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INCIDENCE AND MORTALITY OF FRACTURES BY FRAILTY LEVEL OVER 80 YEARS OF AGE: COHORT STUDY

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ABSTRACT

Objective: This study aimed to estimate the association of frailty with incidence and mortality of fractures at different sites in people aged over 80 years.

Design: Cohort study.

Setting: UK family practices from 2001 to 2014.

Participants: 265,195 registered participants aged 80 years and older.

Measurements: Frailty status, classified into 'fit', 'mild', 'moderate' and 'severe' frailty. Fractures, classified into non-fragility and fragility, including fractures of femur, pelvis, shoulder and upper arm, and forearm/wrist. Incidence of fracture, and mortality within 90 days, were estimated.

Results: There were 28,643 fractures including: non-fragility fractures, 9,101; femur, 12,501; pelvis, 2,172; shoulder and upper arm, 4,965; and forearm/wrist, 6,315. The incidence of each fracture type was higher in women and increased with frailty category (femur, severe frailty compared to 'fit', IRR 2.4, 2.3 to 2.6). Fractures of the femur (95-99 years compared with 80-84 years, 2.7, 2.6 to 2.9) and pelvis (2.9, 2.5 to 3.3) were strongly associated with age but non-fragility and forearm fractures were not. Mortality within 90 days was greatest for femur fracture (adjusted hazard ratio, HR, compared to forearm fracture 4.3, 3.7 to 5.1). Mortality was higher in men and increased with age (HR, 5.3, 4.3 to 6.5 in those over 100 years old compared to 80-84 years) but was less strongly associated with frailty category.

Conclusions: The incidence of fractures at all sites is strongly associated with advancing frailty and female gender, while fracture mortality is greater in men and is associated with age rather than frailty category.

Key words: fractures, frailty, 80 years and over, mortality, femur neck fracture

Strengths and Limitations

- This study consists of a large, longitudinal and representative sample of older adults aged 80 and over registered in primary care.
- Incidence rates of different types fractures are explored by gender, age group and frailty status.
- We acknowledge that dates of fractures recorded in our study might not be accurate if patients were admitted to hospital and their records at their General Practice might have been updated later.

INTRODUCTION

Fractures in older people are a huge public health challenge as immediate complications and longer-term declines in health status may lead to hospital admissions, increased care needs and a reduction in the quality of life. [1] Previous studies suggest that frailty may be associated with increased risk of fracture, [2-5] but few studies have reported on the incidence of fracture, and mortality following fracture, at different sites.

The frailty syndrome is characterised by dysregulation in multiple body systems resulting in homeostatic imbalances that may eventually lead to adverse outcomes such as falls, fractures, disability, institutionalization, hospitalization and mortality. [2] Several attempts have been made to operationalize the concept of frailty with the most widely-used models including Frailty Phenotype [6], a physical syndrome consisting of five physical characteristics, and Frailty Index [7], which views frailty as an accumulation of deficits. The literal meaning of being frail means to 'break easily' suggesting that frail individuals are more likely to experience fractures.[8] In addition to age-related decline in bone mass, ageing individuals tend to lose stability and are more likely to fall and experience a fracture. [9] Frailty Indices are increasingly used to predict clinical outcomes in older people [10] but associations of frailty with fracture may be partially tautological if falls and fractures are included in the assessment of frailty. [11]

Fragility fractures are those that occur from mechanical forces that do not usually cause a fracture, these are known as low-energy or low-level trauma, such as falls resulting from a standing height. Fragility fractures are often a sign of osteoporosis and common in the elderly and these create problems in activities of daily living, physical function, disability, pain, fear of falling and increased mortality.[12] It has been estimated that the medical costs from fragility fractures in the UK were about £1.8 billion in 2000, with a possible increase to £2.2 billion by 2025. [13]

This study aimed to understand the risk that frailty status poses for fractures at different sites, estimating the association of frailty with both the incidence and mortality associated with fractures at different sites in people aged more than 80 years.

METHODS

Data Source

This study drew on data from the Clinical Practice Research Datalink (CPRD), one of the world's largest databases of primary care electronic health records (EHRs), including approximately 7% of UK general practices, with anonymised data collected from 1990 to present. The registered active population of about 5 million is generally representative of the UK population in terms of age and sex.[14] Data collected into CPRD comprise clinical diagnoses, records of blood pressure and other clinical measurements, prescriptions, results of investigations and referrals to specialist services. The protocol for this study received scientific and ethical approval from the Independent Scientific Advisory Committee for CPRD studies (ISAC Protocol 13_151). The CPRD has broad National Research Ethics Service Committee (NRES) ethics approval for observational research studies.

Study Design and Participants

We drew a random sample of participants who had their 80th, 85th, 90th, 95th and 100th birthdays while registered in CPRD between 1990 and 2014 including a maximum of 50,000 each of men and women, with replacement, in each age group. There were less than 50,000 men and 50,000 women eligible in the older age groups and, after accounting for participants sampled in more than one age-group, the total sample comprised 299,495 participants. Participants entered the analysis at the age they were sampled. To focus on a more recent period, the present analysis was restricted to 265,195 participants, who were registered between 1st January 2001 and 31st December 2009 with latest follow-up at 31st

December 2014. Fracture incidence was calculated in the 265,195 participants in those who had a fracture within the study period. In participants who had the same type of fracture recorded within 12 months of the first fracture, the fracture record was excluded. To calculate the risk of mortality after the first fracture only participants with the first fracture were considered which included 28,643 patients. Individuals with multiple fractures recorded on the same day were excluded which resulted in a cohort of 24,168 participants. Deaths from any cause was determined from CPRD records. The risk of mortality was assessed in participants up to 90 days of the first fracture.

Main Measures

An index of frailty status was calculated for each participant using a previously described electronic Frailty Index (eFI).[11] The eFI was defined based on a cumulative deficit model, which accounts for the number of deficits present in an individual.[15] The original eFI incorporates falls and fractures among 36 deficits. For the present analyses, we omitted falls and fractures from the assessment of frailty, as fractures were the outcome and falls were closely associated with fractures. We also omitted quantitative traits and polypharmacy from the assessment of frailty. The eFI score was calculated by the presence or absence of individual deficits as a proportion of the total possible based on medical diagnoses recorded during the first 12 months of follow-up. Categories of fit, mild, moderate and severe frailty were defined following Clegg et al. [11]

The occurrence of fractures was assessed from records of medical diagnostic codes recorded into patients' electronic health records. We adapted the categorisation used by Torstensson et al. [16] to categorise fractures into 'non-fragility' and 'fragility' fractures. Fragility fractures most commonly occur in the femur, pelvis, shoulder and upper arm, and forearm and wrist. [16, 17] Other fractures which were not coded into this categories were coded as non-fragility fractures. Records of fracture at the same site within a 12-month

period were assumed to refer to a single fracture. Participants with fractures at more than one site recorded on the same date were omitted from the mortality analysis.

Statistical Analysis

Incidence rates (IR) for each type of fracture were estimated using person time for all registered patients as the denominator. Poisson regression was employed to estimate adjusted incidence rate ratios and their confidence intervals. Covariates included site of fracture, gender, age group and frailty status. Mortality within 90 days of the occurrence of a first fracture was estimated in a time-to-event framework as previous evidence has shown the mortality rate after a fracture is highest within 90 days of the fracture. [18]The Cox proportional hazards model was employed to estimate adjusted hazard ratios for mortality within 90 days of fracture by site, age group, gender and frailty status. Statistical analysis was carried out using STATA version 14 and forest plots were constructed using the 'forestplot' package in the R program.

RESULTS

The incidence cohort comprised of 265,195 patients, including 116,394 (43.9%) men and 148,801 (56.1%) women aged 80 years and over between 2001 to 2014. There were 28,643 patients, with 34,896 fractures including: non-fragility, 9,072; femur, 12,408; pelvis, 2,161; shoulder and upper arm, 4,948; and forearm/wrist, 6,307.

Table 1 presents the number of fractures and incidence rates by gender, age-group and frailty category. Rates of fracture were generally higher in women than men, with femur fracture being the most frequent fracture type. The overall incidence of femur fracture in women was 16.5 per 1,000 participant years (95% confidence interval (CI), 16.2 to 16.8).

Pelvic fractures in men were least frequent with a rate of 0.8 (95% CI, 0.7 to 0.9) per 1,000 participant years. The incidence of fracture at each site showed a graded increase with advancing frailty category. The incidence of non-fragility fracture increased from 4.9 (4.6 to 5.1) in 'fit' individuals, to 8.7 (8.4 to 9.0) in 'mild' frailty, 12.6 (12.2 to 13.1) in 'moderate' frailty and 17.7 (16.8 to 18.6) in 'severe' frailty, with similar trends being observed for fragility fractures.

Figure 1 presents adjusted incidence rate ratios (IRR) for each fracture type. The incidence of all types of fractures was higher in women compared to men, with the highest IRRs being for fragility fractures including pelvic fracture (IRR 3.5, 3.1 to 4.0), followed by fractures of forearm/wrist (IRR 3.2). Non-fragility fractures showed a lower IRR of 1.8 (1.7 to 1.9) in women compared to men. The incidence of all types of fractures increased with frailty status. Compared to those in the fit group, those who were severely frail had an IRR for pelvic fracture of 3.7 (3.1 to 4.3) and for non-fragility 3.2 (3.0 to 3.5). The incidence of femur, pelvic and shoulder upper arm fractures increased with age but there was a slight decrease in the incidence of these fractures in the 100+ age group. Fractures of the forearm and wrist and non-fragility fractures showed negligible association with age-group after adjusting for gender and frailty category.

After excluding 44,475 patients with fractures at more than one site on the same date, the mortality cohort consisted of 24,168 participants. There were 2865 deaths (men 934; women 1931) within 90 days of a fracture (Table 2). Mortality was higher in men (14.1%) compared to women (11.5%) irrespective of fracture site. Femur fracture was associated with highest mortality (men 22.4%, women 17.9%) while fractures of the forearm/wrist were associated with lowest mortality (men 4.5%; women 4.2%). A similar trend was seen for all types of fractures. Mortality at all sites was generally only weakly associated with increasing frailty category (fit, 10.6%; severe frailty 13.6%).

The risk of mortality was highest in those who had a femur fracture compared to those who had a forearm/wrist fracture (reference) with a HR of 4.3 and 95% CI (3.7 to 5.1) (Table 3). The risk of mortality was similar in non-fragility (HR=1.8) and shoulder and upper arm (HR=2.3) compared to the reference. Women had a lower risk of mortality compared to men with a HR of 0.7, 95% CI (0.6 to 0.8). The risk of mortality after a fracture increased with age, compared to those who were aged 80-84, those who were aged 100+ had a HR of 5.3, 95% CI (4.3 to 6.5). The risk of mortality after a fracture increased slightly with increase in frailty status although the association was significant only in those who were moderately and severely frail, i.e. compared to those who were fit, those who were severely frail had a HR of 1.2 (95% CI 1.1 to 1.4).

DISCUSSION

Main Findings

In this cohort of people aged 80 years or older, the incidence of fracture is strongly associated with increasing frailty and female gender, while mortality following fracture is generally greater in men and is more strongly associated with age than frailty status. Femur fractures are most frequent and more common in women and these were associated with highest mortality. The incidence of pelvis fracture was also higher in women and increased with age and frailty status. A similar trend was observed with a shoulder upper arm and femur fractures. The incidence of forearm/wrist fracture incidence was low and was significantly lower in those who were aged 100 years and over. The risk of mortality in those who had a fracture increased with age and the trend was seen for all types of fractures. A similar association was seen with increase in frailty status.

Strengths and Limitations

The study has several strengths, including a large, longitudinal and nationally representative sample of the general population registered in primary care. We calculated incidence rates of fracture using the first occurrence of a single type of fracture in any study year. Repeat records of fractures of the same type in the same year were omitted as it is possible that duplicate information about the same event might have been recorded in CPRD. However, this might lead to slight underestimation of true incidence rates. Fractures sites might sometimes be miscoded, although previous data suggest that records of hip and vertebral fractures are valid in CPRD. [19] It is also possible there were errors in the date of fracture recorded, if patients were admitted to hospital and GP records updated later. We caution that a clear distinction cannot always be made between ‘fragility’ and ‘non-fragility’ fractures

because either type of fracture may occur at the same site. In order to facilitate comparison with previous research, we adopted a classification reported in a previous study.[16]

Comparison with other studies

Previous studies generally show that the incidence of fractures is higher in women than in men.[20-25]. Requena et al,[26] compared the incidence rates and trends of fractures in 5 European countries (Denmark, Germany, Netherlands, Spain and U.K.) using electronic healthcare record databases. They showed that the incidence of hip and femur fractures increased rapidly with age in both men and women. Although their data did not explore the 100+ age group, our findings suggest a reduction in incidence for both pelvic and femur fractures at the oldest ages. A study of osteoporotic fractures in women showed that frailty was significantly associated with hip fractures, but only weakly associated with fractures at other sites which was inconsistent with our findings. [22] Differences in the assessment of frailty might account for this difference. Associations of frailty including weight loss [23], inflammation [24] sarcopenia [25], hormones [26], cognitive decline and depression [27] might contribute towards the increased incidence of fractures seen in frail individuals. Previous studies suggest that 20% of patients with a hip fracture die within one year.[27, 28][29] Mortality risk after fracture has been associated with age, location of fracture, and gender with males having a higher risk of mortality after a fracture.[1]

Conclusion

Our results show that the incidence of fractures increases with frailty level. Mortality within 90 days of the fracture was less strongly associated with frailty status. Mortality after fracture may be associated with comorbidities that were included in frailty assessment.[30] This research highlights the need to identify fracture prevention strategies. [26] [31, 32] and to improve fracture care management by orthopaedic surgeons and geriatricians in order to optimize the outcomes in frail older adults.[33] [34]

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Footnotes

Contributors RR designed, contributed to data analysis and drafted the paper. MCG supervised and assisted with draft and conclusions. JC contributed to data analysis. NC, SJ and AD contributed to the write up and conclusions. All authors read and approved the final manuscript.

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Competing interests None.

Data sharing statement Data ownership belongs to CPRD, data sharing is not possible.

Table 1: Number and incidence of fractures by fracture site, gender, age group and Frailty status.

Gender		Person Years	Non-Fragility	Femur	Pelvis	Shoulder Upper Arm	Forearm/Wrist
Male	N	421818.9	2624	3318	344	1331	1191
	Incidence [a]		6.2 (6.0 to 6.5)	7.8 (7.6 to 8.1)	0.8(0.7 to 0.9)	3.2 (3.0 to 3.3)	2.8 (2.7 to 3.0)
Female	N	550969.4	6448	9090	1817	3617	5116
	Incidence		11.7 (11.4 to 12.0)	16.5 (16.2 to 16.8)	3.3 (3.2 to 3.5)	6.6 (6.4 to 6.8)	9.3 (9.0 to 9.5)
Age group							
80-84	N	288407.8	2230	1952	303	1034	1615
	Incidence		7.7 (7.4 to 8.1)	6.8 (6.5 to 7.1)	1.1 (0.9 to 1.2)	3.6 (3.4 to 3.8)	5.6 (5.3 to 5.9)
85-89	N	331587.1	3096	3915	652	1647	2113
	Incidence		9.3 (9.0 to 9.7)	11.8 (11.4 to 12.2)	2.0 (1.8 to 2.1)	5.0 (4.7 to 5.2)	6.4 (6.1 to 6.7)
90-94	N	240064.2	2492	4030	727	1447	1715
	Incidence		10.4 (10.0 to 10.8)	16.8 (16.3 to 17.3)	3.0 (2.8 to 3.3)	6.0 (5.7 to 6.3)	7.1 (6.8 to 7.5)
95-99	N	94364.96	1083	2199	413	698	766
	Incidence		11.5 (10.8 to 12.2)	23.3 (22.3 to 24.3)	4.4 (4.0 to 4.9)	7.4 (6.9 to 8.0)	8.1 (7.6 to 8.7)
>100	N	18364.2	171	312	66	122	98
	Incidence		9.3 (8.0 to 10.8)	17.0 (15.2 to 19.0)	3.6 (2.8 to 4.5)	6.6 (5.5 to 7.9)	5.3 (4.4 to 6.5)
Frailty Category							
Fit	N	275917.6	1342	2016	274	914	1194
	Incidence		4.9 (4.6 to 5.1)	7.3 (7.0 to 7.6)	1.0 (.9 to 1.1)	3.3 (3.1 to 3.5)	4.3 (4.1 to 4.6)
Mild	N	378914.6	3292	4678	770	1800	2363
	Incidence		8.7 (8.4 to 9.0)	12.4 (12.0 to 12.7)	2.0 (1.9 to 2.2)	4.8 (4.5 to 5.0)	6.2 (6.0 to 6.5)
Moderate	N	233570.6	2946	3911	709	1506	1898
	Incidence		12.6 (12.2 to 13.1)	16.7 (16.2 to 17.3)	3.0 (2.8 to 3.3)	6.5 (6.1 to 6.8)	8.1 (7.8 to 8.5)
Severe	N	84385.52	1492	1803	408	728	852
	Incidence		17.7 (16.8 to 18.6)	21.4 (20.4 to 22.4)	4.8 (4.4 to 5.3)	8.6 (8.0 to 9.3)	10.1 (9.4 to 10.8)

[a] incidence rates are per 1,000 person years (95% confidence interval)

Figure 1 : Incident Rate Ratio for fractures by site, gender, age group and frailty status. Estimates are adjusted for each variable shown.

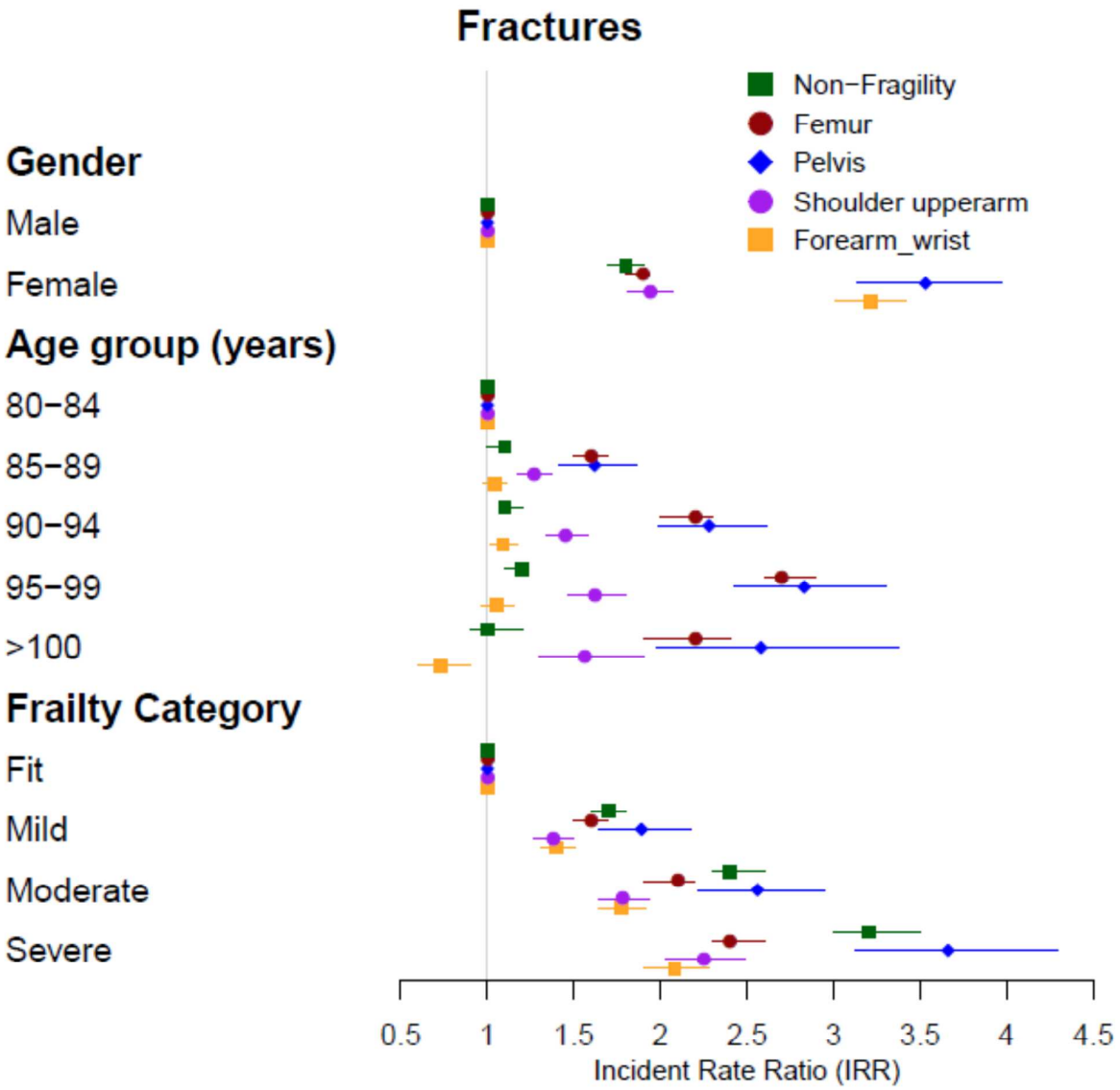


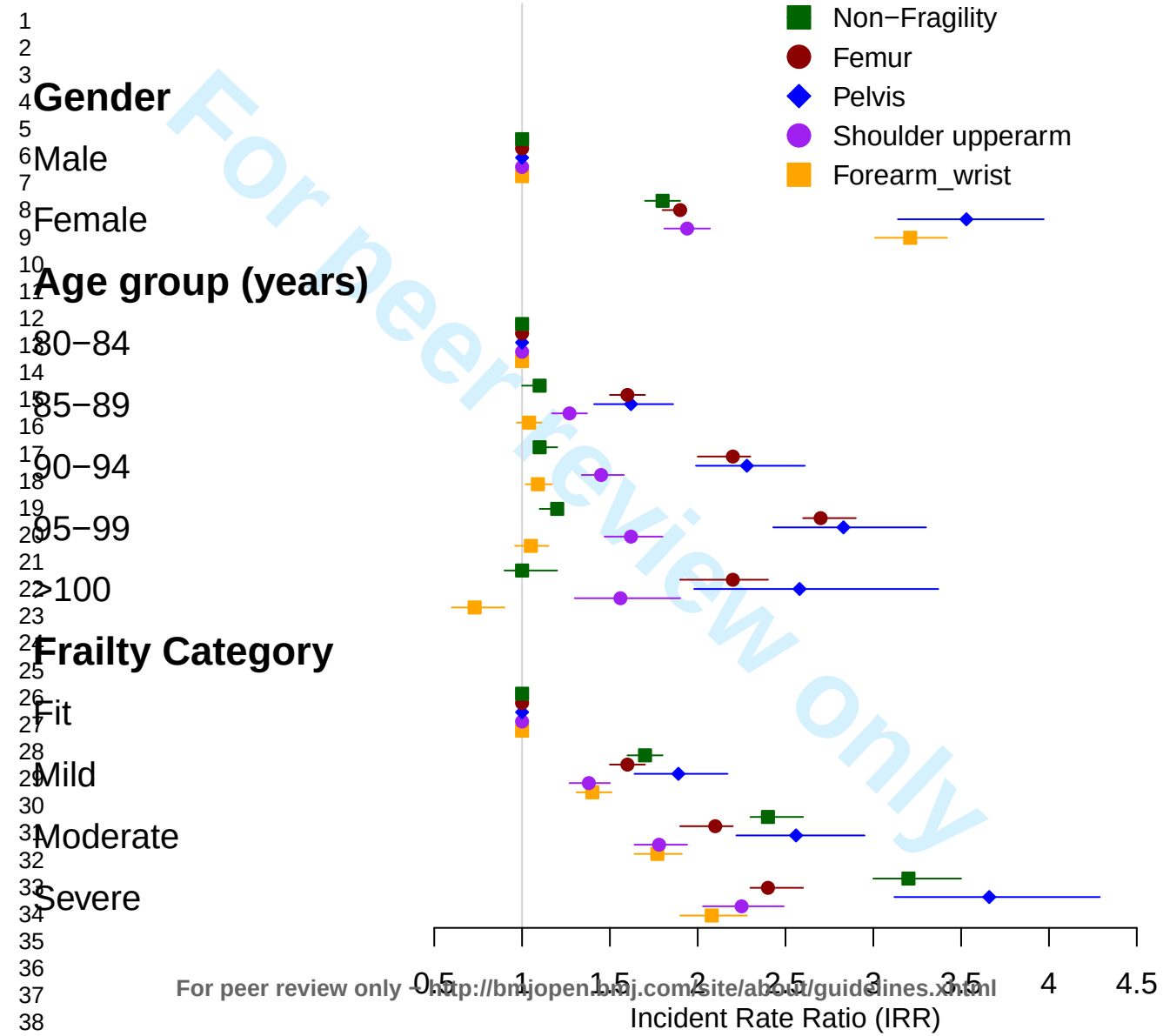
Table 2: 90-day mortality by site of fracture and by gender, age group and frailty status. Figures are number of deaths. Mortality rate (%), 95% confidence interval.

	ALL	Non-Fragility	Femur	Pelvis	Shoulder Upper Arm	Forearm/Wrist
	Dead N, Failure Rate % (95% Confidence Interval)					
Gender						
Male	934	159	591	32	112	40
	14.1 (13.3 to 15.0)	8.2 (7.0 to 9.5)	22.4 (20.9 to 24.0)	15.0 (10.8 to 20.5)	12.2 (10.3 to 14.5)	4.5 (3.3 to 6.1)
Female	1931	305	1156	131	208	131
	11.5 (11.0 to 11.9)	7.5 (6.8 to 8.4)	17.9 (17.0 to 18.9)	12.5 (10.7 to 14.7)	9.6 (8.5 to 11.0)	4.2 (3.5 to 4.9)
Age group						
80-84	268	51	168	8	25	16
	5.5 (4.9 to 6.1)	3.3 (2.5 to 4.3)	11.7 (10.2 to 13.5)	4.4 (2.2 to 8.7)	3.9 (2.6 to 5.7)	1.5 (0.9 to 2.4)
85-89	721	134	421	38	85	43
	9.5 (8.9 to 10.2)	6.6 (5.6 to 7.8)	14.9 (13.6 to 16.2)	9.9 (7.3 to 13.3)	8.4 (6.8 to 10.3)	3.3 (2.4 to 4.4)
90-94	1028	166	617	63	113	69
	14.6 (13.8 to 15.4)	10.1 (8.8 to 11.7)	20.7 (19.3 to 22.2)	14.9 (11.8 to 18.7)	12.4 (10.4 to 14.7)	6.3 (5.0 to 7.9)
95-99	715	91	455	48	83	38
	20.8 (19.4 to 22.2)	13.6 (11.2 to 16.4)	28.1 (26.0 to 30.4)	20.0 (15.4 to 25.6)	18.9 (15.5 to 22.8)	8.1 (5.9 to 10.9)
>100	133	22	86	6	14	5
	28.4 (24.5 to 32.7)	22.4 (15.3 to 32.0)	38.7 (32.6 to 45.5)	20.3 (9.6 to 39.8)	20.4 (12.6 to 32.0)	10.1 (4.3 to 22.6)
Frailty Category						
Fit	430	61	275	22	46	26
	10.6 (9.7 to 11.6)	6.6 (5.2 to 8.4)	18.1 (16.2 to 20.1)	13.5 (9.1 to 19.7)	7.5 (5.7 to 9.9)	3.2 (2.2 to 4.7)
Mild	1064	178	658	53	120	55
	12.0 (11.3 to 12.7)	8.0 (7.0 to 9.3)	18.8 (17.5 to 20.1)	11.4 (8.9 to 14.7)	10.5 (8.9 to 12.4)	3.6 (2.8 to 4.6)
Moderate	920	149	554	54	104	59
	12.7 (12.0 to 13.5)	7.8 (6.7 to 9.1)	19.7 (18.3 to 21.2)	14.9 (11.8 to 18.7)	11.6 (9.7 to 13.9)	5.0 (3.9 to 6.4)
Severe	451	76	260	34	50	31
	13.6 (12.4 to 14.8)	8.2 (6.6 to 10.1)	20.8 (18.6 to 23.2)	15.3 (11.2 to 20.8)	11.9 (9.1 to 15.3)	6.2 (4.4 to 8.8)

Table 3: Hazard ratios 90 -day mortality after their fracture by fracture type, gender, age group and frailty status.

	N	Dead	HR (95 % Confidence Intervals)	p value
Non-Fragility	6,132	464	1.8 (1.5 to 2.13)	<0.001
Femur	9,409	1747	4.3 (3.7 to 5.06)	<0.001
Pelvis	1,328	163	2.8 (2.2 to 3.41)	<0.001
Shoulder Upper arm	3,166	320	2.3 (1.9 to 2.79)	<0.001
Forearm Wrist	4,133	171	**Reference**	
Gender				
Male	6,788	934	**Reference**	
Female	17,380	1,931	0.7 (0.6 to 0.8)	<0.001
Age Group				
80-84	5,010	268	**Reference**	
85-89	7,795	721	1.6 (1.4 to 1.8)	<0.001
90-94	7,290	1,028	2.4 (2.1 to 2.7)	<0.001
95-99	3,585	715	3.7 (3.2 to 4.2)	<0.001
>100	488	133	5.3 (4.3 to 6.5)	<0.001
Frailty Category				
Fit	4,155	430	**Reference**	
Mild	9,114	1,064	1.1 (1.0 to 1.2)	0.148
Moderate	7,468	920	1.1 (1.0 to 1.3)	0.028
Severe	3,431	451	1.2 (1.1 to 1.4)	0.003

Fractures



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1, line 2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2, line 2-22**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 4, line 3-25**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 5, lines 1-3**
Methods		
Study design	4	Present key elements of study design early in the paper **Pages 5-6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Pages 5-6**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Pages 5-7**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed Page 6, lines 1-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 5-7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Pages 5-7**
Bias	9	Describe any efforts to address potential sources of bias **Page 6, lines 13-17**
Study size	10	Explain how the study size was arrived at **Page 5, (lines 20-27), Page 6 (lines 1-8)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why: **Page 7 ,(lines 5-14)**
Statistical methods	12	Describe all statistical methods, including those used to control for confounding **Page 7 ,(lines 5-14)**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 7 ,(lines 5-14)**
		(*c*) Explain how missing data were addressed **Page 7 ,(lines 5-14)**

	(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
	(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 7, lines 17-20**
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 7, lines 21-24**
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)**Page 7**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Page 7, Table 1 and Figure 1**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. **Page 8-9**
		(*b*) Report category boundaries when continuous variables were categorized **Page 6, lines 19-20**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 10, lines 3-10**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 10, lines 15-24, page 11 lines 1-2**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 11, lines 20-24**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 10**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 15, line 6**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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INCIDENCE AND MORTALITY OF FRACTURES BY FRAILTY LEVEL OVER 80 YEARS OF AGE: COHORT STUDY USING UK ELECTRONIC HEALTH RECORDS

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INCIDENCE AND MORTALITY OF FRACTURES BY FRAILTY LEVEL OVER 80 YEARS OF AGE: COHORT STUDY USING UK ELECTRONIC HEALTH RECORDS

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Short title: Fracture incidence and mortality

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	Abstract	268 words
	Text	2796 words
	Tables	5
	Figures	3

ABSTRACT

Objective: This study aimed to estimate the association of frailty with incidence and mortality of fractures at different sites in people aged over 80 years.

Design: Cohort study.

Setting: UK family practices from 2001 to 2014.

Participants: 265,195 registered participants aged 80 years and older.

Measurements: Frailty status, classified into 'fit', 'mild', 'moderate' and 'severe' frailty. Fractures, classified into non-fragility and fragility, including fractures of femur, pelvis, shoulder and upper arm, and forearm/wrist. Incidence of fracture, and mortality within 90 days and one year, were estimated.

Results: There were 28,643 fractures including: non-fragility fractures, 9,101; femur, 12,501; pelvis, 2,172; shoulder and upper arm, 4,965; and forearm/wrist, 6,315. The incidence of each fracture type was higher in women and increased with frailty category (femur, severe frailty compared to 'fit', IRR 2.4, 2.3 to 2.6). Fractures of the femur (95-99 years compared with 80-84 years, 2.7, 2.6 to 2.9) and pelvis (2.9, 2.5 to 3.3) were strongly associated with age but non-fragility and forearm fractures were not. Mortality within 90 days was greatest for femur fracture (adjusted hazard ratio, HR, compared to forearm fracture 4.3, 3.7 to 5.1). Mortality was higher in men and increased with age (HR, 5.3, 4.3 to 6.5 in those over 100 years old compared to 80-84 years) but was less strongly associated with frailty category. Similar associations with fractures were seen at one-year mortality.

Conclusions: The incidence of fractures at all sites was higher in women and strongly associated with advancing frailty status, while the risk of mortality after a fracture was greater in men and was associated with age rather than frailty category.

Key words: fractures, frailty, 80 years and over, mortality, femur neck fracture

INTRODUCTION

Fractures in older people are a huge public health challenge as immediate complications and longer-term declines in health status may lead to hospital admissions, increased care needs and a reduction in the quality of life.[1] Previous studies suggest that frailty may be associated with increased risk of fracture, [2-5] but few studies have reported on the incidence of fracture, and mortality following fracture, at different sites.

The frailty syndrome is characterised by dysregulation in multiple body systems resulting in homeostatic imbalances that may eventually lead to adverse outcomes such as falls, fractures, disability, institutionalization, hospitalization and mortality. [2] Several attempts have been made to operationalize the concept of frailty with the most widely-used models including Frailty Phenotype, [6] a physical syndrome consisting of five physical characteristics, and Frailty Index ,[7] which views frailty as an accumulation of deficits. The literal meaning of being frail means to 'break easily' suggesting that frail individuals are more likely to experience fractures.[8] In addition to age-related decline in bone mass, ageing individuals tend to develop balance and gait problems and are more likely to fall and experience a fracture. [9] Frailty Indices are increasingly used to predict clinical outcomes in older people [10] but associations of frailty with fracture may be partially tautological if falls and fractures are included in the assessment of frailty. [11]

Fragility fractures are those that occur from mechanical forces that do not usually cause a fracture, these are known as low-energy or low-level trauma, such as falls resulting from a standing height. Fragility fractures are often a sign of osteoporosis and common in the elderly and these create problems in activities of daily living, physical function, disability, pain, fear of falling and increased mortality. [12] It has been estimated that the medical costs from fragility fractures in the UK were about £1.8 billion in 2000, with a possible increase to £2.2 billion by 2025. [13]

This study aimed to add to our understanding of the effect of frailty on patients with fractures are different sites. We aimed to evaluate the risk that frailty status poses for fractures at different sites, estimating the association of frailty with both the incidence and mortality associated with fractures at different sites in people aged more than 80 years.

METHODS

Data Source

This study drew on data from the Clinical Practice Research Datalink (CPRD), one of the world's largest databases of primary care electronic health records (EHRs), including approximately 7% of UK general practices, with anonymised data collected from 1990 to present. The registered active population of about 5 million is generally representative of the UK population in terms of age and sex. [14] Data collected into CPRD comprise clinical diagnoses, records of blood pressure and other clinical measurements, prescriptions, results of investigations and referrals to specialist services. The protocol for this study received scientific and ethical approval from the Independent Scientific Advisory Committee for CPRD studies (ISAC Protocol 13_151). The CPRD has broad National Research Ethics Service Committee (NRES) ethics approval for observational research studies.

Study Design and Participants

We drew a random sample of participants who had their 80th, 85th, 90th, 95th and 100th birthdays while registered in CPRD between 1990 and 2014 including a maximum of 50,000 each of men and women, with replacement, in each age group. There were less than 50,000 men and 50,000 women eligible in the older age groups and, after accounting for participants sampled in more than one age-group, the total sample comprised 299,495 participants. Participants entered the analysis at the age they were sampled. To focus on a more recent period, the present analysis was restricted to 265,195 participants, who were

registered between 1st January 2001 and 31st December 2009 with latest follow-up at 31st December 2014. Fracture incidence was calculated in the 265,195 participants in those who had a fracture within the study period. In participants who had the same type of fracture recorded within 12 months of the first fracture, the fracture record was excluded. To calculate the risk of mortality after the first fracture only participants with the first fracture were considered which included 28,643 patients. Individuals with multiple fractures recorded on the same day were excluded which resulted in a cohort of 24,168 participants. Deaths from any cause was determined from CPRD records. The risk of mortality was assessed in participants up to 90 days and one year of the first fracture.

Main Measures

An index of frailty status was calculated for each participant using a previously described electronic Frailty Index (eFI).[11] The eFI was defined based on a cumulative deficit model, which accounts for the number of deficits present in an individual.[15] The eFI is calculated based on the assessment of 36 potential deficits as reported by Clegg et al.[11] For the present analyses, we omitted falls and fractures from the assessment of frailty, as fractures were the outcome and falls were closely associated with fractures. We also omitted quantitative traits and polypharmacy from the assessment of frailty. The eFI score was calculated by the presence or absence of individual deficits as a proportion of the total possible based on medical diagnoses recorded during the first 12 months of follow-up. Categories of fit, mild, moderate and severe frailty were defined following Clegg et al. [11]

The occurrence of fractures was assessed from records of medical diagnostic codes recorded into patients' electronic health records. We adapted the categorisation used by Torstensson et al. [16] to categorise fractures into 'non-fragility' and 'fragility' fractures. Fragility fractures most commonly occur in the femur, pelvis, shoulder and upper arm, and forearm and wrist. [16 17] Other fractures which were not coded into these categories were coded as

non-fragility fractures. Records of fracture at the same site within a 12-month period were assumed to refer to a single fracture. Participants with fractures at more than one site recorded on the same date were omitted from the mortality analysis.

Statistical Analysis

Incidence rates (IR) for each type of fracture were estimated using person time for all registered patients as the denominator. Poisson regression was employed to estimate adjusted incidence rate ratios and their confidence intervals. Covariates included site of fracture, gender, age group and frailty status. Mortality within 90 days of the occurrence of a first fracture was estimated in a time-to-event framework as previous evidence has shown the mortality rate after a fracture is highest within 90 days of the fracture. [18] We also explored one-year mortality after a fracture. The Cox proportional hazards model was employed to estimate adjusted hazard ratios for mortality within 90 days and one year of fracture by site, age group, gender and frailty status. Statistical analysis was carried out using STATA version 14 and forest plots were constructed using the 'forestplot' package in the R program.

RESULTS

The incidence cohort comprised of 265,195 patients, including 116,394 (43.9%) men and 148,801 (56.1%) women aged 80 years and over between 2001 to 2014. There were 28,643 patients, with 34,896 fractures including: non-fragility, 9,072; femur, 12,408; pelvis, 2,161; shoulder and upper arm, 4,948; and forearm/wrist, 6,307.

Table 1 presents the number of fractures and incidence rates by gender, age-group and frailty category. Rates of fracture were generally higher in women than men, with femur fracture being the most frequent fracture type. The overall incidence of femur fracture in women was 16.5 per 1,000 participant years (95% confidence interval (CI), 16.2 to 16.8). Pelvic fractures in men were least frequent with a rate of 0.8 (95% CI, 0.7 to 0.9) per 1,000 participant years. The incidence of fracture at each site showed a graded increase with advancing frailty category. The incidence of non-fragility fracture increased from 4.9 (4.6 to 5.1) in 'fit' individuals, to 8.7 (8.4 to 9.0) in 'mild' frailty, 12.6 (12.2 to 13.1) in 'moderate' frailty and 17.7 (16.8 to 18.6) in 'severe' frailty, with similar trends being observed for fragility fractures.

Figure 1 presents adjusted incidence rate ratios (IRR) for each fracture type by gender. The incidence of all types of fractures was higher in women compared to men, with the highest IRRs being for fragility fractures including pelvic fracture (IRR 3.5, 3.1 to 4.0), followed by fractures of forearm/wrist (IRR 3.2). Non-fragility fractures showed a lower IRR of 1.8 (1.7 to 1.9) in women compared to men. Figure 2 represents adjusted IRR by age group and Figure 3 presents IRR by frailty status. The incidence of each type of fracture increased with frailty status. Compared to those in the fit group, those who were severely frail had an IRR for pelvic fracture of 3.7 (3.1 to 4.3) and for non-fragility 3.2 (3.0 to 3.5). The incidence of femur, pelvic and shoulder upper arm fractures increased with age but there was a slight decrease in the incidence of these fractures in the 100+ age group. Fractures of the forearm and wrist and non-fragility fractures showed negligible association with age-group after adjusting for gender and frailty category.

After excluding 4,475 patients with fractures at more than one site on the same date, the mortality cohort consisted of 24,168 participants. There were 2,865 deaths (men 934;

women 1931) within 90 days of a fracture (Table 2). Mortality was higher in men (14.1%) compared to women (11.5%) irrespective of fracture site. Femur fracture was associated with highest mortality (men 22.4%, women 17.9%) while fractures of the forearm/wrist were associated with lowest mortality (men 4.5%; women 4.2%). A similar trend was seen for all types of fractures. Mortality at all sites was generally only weakly associated with increasing frailty category (fit, 10.6%; severe frailty 13.6%).

The risk of mortality after 90 days of fracture was highest in those who had a femur fracture, compared to those who had a forearm/wrist fracture as reference, with a HR of 4.3 (95% CI 3.7 to 5.1) (Table 3). The risk of mortality was similar in those who had a non-fragility fracture (HR=1.8) and shoulder and upper arm fracture (HR=2.3) compared to reference. Women had a lower risk of mortality after fracture compared to men with a HR of 0.7 (0.6 to 0.8). The risk of mortality after a fracture increased with age. Compared to those who were aged 80-84, those who were aged 100+ had a HR of 5.3 (4.3 to 6.5). The risk of mortality after a fracture increased slightly with increase in frailty status although the association was significant only in those who were moderately and severely frail, i.e. compared to those who were fit, those who were severely frail had a HR of 1.2 (95% CI 1.1 to 1.4). Similar associations with mortality were observed after one year after a fracture, (see table 4 and 5).

DISCUSSION

Main Findings

In people aged 80 years or older, the incidence of fracture is strongly associated with increasing frailty and female gender, while mortality following fracture is generally greater in men and is more strongly associated with age than frailty status. Femur fractures are most frequent and more common in women and these were associated with highest mortality. The incidence of pelvis fracture was also higher in women and increased with age and frailty status. A similar trend was observed with a shoulder upper arm and femur fractures. The incidence of forearm/wrist fracture incidence was low and was significantly lower in those who were aged 100 years and over. The risk of mortality in those who had a fracture increased with age and the trend was seen for all types of fractures. A similar association was seen with increase in frailty status.

Strengths and Limitations

The study has several strengths, including a large, longitudinal and nationally representative sample of the general population registered in primary care. Previous research on CPRD data have validated the conditions recorded in CPRD and it has been suggested the findings to be generalized to the UK population. [19 20] We calculated incidence rates of fracture using the first occurrence of a single type of fracture in any study year. Repeat records of fractures of the same type in the same year were omitted as it is possible that duplicate information about the same event might have been recorded in CPRD. However, this might lead to slight underestimation of true incidence rates. Fracture sites might sometimes be miscoded, although previous data suggest that records of hip and vertebral fractures are valid in CPRD. [21] It is also possible there were errors in the date of fracture recorded, if patients were admitted to hospital and GP records updated later. We caution that a clear distinction cannot

always be made between 'fragility' and 'non-fragility' fractures because either type of fracture may occur at the same site. In order to facilitate comparison with previous research, we adopted a classification reported in a previous study. [16] We did not explore utilisation of preventive medical interventions for osteoporosis as this was beyond the scope of our study. We also did not have information on the type of medical care and rehabilitation services or hospital site at which individuals were treated, which might be associated with outcomes following a fracture. These merit investigation in future studies.

Comparison with other studies

Previous studies show that the incidence of fractures is higher in women than in men. [22-24] A previous study in a cohort based in Leicestershire also showed that the incidence of all fractures increased with age but the study included participants of all ages with individuals aged 85 and over grouped together. [25] The incidence of forearm fractures has been reported to be higher in women [24 26 27]. In UK adults aged 50 years and over the incidence of radius/ulna fractures were higher in women. In the period between 1990 and 2012, the incidence of forearm fractures remained stable in men but decreased in women. [28] Requena et al, [29] compared the incidence rates and trends of fractures in 5 European countries (Denmark, Germany, Netherlands, Spain and U.K.) using electronic healthcare record databases. They showed that the incidence of hip and femur fractures increased exponentially with age for both men and women. Although their data didn't explore the 100+ age group, our findings showed a reduction in incidence for both pelvic and femur fractures in this age group. The study of osteoporotic fractures in women showed that frailty was significantly associated with hip fractures but only weakly related to other types of fractures which was different to our findings. It may be possible these differences in the findings may be due to the fact frailty was assessed by a frailty phenotype model and the cohort being women aged 65-79 years, might be a few reasons for the discrepancies. [22] Factors associated with frailty such as weight loss, [23] inflammation [24] sarcopenia, [25] hormones,

[26] cognitive decline and depression [27] maybe contributing towards the increased incidence of fractures seen in frail individuals.

Previous studies suggest that 20% of patients with a hip fracture die within one year. [30 31] Our findings of men having higher mortality for all types of fractures was consistent with the findings in the Dubbo Osteoporosis Epidemiology Study, which showed that men who were >=60 years who had a fracture of any type had a higher risk of age standardized mortality than women. [32] Similar results of an increased mortality risk after a fracture has been shown in other studies with the risk of mortality associated with age, location of fracture, and gender with males having a higher risk of mortality after a fracture. [1] Our results show a higher incidence of fractures with increase in frailty and the likelihood of mortality within 90 days of the fracture also increased with increase in frailty status, although the relationship was stronger with increase in age than frailty status. Although the incidence of fractures decreased in the 100 + age group mortality rates after a fracture showed an exponential rise in the age groups. The incidence of fractures reducing in the older age groups observed in the centenarians may be due to difference in bone mineral density and a reduced tendency to fall due to increased social support. [23] The underlying comorbidities of the individual might be the reason for the increased mortality observed in individuals after fracture, this might also explain the association between higher risk of mortality after a fracture and an increase in frailty status. [18 33-35]

Conclusion

This research highlights the public health impact of fractures in association with frailty in older adults. Research is needed to understand factors that are associated with increased risk of fractures in the elderly in order to inform fracture prevention strategies. [29] Mortality remains high and most of those who have fractures are unlikely to regain prior physical

performance. [36 37] Evidence is needed to improve fracture and post-fracture management in order to optimize the outcomes following fracture in frail older adults. [38 39]

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Footnotes

Contributors Rathi Ravindrarajah designed, contributed to data analysis and drafted the paper. Professor Martin Gulliford (MG) supervised and assisted with draft and conclusions. Judith Charlton contributed to data analysis. Nisha Hazra, Professor Stephen Jackson and Dr.Alex Dregan (AD) contributed to the write up and conclusions. All authors read and approved the final manuscript.

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Competing interests None.

Data sharing statement Data ownership belongs to CPRD, data sharing is not possible.

Table 1: Number and incidence of fractures by fracture site, gender, age group and Frailty status.

Gender		Person Years	Non-Fragility	Femur	Pelvis	Shoulder Upper Arm	Forearm/Wrist
Male	N	421818.9	2624	3318	344	1331	1191
	Incidence [a]		6.2 (6.0 to 6.5)	7.8 (7.6 to 8.1)	0.8(0.7 to 0.9)	3.2 (3.0 to 3.3)	2.8 (2.7 to 3.0)
Female	N	550969.4	6448	9090	1817	3617	5116
	Incidence		11.7 (11.4 to 12.0)	16.5 (16.2 to 16.8)	3.3 (3.2 to 3.5)	6.6 (6.4 to 6.8)	9.3 (9.0 to 9.5)
Age group							
80-84	N	288407.8	2230	1952	303	1034	1615
	Incidence		7.7 (7.4 to 8.1)	6.8 (6.5 to 7.1)	1.1 (0.9 to 1.2)	3.6 (3.4 to 3.8)	5.6 (5.3 to 5.9)
85-89	N	331587.1	3096	3915	652	1647	2113
	Incidence		9.3 (9.0 to 9.7)	11.8 (11.4 to 12.2)	2.0 (1.8 to 2.1)	5.0 (4.7 to 5.2)	6.4 (6.1 to 6.7)
90-94	N	240064.2	2492	4030	727	1447	1715
	Incidence		10.4 (10.0 to 10.8)	16.8 (16.3 to 17.3)	3.0 (2.8 to 3.3)	6.0 (5.7 to 6.3)	7.1 (6.8 to 7.5)
95-99	N	94364.96	1083	2199	413	698	766
	Incidence		11.5 (10.8 to 12.2)	23.3 (22.3 to 24.3)	4.4 (4.0 to 4.9)	7.4 (6.9 to 8.0)	8.1 (7.6 to 8.7)
>100	N	18364.2	171	312	66	122	98
	Incidence		9.3 (8.0 to 10.8)	17.0 (15.2 to 19.0)	3.6 (2.8 to 4.5)	6.6 (5.5 to 7.9)	5.3 (4.4 to 6.5)
Frailty Category							
Fit	N	275917.6	1342	2016	274	914	1194
	Incidence		4.9 (4.6 to 5.1)	7.3 (7.0 to 7.6)	1.0 (.9 to 1.1)	3.3 (3.1 to 3.5)	4.3 (4.1 to 4.6)
Mild	N	378914.6	3292	4678	770	1800	2363
	Incidence		8.7 (8.4 to 9.0)	12.4 (12.0 to 12.7)	2.0 (1.9 to 2.2)	4.8 (4.5 to 5.0)	6.2 (6.0 to 6.5)
Moderate	N	233570.6	2946	3911	709	1506	1898
	Incidence		12.6 (12.2 to 13.1)	16.7 (16.2 to 17.3)	3.0 (2.8 to 3.3)	6.5 (6.1 to 6.8)	8.1 (7.8 to 8.5)
Severe	N	84385.52	1492	1803	408	728	852
	Incidence		17.7 (16.8 to 18.6)	21.4 (20.4 to 22.4)	4.8 (4.4 to 5.3)	8.6 (8.0 to 9.3)	10.1 (9.4 to 10.8)

[a] incidence rates are per 1,000-person years (95% confidence interval)

Figure 1 : Incident Rate Ratio for fractures by site and gender. Estimates are adjusted for age group and frailty status.

Figure 2 : Incident Rate Ratio for fractures by site and age group. Estimates are adjusted for gender and frailty status.

Figure 3 : Incident Rate Ratio for fractures by site and frailty status. Estimates are adjusted for gender and age group.

Table 2: 90-day mortality by site of fracture and by gender, age group and frailty status. Figures are number of deaths. Mortality rate (%), 95% confidence interval.

	ALL	Non-Fragility	Femur	Pelvis	Shoulder Upper Arm	Forearm/Wrist
	Dead N, Mortality Rate % (95% Confidence Interval)					
Gender						
Male	934	159	591	32	112	40
	14.1 (13.3 to 15.0)	8.2 (7.0 to 9.5)	22.4 (20.9 to 24.0)	15.0 (10.8 to 20.5)	12.2 (10.3 to 14.5)	4.5 (3.3 to 6.1)
Female	1931	305	1156	131	208	131
	11.5 (11.0 to 11.9)	7.5 (6.8 to 8.4)	17.9 (17.0 to 18.9)	12.5 (10.7 to 14.7)	9.6 (8.5 to 11.0)	4.2 (3.5 to 4.9)
Age group						
80-84	268	51	168	8	25	16
	5.5 (4.9 to 6.1)	3.3 (2.5 to 4.3)	11.7 (10.2 to 13.5)	4.4 (2.2 to 8.7)	3.9 (2.6 to 5.7)	1.5 (0.9 to 2.4)
85-89	721	134	421	38	85	43
	9.5 (8.9 to 10.2)	6.6 (5.6 to 7.8)	14.9 (13.6 to 16.2)	9.9 (7.3 to 13.3)	8.4 (6.8 to 10.3)	3.3 (2.4 to 4.4)
90-94	1028	166	617	63	113	69
	14.6 (13.8 to 15.4)	10.1 (8.8 to 11.7)	20.7 (19.3 to 22.2)	14.9 (11.8 to 18.7)	12.4 (10.4 to 14.7)	6.3 (5.0 to 7.9)
95-99	715	91	455	48	83	38
	20.8 (19.4 to 22.2)	13.6 (11.2 to 16.4)	28.1 (26.0 to 30.4)	20.0 (15.4 to 25.6)	18.9 (15.5 to 22.8)	8.1 (5.9 to 10.9)
>100	133	22	86	6	14	5
	28.4 (24.5 to 32.7)	22.4 (15.3 to 32.0)	38.7 (32.6 to 45.5)	20.3 (9.6 to 39.8)	20.4 (12.6 to 32.0)	10.1 (4.3 to 22.6)
Frailty Category						
Fit	430	61	275	22	46	26
	10.6 (9.7 to 11.6)	6.6 (5.2 to 8.4)	18.1 (16.2 to 20.1)	13.5 (9.1 to 19.7)	7.5 (5.7 to 9.9)	3.2 (2.2 to 4.7)
Mild	1064	178	658	53	120	55
	12.0 (11.3 to 12.7)	8.0 (7.0 to 9.3)	18.8 (17.5 to 20.1)	11.4 (8.9 to 14.7)	10.5 (8.9 to 12.4)	3.6 (2.8 to 4.6)
Moderate	920	149	554	54	104	59
	12.7 (12.0 to 13.5)	7.8 (6.7 to 9.1)	19.7 (18.3 to 21.2)	14.9 (11.8 to 18.7)	11.6 (9.7 to 13.9)	5.0 (3.9 to 6.4)
Severe	451	76	260	34	50	31
	13.6 (12.4 to 14.8)	8.2 (6.6 to 10.1)	20.8 (18.6 to 23.2)	15.3 (11.2 to 20.8)	11.9 (9.1 to 15.3)	6.2 (4.4 to 8.8)

Table 3: Hazard ratios (HR) 90 -day mortality after their fracture by fracture type, gender, age group and frailty status.

	N	Dead	HR (95 % Confidence Intervals)	p value
Non-Fragility	6,132	464	1.8 (1.5 to 2.13)	<0.001
Femur	9,409	1747	4.3 (3.7 to 5.06)	<0.001
Pelvis	1,328	163	2.8 (2.2 to 3.41)	<0.001
Shoulder Upper arm	3,166	320	2.3 (1.9 to 2.79)	<0.001
Forearm Wrist	4,133	171	**Reference**	
Gender				
Male	6,788	934	**Reference**	
Female	17,380	1,931	0.7 (0.6 to 0.8)	<0.001
Age Group				
80-84	5,010	268	**Reference**	
85-89	7,795	721	1.6 (1.4 to 1.8)	<0.001
90-94	7,290	1,028	2.4 (2.1 to 2.7)	<0.001
95-99	3,585	715	3.7 (3.2 to 4.2)	<0.001
>100	488	133	5.3 (4.3 to 6.5)	<0.001
Frailty Category				
Fit	4,155	430	**Reference**	
Mild	9,114	1,064	1.1 (1.0 to 1.2)	0.148
Moderate	7,468	920	1.1 (1.0 to 1.3)	0.028
Severe	3,431	451	1.2 (1.1 to 1.4)	0.003

Table 4: 1-year mortality by site of fracture and by gender, age group and frailty status. Figures are number of deaths. Mortality rate (%), 95% confidence interval.

	ALL	Non-Fragility	Femur	Pelvis	Shoulder Upper Arm	Forearm/Wrist
	Dead N, 1-year Mortality Rate % (95% Confidence Interval)					
Gender						
Male	1832	383	996	32	230	148
	29.8 (28.6 to 30.9)	21.1 (19.3 to 23.0)	40.7 (38.7 to 42.7)	15.0 (10.8 to 20.5)	26.9 (24.0 to 30.1)	18.2 (15.7 to 21.1)
Female	3734	693	1923	131	444	409
	23.7 (23.1 to 24.4)	18.4 (17.2 to 19.7)	32.0 (30.8 to 33.2)	12.5 (10.7 to 14.7)	22.1 (20.3 to 24.0)	14.0 (12.8 to 15.3)
Age group						
80-84	653	149	324	31	69	80
	14.1 (13.2 to 15.2)	10.2 (8.8 to 11.9)	24.0 (21.8 to 26.4)	18.5 (13.4 to 25.3)	11.4 (9.1 to 14.2)	7.9 (6.4 to 9.7)
85-89	1437	293	746	78	187	133
	20.3 (19.4 to 21.2)	15.5 (14.0 to 17.3)	28.2 (26.5 to 29.9)	22.0 (18.0 to 26.8)	19.8 (17.4 to 22.5)	10.9 (9.2 to 12.7)
90-94	1961	374	1017	128	231	211
	30.1 (29.0 to 31.3)	24.8 (22.7 to 27.1)	37.0 (35.2 to 38.8)	33.2 (28.7 to 38.3)	27.5 (24.6 to 30.7)	20.9 (18.5 to 23.6)
95-99	1291	218	711	93	155	114
	40.5 (38.8 to 42.3)	35.0 (31.4 to 39.0)	47.7 (45.1 to 50.4)	41.4 (35.2 to 48.2)	38.0 (33.4 to 43.0)	26.4 (22.5 to 30.9)
>100	224	42	121	10	32	19
	51.3 (46.6 to 56.2)	46.9 (37.0 to 58.0)	57.8 (51.0 to 64.7)	35.2 (20.6 to 55.7)	51.2 (39.3 to 64.4)	41.3 (28.5 to 57.2)
Frailty Category						
Fit	803	133	446	46	103	75
	20.9 (19.6 to 22.2)	14.9 (12.7 to 17.4)	31.1 (28.8 to 33.6)	30.0 (23.4 to 38.0)	17.9 (15.0 to 21.3)	9.6 (7.7 to 11.9)
Mild	1958	356	1075	111	231	185
	23.5 (22.5 to 24.4)	17.1 (15.5 to 18.8)	32.7 (31.1 to 34.3)	25.8 (21.9 to 30.3)	21.3 (19.0 to 23.9)	13.0 (11.3 to 14.8)
Moderate	1889	389	957	112	237	194
	28.3 (27.3 to 29.4)	22.1 (20.2 to 24.1)	36.8 (35.0 to 38.7)	33.2 (28.7 to 38.3)	28.7 (25.7 to 32.0)	17.9 (15.8 to 20.4)
Severe	916	198	441	71	103	103
	30.4 (28.8 to 32.1)	23.7 (21.0 to 26.8)	38.8 (35.9 to 41.7)	34.6 (28.4 to 41.6)	27.1 (22.9 to 32.0)	23.2 (19.5 to 27.5)

Table 5: Hazard ratios (HR) I year mortality after their fracture by fracture type, gender, age group and frailty status.

	N	Dead	HR (95 % Confidence Intervals)	p value
Non-Fragility	6,132	1,076	1.3 (1.2 to 1.4)	<0.001
Femur	9,409	2,919	2.5 (2.3 to 2.7)	<0.001
Pelvis	1,328	340	1.9 (1.7 to 2.2)	<0.001
Shoulder Upper arm	3,166	674	1.6 (1.4 to 1.8)	<0.001
Forearm Wrist	4,133	557	**Reference**	
Gender				
Male	6,788	1,832	**Reference**	
Female	17,380	3,734	0.7 (0.6 to 0.7)	<0.001
Age Group				
80-84	5,010	653	**Reference**	
85-89	7,795	1,437	1.4 (1.3 to 1.5)	<0.001
90-94	7,290	1,961	2.1 (1.9 to 2.3)	<0.001
95-99	3,585	1,291	3.2 (3.0 to 3.6)	<0.001
>100	488	224	4.6 (3.9 to 5.4)	<0.001
Frailty Category				
Fit	4,155	803	**Reference**	
Mild	9,114	1,958	1.1 (1.0 to 1.2)	0.058
Moderate	7,468	1,889	1.3 (1.2 to 1.4)	<0.001
Severe	3,431	916	1.4 (1.3 to 1.5)	<0.001

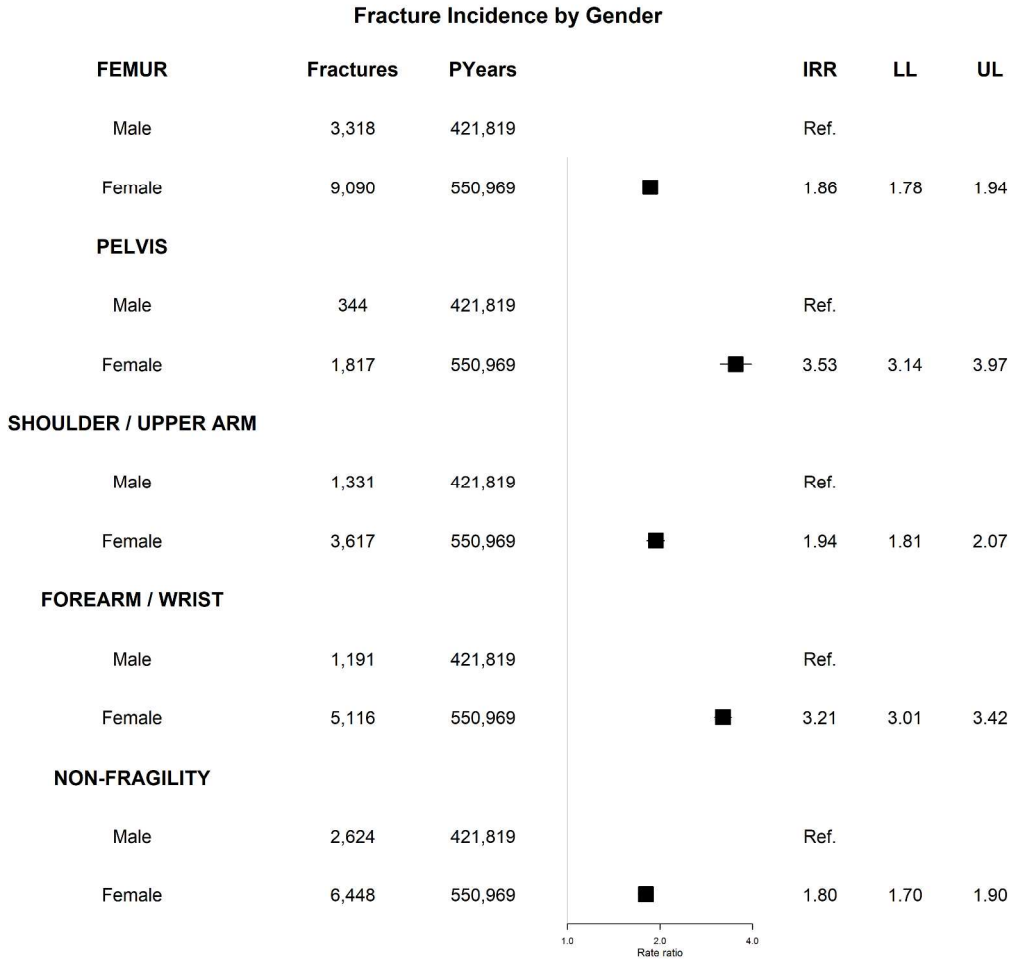

Figure 1 : Incident Rate Ratio for fractures by site and gender. Estimates are adjusted for age group and frailty status.

270x270mm (300 x 300 DPI)

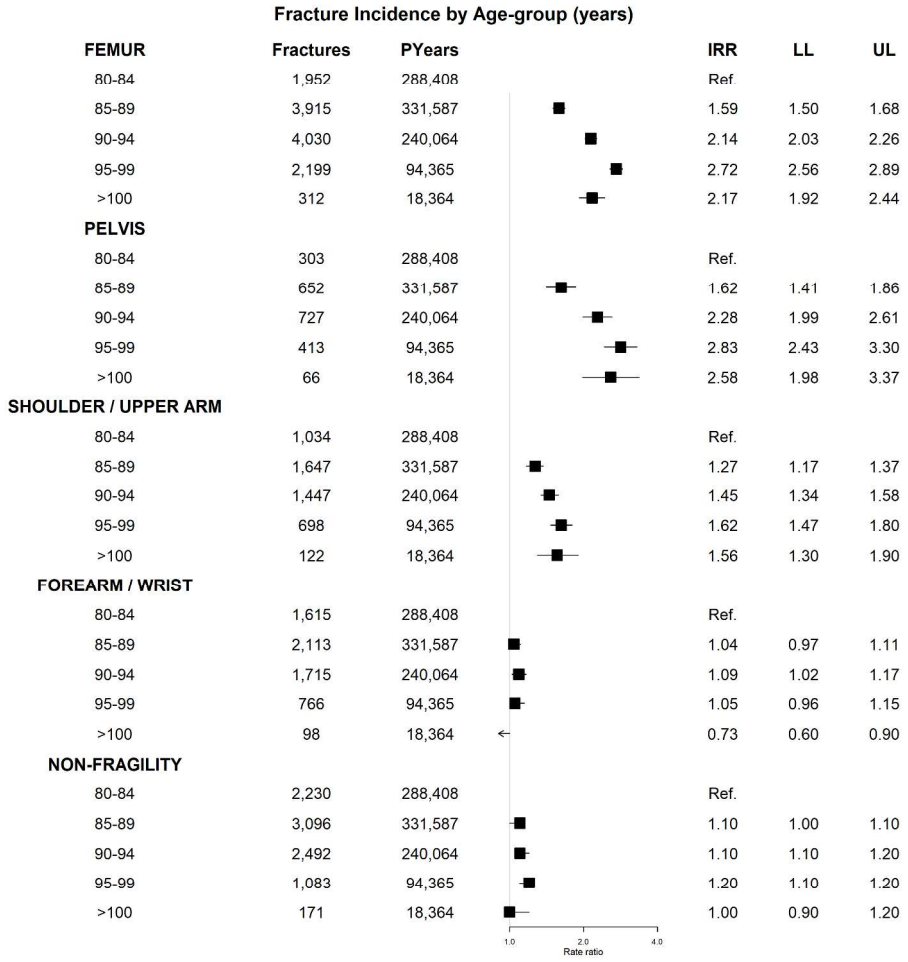

Figure 2 : Incident Rate Ratio for fractures by site and age group. Estimates are adjusted for gender and frailty status.

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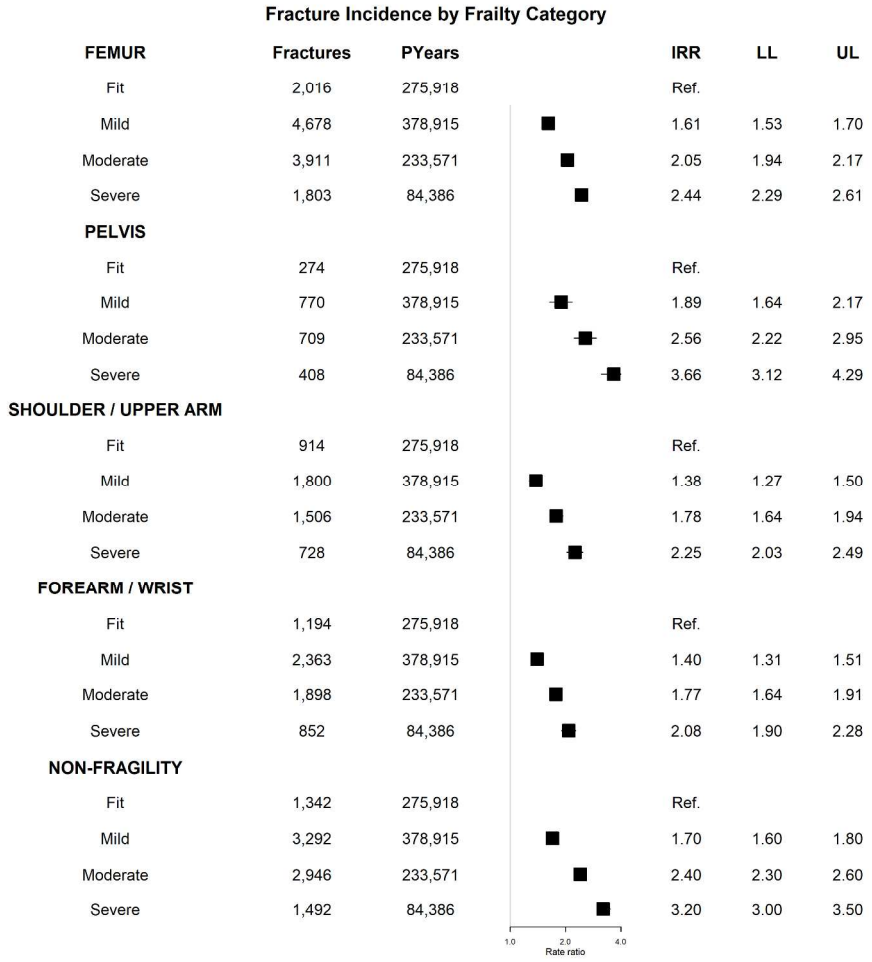

Figure 3 : Incident Rate Ratio for fractures by site and frailty status. Estimates are adjusted for gender and age group.

270x270mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1, line 2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2, line 2-23**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 3, line 3-25,**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 4, lines 1-4**
Methods		
Study design	4	Present key elements of study design early in the paper **Pages 4-5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Pages 4-6**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Pages 4-6**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed Page 6, lines 18-21
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 5-7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Pages 4-6**
Bias	9	Describe any efforts to address potential sources of bias **Page 6, lines 6-15**
Study size	10	Explain how the study size was arrived at **Page 5, (lines 20-27), Page 6 (lines 1-8)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why: **Page 7 ,(lines 5-14)**
Statistical methods	12	Describe all statistical methods, including those used to control for confounding **Page 6 ,(lines 18-21)**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 6 ,(lines 18-21)**
		(*c*) Explain how missing data were addressed **Page 5 ,(lines 2-9)**

	(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
	(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 4, lines 21-27;Page 6, lines 18-21**
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 6, lines 18-24**
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)**Page 5**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Page 6-7, Table 1 and Figure 1-3**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. **Page 7-8**
		(*b*) Report category boundaries when continuous variables were categorized **Page 6, lines 24-26**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 9, lines 3-12**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 9, lines 15-25, page 10 lines 1-5**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 11, lines 20-25**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 9**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 15, lines 3- 6**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.