Hospital admission costs were, again, the driver of these findings. In contrast, the costs in the general population cohort – both per day at risk and per year – were generally stable over time with only minor year-by-year fluctuations.

The year-by-year differences in mean total costs between the VF cohort and the general population cohort – both per day at risk and per year – were highly statistically significant ($p < 0.001$ for all comparisons). Similarly, the overall differences between the cohorts across the entire follow-up were also highly statistically significant ($p < 0.001$ for both outcomes).

There were substantial differences in the distribution of subjects according to accumulated costs over year 1 to 3 and year 4 to 6, respectively (Fig. 2c and d). Few subjects in the general population cohort contributed to the high-cost group (<5 % for both triennia).

3.4. Primary healthcare costs

The costs of primary healthcare services (Table 4) are shown for the

Table 3
Mean healthcare costs (USD) in the *scaling analysis population*.

		Mean costs (SD) per day at risk		Mean costs (SD) per year	
		VF on CT scan	GP	VF on CT scan	GP
Baseline year	Cost of admissions	36.8 (52.0)	5.5 (17.3)	13,458.9 (18,989.8)	1991.7 (6332.9)
	Cost of outpatient visits	12.7 (29.2)	3.9 (12.8)	4655.6 (10,648.1)	1425.7 (4689.5)
	Cost of medications	1.7 (2.1)	0.9 (1.4)	603.8 (770.7)	326.6 (508.5)
	Total costs	**51.2 (64.1)***	**10.3 (24.2)**	**18,718.3 (23,403.6)***	**3744.1 (8856.5)**
Year 1	N at risk at start of the year	332 (100.0 %)	996 (100.0 %)	332 (100.0 %)	996 (100.0 %)
	Cost of admissions	115.1 (314.3)	9.8 (40.2)	12,968.1 (22,489.2)	2370.2 (6874.6)
	Cost of outpatient visits	22.7 (50.3)	4.6 (16.5)	4703.4 (10,659.4)	1476.1 (4935.0)
	Cost of medications	2.3 (3.3)	1.0 (1.5)	506.4 (753.4)	326.0 (487.2)
	Total costs	**140.1 (321.2)***	**15.4 (48.0)**	**18,177.8 (27,069.0)***	**4172.3 (9506.6)**
Year 2	N at risk at start of the year	190 (57.2 %)	940 (94.4 %)	190 (57.2 %)	940 (94.4 %)
	Cost of admissions	51.5 (261.0)	7.8 (29.2)	9301.5 (22,009.2)	2171.3 (5772.3)
	Cost of outpatient visits	11.8 (30.1)	4.4 (17.4)	3782.2 (9812.9)	1501.2 (5782.4)
	Cost of medications	1.9 (2.7)	0.9 (1.5)	595.7 (799.8)	325.8 (533.8)
	Total costs	**65.2 (265.2)***	**13.2 (38.5)**	**13,679.4 (27,211.0)***	**3998.2 (9061.7)**
Year 3	N at risk at start of the year	155 (46.7 %)	902 (90.6 %)	155 (46.7 %)	902 (90.6 %)
	Cost of admissions	44.5 (183.3)	11.3 (48.9)	7676.5 (15,181.3)	2815.1 (8465.0)
	Cost of outpatient visits	10.5 (29.2)	4.1 (14.2)	3089.6 (8320.8)	1376.3 (4664.7)
	Cost of medications	1.7 (2.3)	0.9 (1.5)	594.5 (823.5)	323.3 (519.2)
	Total costs	**56.7 (193.2)***	**16.3 (52.9)**	**11,360.5 (19,634.7)***	**4514.7 (10,717.3)**
Year 4	N at risk at start of the year	136 (41.0 %)	850 (85.3 %)	136 (41.0 %)	850 (85.3 %)
	Cost of admissions	27.3 (57.6)	14.4 (128.8)	7831.4 (15,308.8)	3112.1 (9216.4)
	Cost of outpatient visits	8.7 (28.0)	5.0 (18.0)	2869.2 (9700.9)	1623.0 (5211.3)
	Cost of medications	1.9 (2.3)	1.0 (1.4)	623.9 (809.7)	347.6 (493.0)
	Total costs	**37.8 (71.1)***	**20.4 (132.5)**	**11,324.5 (20,853.5)***	**5082.7 (11,553.7)**
Year 5	N at risk at start of the year	113 (34.0 %)	811 (81.4 %)	113 (34.0 %)	811 (81.4 %)
	Cost of admissions	25.0 (56.5)	11.9 (57.6)	5099.6 (11,140.4)	3050.5 (8894.1)
	Cost of outpatient visits	7.3 (17.8)	4.5 (16.8)	1883.4 (3520.4)	1540.1 (5966.2)
	Cost of medications	1.9 (2.2)	1.0 (1.5)	566.4 (696.4)	363.4 (541.0)
	Total costs	**34.2 (67.3)***	**17.4 (62.2)**	**7549.4 (13,541.5)***	**4954.0 (11,814.5)**
Year 6	N at risk at start of the year	91 (27.4 %)	765 (76.8 %)	91 (27.4 %)	765 (76.8 %)
	Cost of admissions	21.3 (52.8)	10.6 (36.6)	5683.6 (12,694.1)	2803.3 (7568.7)
	Cost of outpatient visits	7.1 (12.7)	3.7 (10.9)	2417.6 (4575.7)	1294.7 (3884.0)
	Cost of medications	1.7 (2.1)	1.1 (1.6)	594.1 (773.3)	371.1 (553.3)
	Total costs	**30.1 (57.5)***	**15.4 (40.2)**	**8695.3 (14,437.7)***	**4469.0 (9372.0)**

The table shows the mean (standard deviation) costs of admissions, outpatient visits, medications, and in total for subjects with VF on the CT scan vs the general population cohort. Also shown is the number of subjects at risk at the beginning of each year of follow-up. Data are stratified according to year of follow-up (baseline year is the last full year before the date of the CT scan). Costs are shown as 1) mean costs per day at risk (left column), where individual-level costs have been split across the number of days at risk in the respective year; 2) mean costs per year for subjects alive at the beginning of the respective year, irrespective of the number of days at risk (right column). Costs are indexed to January 2022, and given in US dollars.
Differences between the cohorts in mean total costs – per day at risk and per year, respectively – evaluated by linear mixed-effects models: *$p < 0.001$. If no asterisk, results are not significant at the $p < 0.05$-level.
CT, computed tomography: GP, general population; SD, standard deviation; USD, US dollars; VF, vertebral fracture.

calendar years according to the year of baseline. Within the *analysis population* (Table 4a), these costs were numerically higher in the VF cohort from the calendar year before the baseline year and until year 4. For year 5, the costs were higher in the no VF cohort, while the costs were similar in year 6. There were no statistically significant differences between the cohorts in any year, nor in the overall assessment ($p = 0.75$).

In the *scaling analysis population* (Table 4b) the primary healthcare costs were significantly higher in VF cohort as compared to the general population cohort for all years, and for the overall assessment ($p < 0.001$).

4. Discussion

In these analyses of the healthcare costs of subjects with VF available on routine CT scans, we found that costs were similar on an overall year-by-year basis as compared to those with no VF on the CT scan, but substantially higher in the first years after the CT scan when taking time at risk into account. However, these differences did not reach statistical significance, and after 3 years follow-up the numerical differences had disappeared. When compared to an age- and sex-matched general population cohort, significant cost differences were observed, with the VF cohort showing substantially higher healthcare costs at baseline and throughout all years of follow-up.

Interestingly, our data show that primary healthcare costs were relatively stable over time across all cohorts. Furthermore, the total healthcare costs in the general population cohort were stable or only slightly increasing over time. In stark contrast, the total healthcare costs of subjects in the VF on CT scan and no VF on CT scan cohorts both decreased substantially over time. We expect that this could be due to several effects: The disease(s) leading to a CT scan are associated with high direct costs and once this disease has been treated, the derived healthcare effects and costs are generally small and decreasing over time. The other potential explanation is that those individuals driving healthcare costs are those who are most sick, and thus at highest risk of dying; i.e., a healthy survivor effect, with those living longer also accruing lower healthcare costs. This explanation is consistent with previous reports that healthcare costs increase substantially towards the time of death [33].

Most studies of healthcare resource utilization and costs in VF patients have focused on clinical VFs, and these consistently show increased healthcare costs as compared to subjects with no fracture

Table 4
Mean (SD) primary healthcare sector costs.

Panel a	Analysis population		
	VF on CT scan	No VF on CT scan	p-value
Year before baseline year	643.8 (785.8)	594.4 (608.6)	0.78
Baseline year	775.1 (858.4)	683.7 (629.1)	0.20
Year 1	661.5 (761.2)	611.0 (567.2)	0.93
Year 2	712.8 (969.5)	586.7 (548.4)	0.46
Year 3	711.1 (854.5)	591.7 (573.2)	0.15
Year 4	639.9 (734.5)	629.4 (584.9)	0.86
Year 5	572.2 (497.1)	666.1 (677.9)	0.91
Year 6	654.0 (716.0)	651.2 (668.4)	0.35
Panel b	Scaling analysis population		
	VF on CT scan	General population cohort	p-value
Year before baseline year	639.6 (775.4)	489.8 (666.0)	<0.01
Baseline year	768.3 (846.2)	521.4 (662.9)	<0.01
Year 1	666.2 (749.6)	534.2 (780.1)	<0.01
Year 2	709.0 (955.9)	524.9 (721.8)	<0.01
Year 3	699.9 (845.1)	498.3 (603.1)	<0.01
Year 4	637.4 (727.8)	533.2 (645.4)	0.03
Year 5	568.6 (493.5)	537.9 (619.1)	0.04
Year 6	645.6 (710.2)	545.4 (635.5)	<0.01

This table shows the mean (SD) primary healthcare sector costs in the *analysis population* (subjects with VF on CT scan vs subjects with no VF on CT scan) in panel a, and the *scaling analysis population* (subjects with VF on CT scan vs the general population cohort) in panel b. Costs are indexed to January 2022, and given in USD. They are stratified according to calendar year in respect to the year of the CT scan (in the general population cohort, this is the CT scan of the matched case).
Differences between the cohorts evaluated by linear mixed-effects models.
CT, computed tomography; SD, standard deviation; USD, US dollars; VF, vertebral fracture.

[13–17]. When stratified according to time period of follow-up, total as well as incremental costs are generally highest early after the VF and subsequently decline; none of these studies, however, adjusted for time at risk on a per-day basis [13,16]. This observation of declining costs over time is – as discussed above – similar to our findings, and we extend these observations by also confirming that total healthcare costs decline over time in those with opportunistically identifiable VF and when taking time at risk on a per-day basis into account. Contrary to studies on clinical VFs, we did not find statistically significant differences when comparing the VF and no VF on CT subjects, which is probably due to two things: 1) All subjects in the CT scan cohort have been referred for a CT scan, thus they are likely to have a substantial morbidity burden. In this context, the effect of also having a VF on the CT scan may be less pronounced than when the comparator is a healthier, general population cohort (i.e., referral bias). Indeed, when compared to the general population, substantial cost differences were noted in our study as well. 2) A lack of power, as will be discussed under the limitations section. Despite the lack of statistical significance, it is important to note the numerical differences between the VF and no VF cohorts early after baseline, when taking time at risk into account (*mean costs per day at risk*). This suggests that subjects with VFs may sustain higher healthcare costs, but that differences in cost accrual time masks this when the costs per year are evaluated.

Some of the aforementioned studies also evaluate the respective cost drivers. For example, one study in the UK applying a 12-month post-fracture follow-up showed higher proportions of women with VF with one or more hospitalizations, emergency room visits, GP visits, and specialist visits – and also a higher use of medications – as compared to non-fracture controls. All components contributed to the overall incremental cost of VFs, although predominantly driven by hospitalizations (54 %) and medications (29 %) [13]. A study in Germany of patients with clinical VF, also applying a 1-year post-fracture follow-up, found similar results with hospitalizations (61 %) and medications (28 %) driving the incremental healthcare costs as compared to subjects without VF [15]. Finally, a UK study based on the General Practice Research Database, showed significantly more pre-fracture and post-fracture general practitioner consultations, referrals, and hospital admissions in women with clinical VF as compared to sex-, age- and practice-matched controls. Total incremental costs increased from pre- to post-fracture year, and in the year after the VF, hospital admissions were estimated to account for 91 % of incremental costs when not taking osteoporosis medications into account [17]. Similarly, hospitalizations were the main cost driver in our study, whereas medications only contributed a minority of the costs across all cohorts.

Our study represents the first assessment of the healthcare costs of subjects with opportunistically identifiable vertebral fractures, and additional studies are needed to expand the understanding of this topic. Limitations of this study are first and foremost a potential lack of power. Hence, within the *analysis population*, the mean total costs per day at risk are numerically higher in the VF than the no VF cohort early after baseline, reaching +12 % in year 1, +52 % in year 2, and +44 % in year 3, yet not attaining statistical significance. A large variability in observed costs, as reflected in the relatively large standard deviations, contributes to this issue, and it is plausible that a larger study would have yielded statistically significant differences. Furthermore, as the CT scans were required to show chest and/or lumbar vertebrae, but not necessarily the entire thoracolumbar spine, thoracolumbar VFs outside the CT field of view are possible. If this occurs in the no VF on CT scan cohort, it would lead to misclassification bias which would drive cohort differences in costs due to such VFs towards zero. Also, as for other registry-based studies, local and national coding practices may affect the replicability of the study. And finally, the costs of psychiatric hospitalizations and outpatient visits are not included in this study.

The study has a number of strengths. First of all, the ability to follow all subjects over time on an individual level with information on those who emigrate or die, allowed us to account for time at risk in the calculation of mean healthcare costs; this has, to our knowledge, not been done before for vertebral fractures at such detailed level. Second, the completeness of the Danish registries, covering healthcare costs in both private and public hospitals throughout Denmark, ensures the validity of our results. Third, to ensure the validity of the VF diagnosis, the final diagnostic reading of the CT scans was performed by external, experienced radiologists blinded to clinical information (for details, please see Skjødt et al. [JBMR Plus, 2023]) [27].

In conclusion, subjects who present with VFs on CT scans performed as part of routine care, and who are not treated with osteoporosis medications at the time of the scan, sustain high healthcare costs as compared to the general population, particularly in the short term. When compared to subjects also undergoing CT scans but without prevalent VFs, mean total costs per year were generally similar across the cohorts, while mean total costs *per day at risk* were initially substantially higher though statistically similar. These nonsignificant differences merit further investigations in larger cohorts, as they hint towards substantial incremental healthcare costs in those with opportunistically identifiable VFs. Furthermore, our study highlights that ignoring time at risk may mislead analyses of healthcare costs, an aspect that should be considered in future studies of VFs.

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CRediT authorship contribution statement

Michael Kriegbaum Skjødt: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Joeri Nicolaes:** Data curation, Writing – review & editing. **Christopher Dyer Smith:** Validation, Writing – review & editing. **Cesar Libanati:** Conceptualization, Data curation, Methodology, Writing – review & editing. **Cyrus Cooper:** Methodology, Writing – review & editing. **Kim Rose Olsen:** Conceptualization, Methodology, Writing – review & editing. **Bo Abrahamsen:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

MKS and BA have received support for this study from UCB/Amgen and Region Zealand Health Scientific Research Foundation (research grants with funds paid to the institution); MKS received support from the University of Southern Denmark (PhD scholarship), UCB (educational grant) outside the submitted work, UCB Nordic (personal speakers fee), is a board member of the Danish Bone Society, and a member of working groups in the Danish Bone Society and the European Calcified Tissue Society; JN and CL are employees of UCB Pharma with stock ownership, and JN is involved in a patent (WO2019/106061) and has received support for travel from UCB Pharma; CDS and KRO have no conflicts to report; CC has received personal fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda, and UCB; BA has received personal speakers fees/consulting fees from UCB, Amgen, Kyowa-Kirin, and Pharmacosmos, and institutional research grants (with funds paid to the institution) from Novartis, Kyowa-Kirin, and Pharmacosmos, and is the president of the European Calcified Tissue Society.

Data availability

MKS and CDS had full access to individual-level data of all subjects in this study and performed the data analysis. Sharing of individual-level data hosted with Statistics Denmark is not possible under Danish law.

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