



## Article

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# BMJ Open Hip fracture incidence and mortality in chronic kidney disease: the GLOMMS-II record linkage cohort study

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## ABSTRACT

**Background** Individuals on renal replacement therapy (RRT) have increased fracture risk, but risk in less advanced chronic kidney disease (CKD) is unclear.

**Objective** To investigate CKD associations with hip fracture incidence and mortality.

**Design** Record linkage cohort study Grampian Laboratory Outcomes Mortality and Morbidity Study II.

**Setting** Single health region in Scotland.

**Participants** All individuals ( $\geq 15$  years) with sustained CKD stages 3–5 and those on RRT, and a 20% random sample of those with normal renal function, in the resident population in 2003.

**Outcome measures** Outcomes were (1) incident hip fracture measured with (A) admissions or (B) deaths, with at least 5.5 years follow-up and (2) post-hip fracture mortality. Unadjusted and adjusted, incident rate ratios (IRRs) and mortality rate ratios were calculated using Poisson regression.

**Results** Of 39 630 individuals identified in 2003 (41% males, mean age 63.3 years), 19 537 had CKD stages 3–5, 345 were on RRT and 19 748 had normal estimated glomerular filtration rate (eGFR). Hip fracture incidence, measured by admissions, was increased in CKD stages 3–5 (compared with normal eGFR), both overall (adjusted IRR 1.49 (95% CI 1.24 to 1.79)) and for individual CKD stages 3a, 3b and 4. Hip fracture incidence, measured using deaths, was increased in those with CKD stages 3b and 4. Post-hip fracture mortality was only increased in CKD stage 4. There was only a small number of individuals and events for CKD stage 5, resulting in insufficient statistical power.

**Conclusion** Hip fracture incidence was higher in CKD stages 3–5 compared with normal eGFR. Post-hip fracture mortality was only increased in CKD stage 4. Reducing hip fracture incidence in CKD through regular fall and fracture risk review should reduce overall deaths after hip fracture in the population.

## INTRODUCTION

Hip fractures are a major public health issue recognised in national clinical guidelines, and more common in women and the elderly.<sup>1 2</sup> In the UK, there is an estimated 70 000–90 000 hip fractures annually.<sup>1</sup> Hip fracture is associated with high mortality; up to one-third of people die within a year.<sup>3</sup>

## Strengths and limitations of this study

- A large, population-based cohort using valid methods for assessing comorbidity and identifying individuals with chronic kidney disease (CKD).
- Reporting hip fracture incidence using both admission and death records, allowing direct comparison with studies that have used either of these methods and highlighting the importance of methods of measurement.
- Using at least two serum creatinine measurements to identify CKD, thus reducing the risk of identifying episodes of acute kidney injury as CKD.
- Use of hospital episode data to ascertain hip fracture, acknowledging that a small number of hip fractures may not lead to hospital admission.
- We only considered hip fractures acknowledging that CKD may be associated with other fracture sites; however, hip fractures would have more complete admission data.

The associated morbidity and economic cost is large, with the annual cost of hip fractures estimated at ~£2 billion for the UK.<sup>1</sup>

Chronic kidney disease (CKD) is also a major and growing healthcare challenge, with an estimated global prevalence of 11%–13%, again higher in the elderly and women.<sup>4</sup> People with CKD are at increased risk of morbidity, mortality and progressive kidney function decline, leading to renal replacement therapy (RRT).<sup>5–7</sup> A well-recognised complication of RRT is renal bone disease. The association between RRT and risk of hip fracture is well established, with a high incidence of hip fractures.<sup>8</sup> Mortality at 1-year post-hip fracture is 55%–64% for dialysis patients,<sup>8 9</sup> a 2.7-fold increase compared with the non-fractured dialysis population.<sup>8 9</sup>

Although changes in bone metabolism are seen in patients with CKD long before the initiation of RRT,<sup>10</sup> the evidence of hip fracture risk in CKD is uncertain, particularly at less advanced stages. Some studies report on renal function measured after hip fracture

has occurred,<sup>11 12</sup> others restrict to those at high risk of fracture.<sup>13</sup> Recent studies reporting hip fracture incidence in those with prior documented CKD have been conflicting, some showing an association<sup>14-16</sup> and others not.<sup>17</sup> In addition, an increased risk of hip fracture-related deaths has been reported only among those with more advanced CKD.<sup>18</sup> Mortality post-hip fracture is high regardless of renal function,<sup>3</sup> although CKD has been linked to higher post-hip fracture mortality in hospital<sup>19</sup> and at 1 year<sup>20</sup> compared with those with normal renal function. Overall, however, many previous studies reporting the effect of CKD on the incidence of hip fracture or mortality post-hip fracture are limited by: older populations<sup>15 16 18 20</sup>; CKD based on only one measurement of renal function<sup>15 17 18 20</sup> or reliance on administrative coding for identification of CKD.<sup>16 19</sup>

With an increasing and ageing population, both the prevalence of CKD and hip fracture incidence will rise, together with associated health and social care costs. As a result of uncertainty about the association between CKD and hip fracture, current guidelines on fracture risk management may be poorly targeted. Therefore, the study aim was to clarify the association of CKD with hip fracture incidence and mortality.

## METHODS

### Population

The Grampian Laboratory Outcomes Mortality and Morbidity Study II (GLOMMS-II) cohort consists of residents ( $\geq 15$  years) in a single health region in the North-east of Scotland (population  $\sim 0.5$  million) in 2003. All with at least one abnormal measure of kidney function (estimated glomerular filtration rate (eGFR)  $< 60$  mL/min/1.73 m<sup>2</sup>); a 20% random sample with normal kidney function; a 20% random sample with no measurement of kidney function and all on maintenance RRT (dialysis and transplants) were included, as described previously.<sup>21-23</sup> A single biochemistry service processes all blood samples (inpatient, outpatient and community) for the region. For this study, individuals with sustained CKD stages 3-5 (not dialysis or transplant), on maintenance RRT (dialysis and transplants), and those with normal kidney function are reported only.

The study protocol was reviewed by Information Services Division Privacy Advisory Committee, NHS Grampian Caldicott Guardian, North of Scotland Research Ethics Service and University of Aberdeen College Ethics Review Board (CERB). The study was carried out in accordance with the principles of the Declaration of Helsinki.

### Exposure

Renal status was assessed at entry to study. CKD was defined and staged according to Kidney Disease: Improving Global Outcomes (KDIGO).<sup>24 25</sup> The index value and date were defined as the first abnormal kidney function measure, (eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>), calculated from a creatinine measured between 1 January and 31 December

2003 (see footnote in table 1).<sup>26</sup> To fulfil the criteria of CKD, the next eGFR at least 3 months after index (or if there were no samples after 3 months postindex, the eGFR prior to 3 months before the index) also had to be  $< 60$  mL/min/1.73 m<sup>2</sup>. In those with normal kidney function throughout 2003 (eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>), the last value and date were taken as the index.

### Covariates

Other covariates included age, sex, proteinuria, comorbidity, rurality and deprivation. Proteinuria was assessed using the last urinary albumin to creatinine or protein to creatinine ratio measured prior to index, and categorised as not measured, normoalbuminuric, microalbuminuric or macroalbuminuric (see footnote in table 1). Comorbidities were identified from hospital episode records for the 5 years prior to 2003 (International Classification of Diseases, 10th Revision (ICD-10) coding). A modified Charlson Comorbidity Index score was calculated<sup>27 28</sup> (see footnote in online supplementary table 1). Postal code-based rurality<sup>29</sup> and deprivation<sup>30</sup> categories were also obtained (see table 1 and footnote in online supplementary table 1).

### Follow-up

From index date in 2003, follow-up was available to 30 June 2009, giving an observation period of at least 5.5 years.

### Outcomes

The primary outcome was hip fracture incidence, measured using (1) hip fracture admission (from hospital admissions data, where hip fracture was recorded as the main or additional diagnosis (ICD-10 code S72)) and (2) hip fracture-related death (from national death records, where hip fracture was recorded as a main or other cause of death). The secondary outcome was post-hip fracture mortality in individuals who had a hip fracture admission, both (1) all-cause mortality (ACM) and (2) specifically hip fracture-related mortality (HFM) where hip fracture was recorded as main or other cause of death.

### Exclusions

Those who had a hip fracture or died on index date, and non-residents of Grampian were excluded.

### Data linkage

The Community Health Index number, a unique patient identifier used throughout the Scottish healthcare system, was used to link GLOMMS-II with hospital episode and death registry data using deterministic matching. The deidentified dataset was hosted by Grampian Data Safe Haven, allowing secure controlled access for researchers while ensuring data security.<sup>31</sup>

### Statistical analyses

Hip fracture incidence rates were calculated using both (1) hip fracture admissions and (2) hip fracture deaths, as 'markers' for hip fracture occurrence. Follow-up time

**Table 1** Characteristics of individuals with and without a hip fracture admission

Characteristic	Hip fracture, n (%)	No hip fracture, n (%)
Total no of patients: 39 630	1084 (2.7)	38 546 (97.3)
Renal status*		
RRT	8 (0.7)	337 (0.9)
CKD stages 3–5	915 (84.4)	18 622 (48.3)
CKD stage 5	2 (0.2)	180 (0.5)
CKD stage 4	77 (7.1)	1321 (3.4)
CKD stage 3b	320 (29.5)	4941 (12.8)
CKD stage 3a	516 (47.6)	12 180 (31.6)
Normal eGFR	161 (14.9)	19 587 (50.8)
Sex		
Males	231 (21.3)	16 137 (41.9)
Females	853 (78.7)	22 409 (58.1)
Age, mean (95% CI), years		
15–44	10 (0.9)	7278 (18.9)
45–54	13 (1.2)	4533 (11.8)
55–64	42 (3.9)	6203 (16.1)
65–74	172 (15.9)	8805 (22.8)
75–84	516 (47.6)	8583 (22.3)
≥85	331 (30.5)	3144 (8.2)
Creatinine, median (IQR), μmol/L	99.5 (85.5–121.1)	88.7 (73.6–109.2)
eGFR (MDRD), mean (95% CI), mL/min/1.73 m <sup>2</sup> †	50.6 (49.5 to 51.7)	66.5 (66.3 to 66.8)
Proteinuria‡		
Normal	79 (7.3)	2888 (7.5)
Microalbuminuric	47 (4.3)	957 (2.5)
Macroalbuminuric	13 (1.2)	683 (1.8)
Not measured	945 (87.2)	34 018 (88.3)
ACR, median (IQR), mg/mmol	1.0 (0.9–5.0)	1.0 (0.9–3.0)
PCR, median (IQR), mg/mmol	21.5 (10.0–49.0)	25.0 (10.0–79.0)
Charlson Comorbidity Index score		
0	699 (64.5)	29 547 (76.7)
1–2	297 (27.4)	7156 (18.6)
3–4	69 (6.4)	1301 (3.4)
≥5	19 (1.8)	542 (1.4)
Urban rural classification§		
Large urban	448 (41.3)	13 512 (35.1)
Other urban	155 (14.3)	5536 (14.4)
Accessible small towns	99 (9.1)	3096 (8.0)
Remote small towns	112 (10.3)	3146 (8.2)
Accessible rural	159 (14.7)	6851 (17.8)
Remote rural	106 (9.8)	3664 (9.5)

Continued

**Table 1** Continued

Characteristic	Hip fracture, n (%)	No hip fracture, n (%)
SIMD (quintile)§		
1 (most deprived)	87 (8.0)	2414 (6.3)
2	182 (16.8)	5794 (15.0)
3	286 (26.4)	8994 (23.3)
4	260 (24.0)	9377 (24.3)
5 (least deprived)	264 (24.4)	9226 (23.9)

\*Renal status based on KDIGO CKD stages: overall CKD stages 3–5, index eGFR <60 mL/min/1.73 m<sup>2</sup>; individual stages 3a, 3b, 4 and 5 CKD, index eGFR 59–45, 44–30, 29–15 and <15 mL/min/1.73 m<sup>2</sup>. CKD stage 5 does not include dialysis or transplants.

†eGFR was calculated using the four-variable isotope dilution mass spectrometry aligned MDRD formula as is used clinically in the region.

‡Proteinuria status defined as: not measured;

no test prior to index date; normoalbuminuric;

measured, not microalbuminuric /macroalbuminuric;

microalbuminuric: ≥2.5 mg/mmol ACR for men, ≥3.5 mg/mmol ACR for women or PCR ≥15 for both;

macroalbuminuric: ≥30 mg/mmol ACR for both men and women or ≥50 mg/mmol PCR.

§SIMD quintile and urban rural classification were unknown for 2746 individuals because of missing postal codes.

Where relevant, missing data were included in the analysis as a separate category.

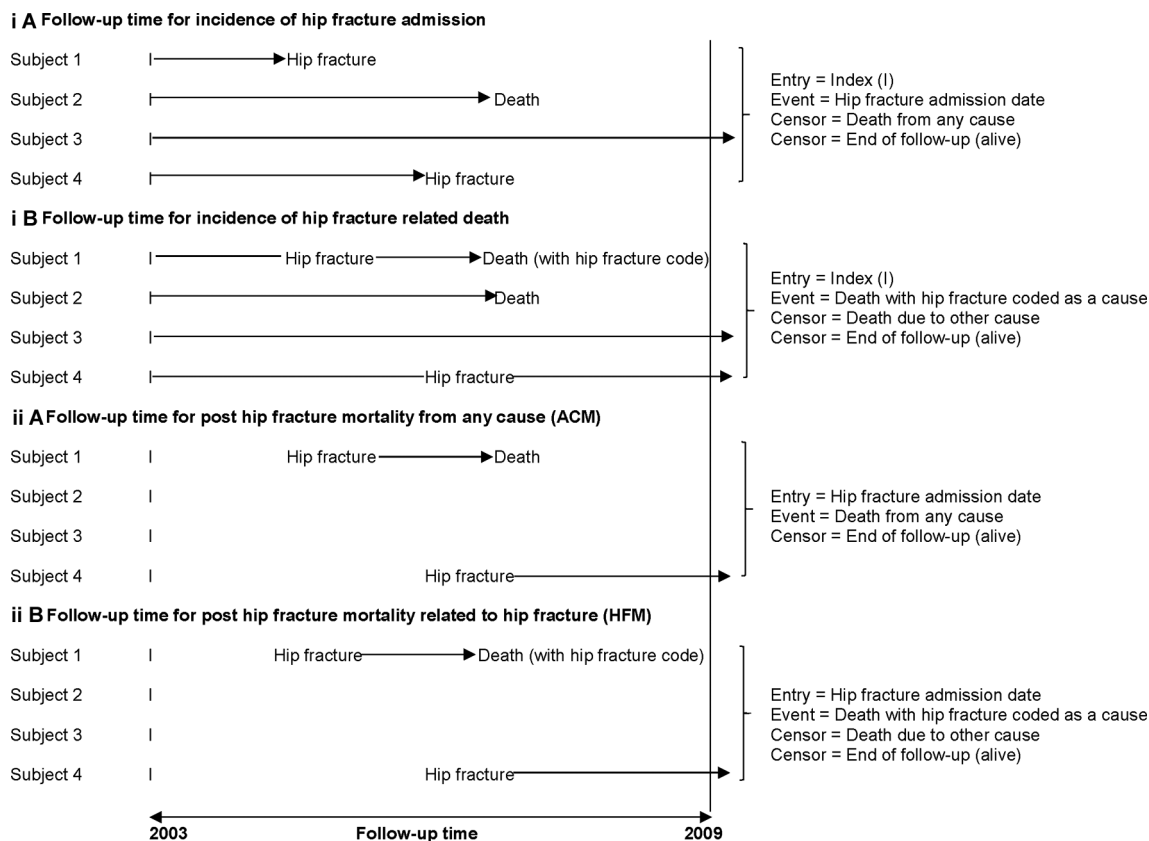
ACR, albumin to creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate;

MDRD, Modification of Diet in Renal Disease; RRT, renal replacement therapy (dialysis and transplants); SIMD,

Scottish Index of Multiple Deprivation; KDIGO, Kidney Disease: Improving Global Outcomes.

for hip fracture admissions (figure 1i(A)) was calculated from index date (study entry) to the date of the first hospital admission for hip fracture, censoring at death or end of follow-up. Follow-up time for hip fracture deaths (figure 1i(B)) was calculated from index date to date of hip fracture-related death, censoring at end of follow-up or date of death from other causes. Unadjusted and adjusted incident rate ratios (IRRs) for the effect of CKD on hip fracture incidence were calculated using Poisson regression with an offset of person-years of exposure. Models for hip fracture admission incidence were developed using forward selection of variables, both using variables with significant effect on univariate analysis and specifically for available risk factors for fractures (see footnote in table 2) identified from national guidelines.<sup>32</sup> Variables were included if they improved model performance (likelihood ratio test). The final model for hip fracture death incidence was adjusted for age and sex only.

Post-hip fracture mortality follow-up time was calculated from the date of a hip fracture-related hospital admission to date of death, censoring at end of follow-up



**Figure 1** Entry to the study, follow-up time and censoring for (i) hip fracture incidence and (ii) post-hip fracture mortality. The index date was defined as the first abnormal eGFR ( $<60 \text{ mL/min/1.73 m}^2$ ) from a creatinine measured between 1 January and 31 December 2003. Where all eGFR values in 2003 were normal, the last value and date were taken as the index. Primary outcome, hip fracture incidence measured using (A) hip fracture admission (from hospital admissions data, where hip fracture was recorded as the main or additional diagnosis (ICD-10 code S72)) and (B) hip fracture-related death (from national death records, where hip fracture was recorded as a main or other cause of death). Secondary outcome, post-hip fracture mortality in individuals who had a hip fracture admission, both (A) all-cause mortality (ACM) and (B) specifically hip fracture-related mortality (HFM) where hip fracture was recorded as main or other cause of death. eGFR, estimated glomerular filtration rate; ICD-10, International Classification of Diseases, 10th Revision.

for ACM (figure 1ii(A)), and for HFM, date of death from other causes also (figure 1ii(B)). Mortality rates were calculated. Unadjusted and adjusted mortality rate ratios (MRRs) were calculated using Poisson regression. The final adjusted model for each outcome (ACM and HFM) was developed as above. Assumptions were checked including proportionality over time. As there was a low number of individuals and events in the RRT group, this group was reported in the descriptive statistics only, but not included in the hip fracture or mortality post-hip fracture risk analyses. Where measures of effect were calculated, 95% CIs were reported. Analyses were performed using StataV.13.0.

## RESULTS

### Baseline characteristics

The flow diagram for generating GLOMMS-II and identifying individuals for this study is shown in figure 2. There were 19 537 individuals with CKD stages 3–5, 345 on RRT and 19 748 with normal eGFR (20% random sample). Those with CKD were older (mean age 74.8 (95% CI 74.6

to 74.9) years), and more likely to be female (64.9%) than those with normal eGFR (52.1 (95% CI 51.8 to 52.3) years, 52.8%) or on RRT (54.4 (95% CI 52.7 to 56.2) years, 44.9%) respectively. Individuals with CKD had more comorbidity than those with normal eGFR (33.3% vs 13.8% with Charlson Comorbidity Index score  $\geq 1$ ) (online supplementary table 1).

### Hip fracture incidence (primary outcome)

Hip fracture incidence was assessed using both (1) hip fracture admissions and (2) hip fracture-related deaths as measures of occurrence.

There were 915 hip fracture admissions for individuals with CKD stages 3–5, 8 among those on RRT and 161 for those with normal eGFR. Compared with those with no hip fracture admission, individuals with a hip fracture were more likely to be female, older, have more comorbidity and have CKD stages 3–5 (table 1). As there were few fracture admissions among individuals on RRT, these individuals' results are not reported further.

CKD stages 3–5 overall was associated with an increased incidence of hip fracture admission compared with

**Table 2** Incidence of hip fracture in CKD, measured with (a) admissions and (b) deaths

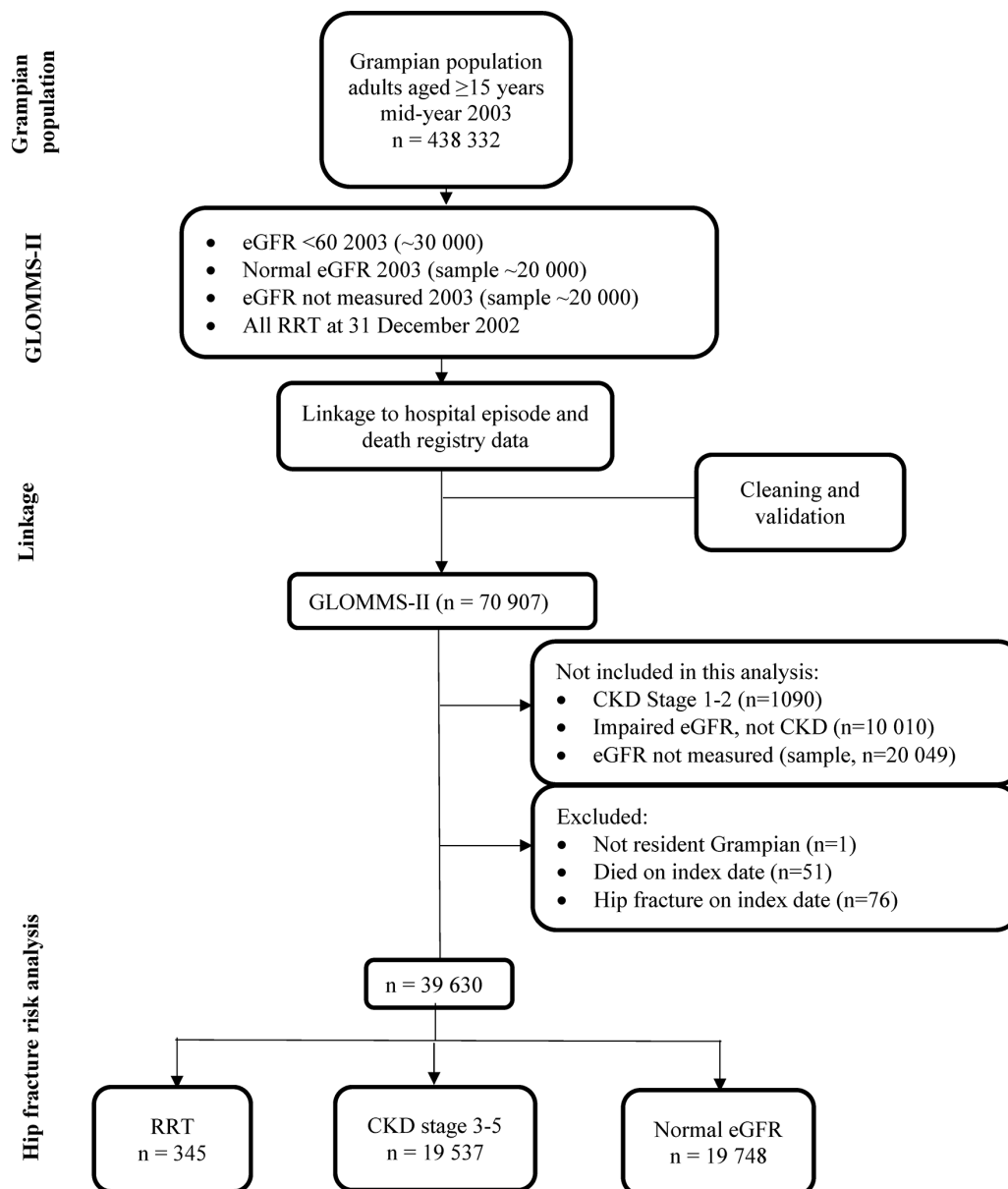
Renal status	Total	Events n	PY follow to up (1000)	Rate per 1000 PY (95% CI)	Unadjusted IRR (95% CI)	Age/sex adjusted IRR (95% CI)	Adjusted IRR (95% CI) final model*	SIGN final model†
<b>(a) Association of CKD and incidence of hip fracture admission</b>								
CKD stages 3–5‡	19 537	915	91.4	10.0 (9.4 to 10.7)	6.90 (5.83 to 8.15)	1.58 (1.32 to 1.90)	1.49 (1.24 to 1.79)	1.53 (1.27 to 1.84)
CKD stage 5‡	182	2	0.6	3.3 (0.8 to 13.2)	2.27 (0.56 to 9.16)	0.78 (0.19 to 3.15)	0.69 (0.17 to 2.78)	
CKD stage 4	1398	77	4.8	15.9 (12.7 to 19.9)	10.96 (8.36 to 14.39)	1.98 (1.49 to 2.63)	1.74 (1.30 to 2.33)	
CKD stage 3b	5261	320	22.6	14.1 (12.7 to 15.8)	9.74 (8.06 to 11.77)	1.83 (1.49 to 2.24)	1.70 (1.38 to 2.09)	
CKD stage 3a	12 696	516	63.3	8.2 (7.5 to 8.9)	5.61 (4.70 to 6.70)	1.47 (1.21 to 1.77)	1.40 (1.16 to 1.70)	
Normal eGFR	19 748	161	110.9	1.5 (1.2 to 1.7)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<b>(b) Association of CKD and incidence of hip fracture-related death</b>								
CKD stages 3–5‡	19 537	198	92.8	2.1 (1.9 to 2.5)	7.91 (5.39 to 11.61)	1.27 (0.85 to 1.88)		
CKD stage 5‡	182	0	0.6	–	–	–		
CKD stage 4	1398	26	4.9	5.3 (3.6 to 7.8)	19.59 (11.59 to 33.13)	2.28 (1.32 to 3.92)		
CKD stage 3b	5261	78	23.1	3.4 (2.7 to 4.2)	12.53 (8.22 to 19.08)	1.57 (1.01 to 2.44)		
CKD stage 3a	12 696	94	64.1	1.5 (1.2 to 1.8)	5.43 (3.60 to 8.19)	1.03 (0.68 to 1.58)		
Normal eGFR	19 748	30	111.2	0.3 (0.2 to 0.4)	1.00 (Reference)	1.00 (Reference)		

\*Final model adjusted for age, sex, Charlson Comorbidity Index score, deprivation, proteinuria and rurality (all variables remained in model).

†SIGN model developed using age, sex, diabetes, connective tissue disease, chronic pulmonary disease, dementia, chronic liver disease, non-haematological malignancy, metastatic solid tumour, peptic ulcer disease, HIV/AIDS, obesity (ICD-10 code E66) and smoking status (ICD-10 code Z72.0, F17.2, Z71.6). We did not have available: drug therapy, certain other coexisting diseases, low BMD (bone mineral density), alcohol use, previous fracture, parental history of osteoporosis and early menopause. The SIGN final (best) model was adjusted for age, sex, diabetes, chronic pulmonary disease, dementia and chronic liver disease.

‡CKD stage 5 does not include dialysis or transplants.

CKD, chronic kidney disease; ICD-10, 10th revision of International Classification of Diseases; IRR, incident rate ratio; PY, patient-years; SIGN, Scottish Intercollegiate Guidelines Network.



**Figure 2** Flow diagram of study population from GLOMMS-II. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GLOMMS-II, Grampian Laboratory Outcomes Morbidity and Mortality Study II; RRT, renal replacement therapy (dialysis and transplants).

those with normal eGFR, rates of 10.0 (95% CI 9.4 to 10.7) and 1.5 (95% CI 1.2 to 1.7) per 1000 patient-years (PY), respectively. The unadjusted hip fracture admission IRR for CKD stages 3–5 overall compared with normal eGFR was 6.90 (95% CI 5.83 to 8.15) (table 2a). This was increased in both men and women, unadjusted IRR 5.28 (95% CI 3.89 to 7.16) and 6.85 (95% CI 5.59 to 8.38), respectively (online supplementary table 2). The increased risk was present for every age group, but more marked in younger age groups, the unadjusted IRR (CKD stages 3–5 vs normal eGFR) was 7.63 (95% CI 1.54 to 37.82) and 1.48 (95% CI 1.14 to 1.91) for those aged 15–44 and 75–84 years, respectively (online supplementary table 2). After adjusting for age, sex, comorbidity, deprivation, proteinuria and rurality (final model), hip fracture risk remained increased for CKD

stages 3–5 overall (IRR 1.49 (95% CI 1.24 to 1.79)) and for CKD stages 3a, 3b and 4 individually. There were, however, only small numbers of individuals and events for CKD stage 5. The model adjusting for available fracture risk factors identified from national guidelines<sup>32</sup> showed similar results (table 2a).

Hip fracture incidence was also assessed with hip fracture-related deaths as a measure of occurrence. Few individuals died with a hip fracture-related death; 1.0% of those with CKD stages 3–5 and 0.2% of those with normal eGFR. This equates to 2.1 (1.9–2.5) versus 0.3 (0.2–0.4) per 1000 PY respectively; an eightfold difference. After adjusting for age and sex (table 2b), the overall IRR for CKD stages 3–5 effect was 1.27 (0.85–1.88). However, individual CKD stages 3b and 4 were still associated with hip fracture incidence when

**Table 3** Post-hip fracture admission mortality in CKD, both (a) all-cause mortality and (b) hip fracture-related mortality

Renal status	Total with hip fracture	Events, n	PY follow-up (1000)	Rate per 1000 PY (95% CI)	Unadjusted MRR (95% CI)	Adjusted* MRR (95% CI) final model
<b>(a) All-cause mortality post-hip fracture</b>						
CKD stages 3–5†	915	666	1.4	488.0 (452.4 to 526.6)	1.58 (1.26 to 1.99)	1.09 (0.85 to 1.39)
CKD stage 5b†	2	2	0.0	764.1 (191.1 to 3055.3)	2.47 (0.61 to 10.06)	1.04 (0.24 to 4.51)
CKD stage 4	77	71	0.1	885.3 (701.6 to 1117.1)	2.87 (2.09 to 3.93)	2.04 (1.44 to 2.89)
CKD stage 3b	320	240	0.4	542.2 (477.7 to 615.3)	1.76 (1.37 to 2.25)	1.11 (0.85 to 1.45)
CKD stage 3a	516	353	0.8	420.7 (379.0 to 466.9)	1.36 (1.07 to 1.73)	1.02 (0.80 to 1.32)
Normal eGFR	161	83	0.3	308.9 (249.1 to 383.0)	1.00 (Reference)	1.00 (Reference)
<b>(b) Hip fracture mortality post-hip fracture</b>						
CKD stages 3–5†	915	183	1.4	134.1 (116.0 to 155.0)	1.39 (0.92 to 2.09)	0.79(0.51 to 1.22)
CKD stage 5†	2	0	0.0	–	–	–
CKD stage 4	77	24	0.1	299.3 (200.6 to 446.5)	3.09 (1.78 to 5.39)	1.88 (1.02 to 3.47)
CKD stage 3b	320	72	0.4	162.7 (129.1 to 204.9)	1.68 (1.07 to 2.63)	0.85 (0.53 to 1.37)
CKD stage 3a	516	87	0.8	103.7 (84.0 to 127.9)	1.07 (0.69 to 1.66)	0.71 (0.45 to 1.12)
Normal eGFR	161	26	0.3	96.8 (65.9 to 142.1)	1.00 (Reference)	1.00 (Reference)

The number of hip fracture deaths are not the same in [tables 3b and 2b](#) because:

- Four individuals with CKD stages 3–5 died on date of hip fracture admission and are not included in the number of deaths in [table 3](#).
- A further 15 individuals had no record of a hip fracture admission but had a hip fracture-related death, and are therefore not included in the population for post-hip fracture mortality. Of these, 11 had CKD stages 3–5, with an average age of 87. Some died within a few days of index date. They had multiple and varied other causes of death, hip fracture was not the first or second cause for any. Four had normal eGFR, with an average age of 86. All died within 3 days of index date, and did not have hip fracture recorded as first, second or third cause of death.

\*Adjusted for age, sex, Charlson Comorbidity Index score, deprivation, proteinuria and rurality (all variables remained in model).

†CKD stage 5 does not include dialysis or transplants.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MRR, mortality rate ratio; PY, patient-years.

measured with death. Fifteen individuals had no hip fracture admission recorded, but had a hip fracture-related death.

### Post-hip fracture mortality (secondary outcome)

Among the 915 individuals with CKD stages 3–5 and 161 with normal eGFR who had a hip fracture admission, there were subsequently 666 and 83 all-cause; and 183 and 26 hip fracture-related deaths, respectively. Four patients died on hip fracture admission date and therefore excluded from further analysis. Compared with those alive at the end of follow-up, individuals who died were older (mean age 82.6 (82.1–83.2)) vs 74.7 (73.6–75.8) years), had more comorbidity (Charlson Comorbidity Index score  $\geq 1$ , 42.0% vs 21.4%) and more had CKD stages 3–5 (89.0% vs 75.9%).

Post-hip fracture ACM rates for those who had a hip fracture admission were 488.0 (452.4–526.6) and 308.9 (249.1–383.0) per 1000 PY for those with CKD stages 3–5 and normal eGFR, respectively ([table 3a](#)). CKD stages 3–5 overall were initially associated with ACM. However, after adjusting for age, sex, comorbidity, deprivation, proteinuria and rurality (final model), only the post-hip fracture ACM MRR for CKD stage 4 was increased (2.04 (1.44–2.89)).

Post-hip fracture HFM rates for individuals who had a hip fracture admission were 134.1 (95% CI 116.0 to

155.0) and 96.8 (95% CI 65.9 to 142.1) per 1000 PY for those with CKD stages 3–5 overall and normal eGFR, respectively ([table 3b](#)). The unadjusted HFM MRR for CKD stages 3–5 overall was 1.39 (95% CI 0.92 to 2.09). After adjusting for age, sex, comorbidity, deprivation, proteinuria and rurality (final model), CKD stages 3–5 overall remained not associated with post-hip fracture HFM (MRR 0.79 (95% CI 0.51 to 1.22)), however, CKD stage 4 remained associated (adjusted MRR 1.88 (95% CI 1.02 to 3.47)).

### Discussion

The incidence of hip fracture measured by admissions was increased in those with CKD stages 3–5 overall, and for individual CKD stages 3a, 3b and 4 compared with those with normal eGFR, particularly in younger age groups. The incidence of hip fracture measured by deaths was also increased in those with CKD stages 3b and 4. Post-hip fracture mortality, however, whether ACM or HFM, was not increased in CKD stages 3–5 overall, although it was for CKD stage 4. There were, however, only small numbers of individuals and events for CKD stage 5.

The mechanisms underlying the association between CKD and fractures are likely to be at the metabolic level, due to abnormalities in the parathyroid–calcium–phosphate axis as a result of reduced kidney function.<sup>33</sup> In



addition, CKD may be a marker for frailty, leading to falls and an increased risk of fracture.

In keeping with some<sup>14 16</sup> but not all<sup>17</sup> reports, we have shown that hip fracture incidence is increased in individuals with CKD. We showed this effect is best demonstrated when hip fracture incidence is measured with admissions but also present when measured with deaths. We demonstrated that this increased risk was present across all ages; few previous studies included all age ranges<sup>16 34</sup> and many only included the elderly.<sup>15 35–37</sup> We have shown that despite both CKD and hip fractures being more common in women, this effect of CKD on hip fracture incidence was also raised in men, something that has rarely been demonstrated.<sup>34</sup> We demonstrated that worse CKD stage was associated with increased fracture admission risk (even after accounting for confounders), as reported by Naylor *et al.*<sup>14</sup> However, we found the effect attenuated and not associated in CKD stage 5 due to less statistical power since, unlike Naylor *et al.*<sup>14</sup> we excluded RRT patients from stage 5 and reported RRT as a separate group. Our finding that hip fracture incidence when measured with deaths was only increased among those with more advanced CKD (stages 3b and 4, but not 3a), supports a previous study in patients  $\geq 75$  years.<sup>18</sup>

We found that post-hip fracture mortality, among those who had a hip fracture admission, was little affected by CKD stages 3–5 overall, except stage 4. Studies in general<sup>38</sup> and RRT populations<sup>39</sup> have reported elevated subsequent mortality in individuals who suffer a hip fracture compared with their age-matched non-fractured peers. However, to our knowledge, few studies have investigated the effect of CKD on mortality post-hip fracture.<sup>19 20 40–42</sup> Three reported increased mortality risk with worse renal function, either eGFR<sup>20</sup> or creatinine,<sup>41 42</sup> and one found no mortality risk with worse creatinine after adjusting for confounders.<sup>40</sup> All of these studies, however, only included older patients and were based on single admission creatinine or eGFR, thus, deranged creatinine could be due to acute kidney injury (AKI). A further study relied on hospital admission coding for hip fractures with surgical repair, and a concurrent code for CKD or otherwise,<sup>19</sup> thus limiting CKD ascertainment. Our finding of an effect with stage 4 CKD is consistent with the literature generally—that mortality risk increases with renal function decline. However, in our study the lack of effect with stage 5 is likely due to less statistical power.

This study had several strengths. To our knowledge, this is the first study to report hip fracture incidence using both admission and death records, allowing direct comparison with studies that have used either of these methods. The lack of a consistent effect of CKD on fracture incidence when measured by admission versus death demonstrates the importance of methods of measurement in assessing such an outcome. Fractures are more likely to be recorded during an admission than at death, since for admission, a fracture is likely to be a major event, whereas for a death, many other factors may have contributed, and time between fracture and death

recording may be lengthy. In our cohort, 1076 individuals had a hip fracture recorded from an admission compared with only 228 having a hip fracture recorded at death. GLOMMS-II, a large, population-based cohort including adults  $\geq 15$  years, uses valid methods for assessing comorbidity,<sup>43</sup> identifying individuals with CKD,<sup>22</sup> and has data linkage to long-term outcome data. Importantly, all biochemistry is provided by a single biochemistry service, whether inpatient, outpatient or community. This minimises loss of baseline and follow-up data, avoids selection biases in recruitment, and enables assessment of the relationship between CKD and hip fracture over the full range of adult ages and CKD stages 3–5 groups. The use of at least two serum creatinine measurements to identify CKD (as per KDIGO),<sup>24 25</sup> is a great strength compared with the majority of previous studies, which used only one measurement, therefore risking identifying episodes of AKI as CKD<sup>15</sup>; AKI itself being a risk factor for mortality and often complicates hospital admissions.<sup>23</sup> Access to biochemistry results allowed us to demonstrate the effect of CKD more completely than studies where CKD diagnosis is based on healthcare coding alone.<sup>16 19</sup>

However, our study had limitations. We assessed hip fracture from hospital episode data, and while most patients with a hip fracture are admitted to hospital, we recognise that a very small number may not be admitted. However, we postulate this would be low numbers (we noted only 15 individuals who died with hip fracture as cause of death without a prior hip fracture admission). We only considered hip fractures, acknowledging that CKD may be associated with other fracture sites, but assuming that hip fractures would have more complete admission data, and have been used as a tracer condition for fragility fractures at other sites.<sup>44</sup> The GLOMMS-II cohort inception was 2003, with follow-up to 2009. However, national data suggest that age-standardised and sex-standardised rates of hip fracture admissions have been stable from 2003 for over a decade.<sup>45</sup> In addition, although new treatments have become available since 2003, treatment of hyperparathyroidism in patients with less advanced CKD, who make up the majority of this cohort, has changed little. We did not take into account the competing risk of death, which has been reported to result in an overestimation of the excess risk of hip fracture,<sup>16</sup> however, we have demonstrated the high fracture burden seen. Therefore, hip fracture avoidance is important and specifically measures to address modifiable risk factors in this population. We were unable to adjust for some factors that have been associated with fracture risk, including previous fracture and low bone mineral density (see footnote under [table 2](#)), however, whatever an individual's risk factors are, we have demonstrated the high risk for the population as a whole. Although we did not include individuals with CKD stage 1 or 2, 94% of those with normal eGFR did not have proteinuria measured. Therefore, we cannot rule out the possibility that some individuals in the normal eGFR comparison group could be CKD stage 1 or 2. Finally, in this analysis, renal status was assessed at

baseline, thus, progression of CKD has not been taken into account. We would therefore recommend that the relationship between CKD progression and risk of fracture be investigated in future research.

The findings of this study are directly applicable to Scottish healthcare, and likely applicable across the UK and many worldwide settings. Vitamin D exposure may be lower at extreme latitudes, and may contribute to fracture rate. However, in our study, the exposed (CKD) and unexposed (normal eGFR) groups were from the same population, and Vitamin D exposure would be equivalent, therefore, the relative risk is likely to be relevant internationally. The results summarise the workload faced by health services as a result of CKD-related bone disease. Our finding that individuals with CKD, particularly more advanced, are at higher risk of hip fracture should encourage better assessment and management of risk factors for fracture and falls, including in younger patients with CKD. Risk factors for fracture include modifiable risk factors (alcohol use, smoking, body mass, bone mineral density and medication) and non-modifiable risk factors (age, gender, previous fracture and early menopause). Frailty has been associated with falls<sup>46</sup> and fractures<sup>46 47</sup> in both the general and dialysis populations; and falls are common in those on dialysis.<sup>48</sup> Falls risk assessment should therefore be integral to fracture risk assessment,<sup>32</sup> and perhaps CKD reviews should therefore include consideration of interventions that might improve impaired balance and fracture risks. A reduction in hip fracture incidence would potentially reduce the number of fracture-related deaths overall.

## CONCLUSION

By using different measures of hip fracture incidence and mortality, we have demonstrated why other studies have shown mixed associations between CKD and hip fracture. Hip fracture incidence was higher in individuals with CKD compared with those with normal eGFR particularly where measured with admissions. However, following a hip fracture, CKD did not increase post-hip fracture mortality except in those with CKD stage 4. Nonetheless, a reduction in hip fracture incidence in those with CKD would reduce the number of deaths after hip fracture in the population.

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AM. All authors revised manuscript content and approved the final version of the manuscript and take responsibility for the integrity of the data analysis.

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**Data sharing statement** Deidentified data used for this study are held by Grampian Data Safe Haven. These data are available provided the necessary permissions have been obtained. Further information is available at <http://www.abdn.ac.uk/iahs/facilities/grampian-data-safe-haven.php> and requests for data may be made to Professor Corri Black on behalf of Grampian Data Safe Haven, [corri.black@abdn.ac.uk](mailto:corri.black@abdn.ac.uk).

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