



Kidney function and its association to imminent, short- and long-term fracture risk—a longitudinal study in older women

L. Malmgren^{1,2} · F.E. McGuigan^{1,3} · A. Christensson^{1,4} · K.E. Akesson^{1,3}

Received: 26 April 2019 / Accepted: 28 August 2019 / Published online: 21 November 2019
© The Author(s) 2019

Abstract

Summary Reduced kidney function is associated with an increased fracture risk, although the relationship between an age-related decline and fractures needs further investigation. We followed kidney function and fracture risk for 10 years. A mild-moderate decline in kidney function was associated with fracture, but not in advanced age.

Introduction With age, kidney function declines. Though well known that chronic kidney disease is associated with increased fracture risk, the extent to which the typical age-related decline contributes is unclear. In the OPRA cohort, a longitudinal study of older non-selected women, we investigated the association between kidney function and fracture.

Methods Cystatin C-based kidney function estimates were available at age 75 ($n = 981$) and 80 ($n = 685$). Women were categorized by kidney function: normal (CKD stages 1 and 2), mild-moderate (3a), poor (3b-5), and imminent, short- and long-term fracture risk investigated. BMD measurements and kidney function for risk prediction were also evaluated; women were categorized by both reduced kidney function (stages 3–5) and osteoporosis status.

Results In the short term, 2–3 years, mild-moderate kidney dysfunction was associated with the highest risk increase: osteoporotic fractures (2 years HR_{adj} 2.21, 95% CI 1.27–3.87) and also up to 5 years (between 75 and 80 years) (HR_{adj} 1.51, 1.04–2.18). Hip fracture risk was similarly increased. This association was not observed from age 80 nor for women with poorest kidney function. Reduced kidney function was associated with higher risk even without osteoporosis (osteoporotic fracture; HR_{adj} 1.66, 1.08–2.54); risk increased by having both osteoporosis and reduced function (HR_{adj} 2.53, 1.52–4.23).

Conclusion Older women with mild-moderate reduction of kidney function are at increased risk of fractures, but not those with the worst function. Our findings furthermore confirm the value of osteoporosis assessment and it is possible that in this age group, age-related decline of kidney function has limited contribution compared with BMD.

Keywords Aging · Bone mineral density · Chronic kidney disease · Estimated glomerular filtration rate · Fracture · Women

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00198-019-05152-x>) contains supplementary material, which is available to authorized users.

✉ K.E. Akesson
kristina.akesson@med.lu.se

- ¹ Department of Clinical Sciences Malmö, Lund University, 214 28 Malmö, Sweden
- ² Department of Geriatrics, Skåne University Hospital, 205 02, Malmö, Sweden
- ³ Department of Orthopedics, Skåne University Hospital, 214 28, Malmö, Sweden
- ⁴ Department of Nephrology, Skåne University Hospital, S-205 02 Malmö, Sweden

Introduction

Older women are at increased risk for fragility fractures and the lifetime fracture risk for women above age 50 may be as high as 50% [1]. Hand in hand with old age is a decline in kidney function [2]. Since the kidneys regulate homeostasis of PTH, phosphate, calcium and vitamin D, any disruption in function can be expected to disturb bone remodeling and have implications for skeletal health.

Among individuals with a clinical diagnosis of chronic kidney disease (CKD), a number suffer from chronic kidney disease-mineral and bone disorder (CKD-MBD) [3, 4] and in these individuals, studies suggest that the risk of hip and non-vertebral fractures is increased [5–10]. However, the majority of older people will experience a moderate decline in renal function as part of the normal age-related deterioration,

possibly without developing the specific kidney-associated bone metabolic abnormalities.

We have previously shown that among community-dwelling women age 75 and over, a large proportion have reduced kidney function equivalent to CKD stages 3–5 [11]. Importantly, even without a diagnosis of CKD-MBD, we have shown that reduced kidney function in these women is associated with bone loss and altered mineral homeostasis [12]. Globally, this extrapolates to a large share of the older population potentially susceptible to bone fragility and therefore fracture. Despite this, knowledge is limited in terms of translating this into fracture prediction in the general population without a diagnosis of CKD, especially in the perspective of different time frames for risk, which is highly relevant.

Hence, the purpose of this study is to investigate the association between age-related reduced kidney function and fracture risk in older women. Hypothesizing an association between these two common states in the elderly, firstly, we aim to understand risk in relation to degree of reduced kidney function. Secondly, we aim to determine clinically relevant time frames for fracture risk prediction using imminent, short- and long-term perspectives. Thirdly, we aim to estimate the relevance of bone density measurement in combination with kidney function for fracture risk, i.e., determine the relevance of new Kidney Disease Improving Global Outcome (KDIGO) guidelines.

For this investigation, estimated glomerular filtration rate (eGFR) using cystatin C (cysC) was calculated in the longitudinal and prospective Osteoporosis Prospective Risk Assessment (OPRA) cohort of 1044 women all aged 75 at baseline and followed for 10 years.

Material and methods

Subjects

The OPRA cohort, described previously [13], is a longitudinal and population-based cohort. On their 75th birthday, 1604 Caucasian women, randomly chosen from Malmö city files (between 1995 and 1998) without exclusion criteria, were invited by letter. At baseline, 1044 women attended investigation (65% response rate). Reinvestigations were made after 5 years ($n = 715$ (75% response rate)) and 10 years ($n = 382$ (76% response rate)). Response rate at follow-up and reasons for non-attendance, including deaths, are described in detail [11], as are numbers analyzed for each variable [12]. In this report, we include only women for whom cysC-based eGFR values were available, corresponding to 981 (age 75), 685 (age 80), and 365 women (age 85). At all visits, participants completed an extensive questionnaire on health and lifestyle factors. Weight (kg) and height (cm) were measured using standardized methods and BMI (kg/m^2) was calculated. The study was performed in accordance with the Helsinki declaration and approved by the Lund University

Ethical Review Board. Participants provided written informed consent.

Blood chemistry

Plasma cysC from all visits were analyzed in batch in 2015 using a Cobas auto-analyzer, adjusted to the international reference preparation ERM-DA 471/IFCC, at the Department of Clinical Chemistry (CV ranging from 2.2 to 1.1%), Skåne University Hospital, Malmö, Sweden. Routine blood chemistry was analyzed by standard methods. Urine albumin, important for CKD staging, was not measured.

Kidney function

To most accurately estimate glomerular filtration rate (eGFR) in older individuals, we used cysC [14, 15] and calculated eGFR ($\text{mL}/\text{min}/1.73\text{m}^2$) using the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI) [16].

$$\begin{aligned} P\text{-cysC} \leq 0.8 &: 133 \times (P\text{-cysC}/0.8)^{-0.499} \times 0.996^{\text{Age}} \times 0.932 \\ P\text{-cysC} > 0.8 &: 133 \times (P\text{-cysC}/0.8)^{-1.328} \times 0.996^{\text{Age}} \times 0.932 \end{aligned}$$

Incident fracture registration

Collection and identification of incident fractures has been described in detail previously [17]. Briefly, incident fractures from study start (age 75) until October 31, 2012, were identified by continuously searching the files of the Radiology Department serving the Department of Orthopedics, Skåne University Hospital Malmö and medical files. As this is the only unit treating adult and pediatric fractures in the catchment area, information loss is exceptionally low [18]. In this study, we report fractures only up until second follow-up at age 85 (between Dec 2005 and June 2009), providing a maximum fracture follow-up of 10.4 years (mean 8.8 years). High-energy or pathological fractures were excluded. Osteoporotic fractures were defined as any of the following: hip, pelvis, vertebral, distal radius, or proximal humerus.

Bone mineral density

Areal BMD (g/cm^2) was measured with a Lunar DPX-L (GE Lunar, Madison, WI) using dual-energy x-ray absorptiometry (DXA). Precision error ranged from 0.009 to 0.010 g/cm^2 at the femoral neck (FN). Duplicate measurements from healthy individuals were used to assess the precision of DXA and no drifts in phantom measured results were observed during follow-up [19]. Osteoporosis was defined as femoral neck (FN) T-score ≤ -2.5 .

Statistics

Descriptive data is presented as mean with standard deviation (SD) or median with interquartile range (IQR).

Women were divided into 3 categories based on reduction of kidney function: normal (normal to mild reduction, eGFR ≥ 60 mL/min/1.73m² (equivalent to CKD stages 1 and 2); intermediate (mild-moderate reduction, eGFR 45–59 mL/min/1.73m² (equivalent to CKD stage 3a), and poor (moderate-severe reduction, eGFR < 45 mL/min/1.73m² (equivalent to stages 3b–5) [4]. In additional analyses, intermediate and poor categories were combined into a single group reduced kidney function, defined as eGFR < 60 mL/min/1.73m².

Fracture incidence in 5-year intervals during follow-up is reported using number of first fractures (between 75–80 and 80–85 years). Fracture incidence per 1000 person-years was calculated as $1000 \times \text{total number of fractures} / \text{total follow-up time}$ (time to death OR end of follow-up). Fracture incidence was estimated for hip and osteoporotic fracture and rate ratios calculated.

Fracture risk for women with intermediate or poor kidney function was estimated using Cox proportional hazard models (reference category, normal function), using first fracture event and time at risk (calculated individually as time to fracture, OR death OR end of follow-up). Data is presented unadjusted and adjusted for weight, smoking, and vitamin D (model 1) with additional adjustments for FN BMD (model 2).

Time frames for estimated fracture risk were imminent (1 year) and short term (2 and 3 years), i.e., kidney function at age 75 and incident fractures occurring between age 75–76, 75–77, and 75–78; and long term (5 years), i.e., kidney function age 75, and fractures occurring between age 75 and 80. To evaluate the association between kidney function and fracture in advanced age, we “reset” baseline as kidney function at age 80 and similarly calculated 1, 2, 3, and 5-year fracture risk (Online resource 1). In addition, for the purpose of comparison with other fracture prediction tools, we also present 10-year fracture risk calculations as online resources.

In addition to these cross-sectional analyses, fracture risk was also calculated using only those women who survived the whole follow-up of 10 years ($n = 695$), regardless of visit participation at the reinvestigations.

To assess the utility of routine BMD measurement to predict fracture risk in women with reduced kidney function, and provide much needed prospective data [3], we analyzed combinations of kidney function (normal/reduced) and osteoporosis status (i.e., FN T-score ≤ -2.5). Lumbar spine was not used for diagnosis of osteoporosis due to the high incidence of degenerative changes at this site in elderly individuals [20]. Four categories were created (1) *normal* kidney function (eGFR ≥ 60 mL/min/1.73m²) *without* osteoporosis, (2)

reduced kidney function *without* osteoporosis, (3) *normal* kidney function *with* osteoporosis, and (4) *reduced* kidney function *with* osteoporosis. As described above, Cox proportional hazard models were used (reference category, group 1, i.e., normal kidney function without osteoporosis). Log-log plots were used to confirm the proportional hazard assumptions. Kaplan Meier curves were used to describe fracture-free survival in these different groups. p value for difference was calculated using the log rank test.

A priori power analyses were calculated based on the assumption of 0.13 g/cm² SD in BMD; this study has $> 80\%$ power to detect a 0.056 g/cm² difference between equal groups (5% significance level). Analyses were made with SPSS (IBM SPSS, Version 22.0. Armonk, NY: IBM Corp). A $p < 0.05$ was considered nominally significant.

Results

Kidney function and other characteristics of the OPRA cohort relevant to this study are shown, for each visit, in Table 1. Corticosteroid use, although low overall at age 75, increased across categories of kidney function (2%, 4%, and 6% in the normal, intermediate, and poor categories respectively, $p = 0.009$). At follow-up, it did not differ. Bisphosphonate and calcium/vitamin D use was similar at all timepoints (data not shown).

During the first 5-year follow-up period, osteoporotic fracture incidence in the normal, intermediate, and poor kidney function categories was 15% (86/570 women), 21% (54/252), and 18% (29/159), respectively (Table 2). Baseline kidney function did not differ in women with or without hip fractures. However, women who sustained an osteoporotic fracture (between age 75 and 80) had lower baseline kidney function than women without osteoporotic fracture (eGFR 60.5 mL/min/1.73m² (95% CI 57.9–63.2) versus 63.8 (62.6–65.1); $p = 0.027$). Mean kidney function at age 80 did not differ between those who fractured or not over the following 5 years (i.e., between age 80 and 85 (data not shown)). In contrast, considering fracture incidence per 1000 person-years, women with the poorest baseline kidney function had the lowest fracture incidence from age 75 to 85, although non-significant (Online resource 2).

Kidney function and imminent and short-term fracture risk

Compared with women with normal kidney function, women with intermediate function at age 75 had higher short-term risk of fracture and the association tended to be strengthened after adjustment for confounders; weight, smoking, vitamin D levels, and BMD (Table 3, Fig. 1a). The elevated risk was seen for both hip and osteoporotic fractures within 2 and 3 years (hip fracture HR_{adj} 4.15 and

Table 1 Clinical data of the OPRA cohort at ages 75, 80, and 85

	Age 75 (<i>n</i> 981)		Age 80 (<i>n</i> 685)		Age 85 (<i>n</i> 365)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age (years)	75.2	(0.1)	80.2	(0.2)	85.2	(0.14)
BMI (kg/m ²)	26.3	(4.2)	26.0	(4.2)	25.4	(4.0)
Weight (kg)	68	(12)	66	(11)	64	(11)
Height (cm)	161	(6)	159	(6)	158	(6)
Total body BMD (g/cm ²)	1.007	(0.097)	0.997	(0.097)	0.991	(0.102)
Femoral neck BMD (g/cm ²)	0.765	(0.137)	0.715	(0.128)	0.689	(0.136)
Osteoporosis [#]	255	(26)	282	(41)	175	(48)
P-cysC*(mg/L)	1.06	(0.31)	1.18	(0.34)	1.28	(0.39)
eGFR _{cysC} (mL/min/1.73m ²)	63	(18)	54	(15)	47	(14)
S-PTH* (pmol/L)	4.2	(2.3)	4.6	(2.7)	4.2	(3.1)
P-Phosphate* (mmol/L)	1.11	(0.23)	1.09	(0.19)	1.13	(0.17)
P-Calcium (mmol/L)	2.40	(0.07)	2.41	(0.13)	2.34	(0.09)
S-25(OH)D (nmol/L)	62	(19)	78	(30)	79	(26)
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)
Current smoker	136	(14)	73	(11)	20	(6)
Steroid user	29	(3)	33	(5)	17	(5)
Bisphosphonate user	32	(3)	47	(7)	44	(12)

eGFR_{cysC} calculated using the CKD-EPI formula; reported values are mean (SD) except those marked *which are median (IQR); [#] osteoporosis defined as a FN T-score ≤ -2.5

3.12, osteoporotic fracture HR_{adj} 2.21 and 1.85). Although non-significant, a possible trend towards increased risk of hip fracture within 3 years (HR_{adj} 1.62) and osteoporotic fracture within 2 and 3 years (HR_{adj} 1.18 to 1.41) was seen for women with poor function. Based on the short time period of 1 year (imminent risk), no association between kidney function and fracture was observed. Resetting baseline to kidney function at age 80, the association between kidney function and imminent and short-term fracture risk was directionally similar, while it was not significant.

Kidney function and long-term fracture risk

Similar to short-term risk, reduced kidney function was associated with long-term fracture risk. Women with intermediate kidney function at age 75 had a two-fold higher risk of hip fracture over 5 years (HR_{adj} 2.00, 95% CI 1.00–3.98) compared with those with normal kidney function and fracture risk was also elevated for osteoporotic fractures (HR_{adj} 1.51, 1.04–2.18). For those with poor function, the trend was directionally similar but non-significant (Table 3, Fig. 2a). Evaluating reduced kidney

Table 2 Distribution of kidney function by age and fracture

	Normal kidney function		Intermediate kidney function		Poor kidney function	
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)
Estimated at age 75	570	(58%)	252	(26%)	159	(16%)
Estimated at age 80	236	(35%)	265	(39%)	184	(27%)
No with a fracture between 75 and 80 years						
Hip fracture	21	(4%)	18	(7%)	7	(4%)
Osteoporotic fracture	86	(15%)	54	(21%)	29	(18%)
No with a fracture between 80 and 85 years*						
Hip fracture	17	(7%)	27	(10%)	16	(9%)
Osteoporotic fracture	47	(20%)	70	(26%)	41	(22%)

Kidney function mL/min/1.73m²: normal (eGFR ≥ 60 , stages 1 and 2); intermediate (eGFR 45–59, stage 3a); poor (eGFR < 45, stages 3b–5); *based on the 685 women attending 5-year follow-up

Table 3 Hip and osteoporotic fracture risk—imminent, short and long term—for intermediate and poor kidney function compared with women with normal kidney function at ages 75 and 80

	Kidney function age 75		Kidney function age 80	
	Intermediate (<i>n</i> = 252)	Poor (<i>n</i> = 159)	Intermediate (<i>n</i> = 265)	Poor (<i>n</i> = 184)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Imminent, short- and long-term fracture risk				
One-year risk				
<i>N</i> fractures	3	0	4	1
Hip Fracture	0.97 (0.25–3.73)	NA	1.19 (0.27–5.30)	NA
Adjusted-model 1	0.88 (0.22–3.53)	NA	1.95 (0.35–10.96)	NA
Adjusted-model 2	1.01 (0.23–4.38)	NA	1.94 (0.35–10.92)	NA
<i>N</i> fractures	12	6	11	9
Osteoporotic Fracture	1.36 (0.67–2.79)	1.11 (0.44–2.75)	0.98 (0.41–2.30)	1.18 (0.48–2.91)
Adjusted-model 1	1.36 (0.64–2.88)	1.22 (0.48–3.07)	1.17 (0.43–3.17)	1.41 (0.48–4.13)
Adjusted-model 2	1.42 (0.65–3.11)	0.69 (0.20–2.36)	1.17 (0.43–3.18)	0.89 (0.27–2.93)
Two-year risk				
<i>N</i> fractures	13	1	8	10
Hip Fracture	3.68 (1.52–8.87)*	NA	1.20 (0.42–3.47)	2.23 (0.81–6.14)
Adjusted-model 1	3.59 (1.44–8.93)*	NA	1.37 (0.42–4.39)	2.00 (0.61–6.56)
Adjusted-model 2	4.15 (1.57–10.96)*	NA	1.32 (0.37–4.77)	1.82 (0.50–6.68)
<i>N</i> fractures	29	13	29	20
Osteoporotic Fracture	2.23 (1.34–3.71)*	1.62 (0.85–3.11)	1.31 (0.74–2.31)	1.34 (0.72–2.49)
Adjusted-model 1	2.22 (1.29–3.79)*	1.78 (0.92–3.44)	1.42 (0.76–2.68)	1.26 (0.61–2.60)
Adjusted-model 2	2.21 (1.27–3.87)*	1.18 (0.53–2.63)	1.40 (0.73–2.69)	0.87 (0.39–1.93)
Three-year risk				
<i>N</i> fractures	15	4	15	10
Hip Fracture	2.86 (1.34–6.11)*	1.25 (0.40–3.89)	1.52 (0.67–3.47)	1.51 (0.61–3.72)
Adjusted-model 1	2.97 (1.36–6.51)*	1.40 (0.45–4.38)	1.55 (0.64–3.75)	1.13 (0.40–3.24)
Adjusted-model 2	3.12 (1.36–7.14)*	1.62 (0.50–5.20)	1.53 (0.60–3.89)	1.01 (0.33–3.03)
<i>N</i> fractures	35	19	42	26
Osteoporotic Fracture	1.74 (1.12–2.69)*	1.54 (0.91–2.63)	1.32 (0.83–2.13)	1.21 (0.72–2.06)
Adjusted-model 1	1.82 (1.15–2.87)*	1.75 (1.02–3.01)*	1.34 (0.81–2.24)	0.91 (0.48–1.71)
Adjusted-model 2	1.85 (1.16–2.96)*	1.41 (0.76–2.60)	1.37 (0.81–2.32)	0.68 (0.34–1.35)
Five-year risk				
<i>N</i> fractures	18	7	27	16
Hip Fracture	2.00 (1.06–3.75)*	1.32 (0.56–3.10)	1.47 (0.80–2.69)	1.30 (0.66–2.57)
Adjusted -model 1	2.05 (1.07–3.94)*	1.44 (0.61–3.42)	1.56 (0.81–3.00)	1.20 (0.56–2.59)
Adjusted -model 2	2.00 (1.00–3.98)*	1.41 (0.55–3.57)	1.56 (0.80–3.06)	1.11 (0.50–2.44)
<i>N</i> fractures	54	29	70	41
Osteoporotic Fracture	1.50 (1.06–2.10)*	1.37 (0.90–2.09)	1.38 (0.95–2.00)	1.20 (0.79–1.82)
Adjusted -model 1	1.56 (1.10–2.22)*	1.52 (0.99–2.32)	1.37 (0.92–2.03)	0.97 (0.61–1.56)
Adjusted -model 2	1.51 (1.04–2.18)*	1.23 (0.76–2.01)	1.41 (0.94–2.10)	0.82 (0.50–1.35)

p values calculated using Cox Regression (reference category is normal kidney function, *n* = 570 age 75; *n* = 236 age 80);

**p* < 0.05.; NA—not analyzed due to a low number of fractures

Kidney function mL/min/1.73m²: normal (eGFR ≥ 60, stages 1 and 2); intermediate (eGFR 45–59, stage 3a); poor (eGFR < 45, stages 3b–5). Model 1—adjusted for weight, smoking, and vitamin D levels; model 2—adjusted for weight, smoking, vitamin D levels, and FN BMD

function (i.e., stages 3–5, intermediate and poor combined) versus normal function, fracture risk was higher in women with reduced function (osteoporotic HR_{adj}

1.41, 1.01–1.97; hip HR_{adj} 1.78, 0.95–3.37). Based on kidney function assessed at age 80, no significant association was observed between kidney function and long-

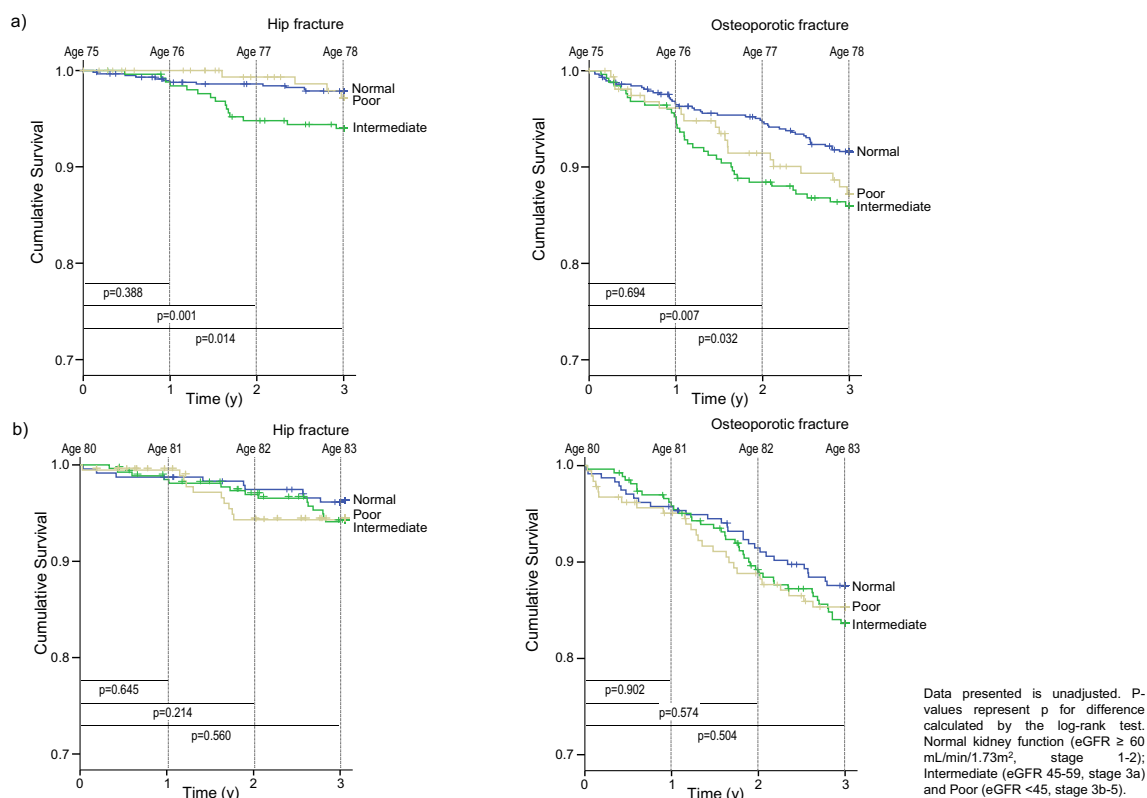


Fig. 1 Imminent and short-term fracture-free survival. **a** Kidney function at age 75 and fractures between 75 and 78. **b** Kidney function at age 80 and fractures between 80 and 83

term fracture risk (Table 3, Fig. 2b). Applying a 10-year risk perspective from age 75, reduced kidney function was not associated with significantly increased fracture risk (Online resource 3 and 4).

Potential influence of survival on risk estimates

Associations between kidney function and increased fracture risk observed in the cross-sectional analysis were validated in the subset of women who survived the entire follow-up ($n = 695$). Among surviving women, those with intermediate kidney function at age 75 had an elevated 5-year risk of hip fracture ($HR_{adj} 3.36$, 95% CI 1.36–8.33). As before, poor kidney function for prediction did not reach statistical significance (hip $HR_{adj} 2.80$, 95% CI 0.85–9.25). In these longitudinal analyses, results for osteoporotic fracture or the other longer time period (80–85 y) were largely similar (data not shown).

Reduced kidney function and osteoporosis

In these analyses, we compare 5-year fracture risk based on combinations of normal or reduced kidney function with or without osteoporosis in order to determine if

BMD added information beyond that of kidney function alone. Supporting our previous observations, reduced kidney function was associated with higher fracture risk even without osteoporosis (hip $HR_{adj} 3.08$ (95% CI 1.05–9.07) and osteoporotic $HR_{adj} 1.66$ (95% CI 1.08–2.54). As expected, fracture risk was high among those with osteoporosis, but risk seemed to further increase in women with both osteoporosis and reduced kidney function compared with those with osteoporosis and normal function (Table 4, Fig. 3).

Discussion

Chronic kidney disease is detrimental to bone health, but the clinical implications of a mild to moderate, age-related loss of function in unselected and otherwise healthy seniors need to be further addressed. Using cysC-based estimations of kidney function, this study aimed to address this question in a cohort of community-dwelling elderly women, a population whose age puts them already at great risk of fracture. We hypothesized that age-related kidney function decline would be associated with fracture risk, but while women with a mild-moderate decline had an up to two-fold risk increase, women

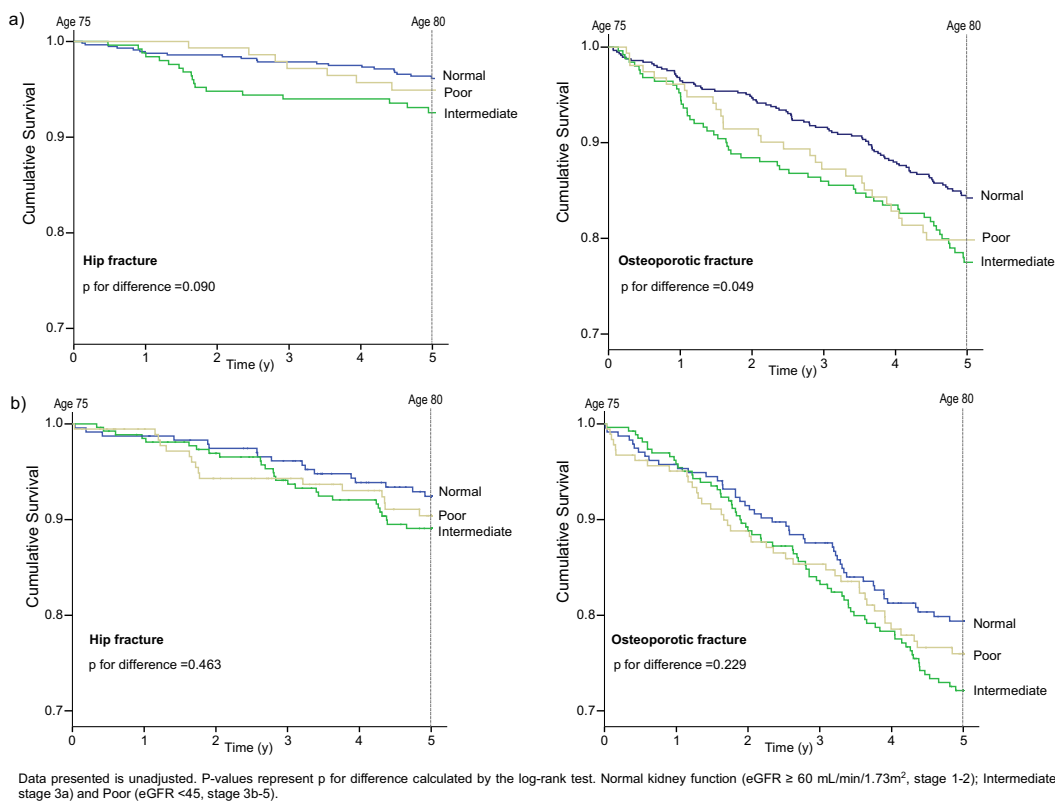


Fig. 2 Long-term fracture-free survival. **a** Kidney function at age 75 and fractures between 75 and 80. **b** Kidney function at age 80 and fractures between 80 and 85

with the worst kidney function showed no increased risk. It was also apparent that eGFR predicts fracture risk best within short-term time frames from the age of 75. Although a directionally similar trend was seen in advanced age, results were non-significant. We also show that even in the absence of osteoporosis, women with reduced kidney function have an increased fracture risk, while the combination of reduced kidney function and diagnosed osteoporosis increased the risk further. These findings indicate that implications for bone health and fracture risk might occur in the very common modest reduction of kidney function in the elderly, and also possibly before a diagnosis of CKD-MBD. However, the association between kidney function and fracture risk in this age group is probably limited compared with that of osteoporosis.

To date, understanding of whether reduced kidney function in the normal elderly poses a short- or long-time threat to skeletal health has been hampered primarily by the lack of standardization between studies, while others are problematic to interpret [21, 22]. Participant ages have been variable as have the follow-up times, time frames for risk prediction, bone density measurements, plasma measurements, and methods for calculating eGFR and CKD staging. Also, many studies have been conducted in selected cohorts of patients already diagnosed with kidney disease, not mirroring the general elderly population. This is reflected in lack of consistency

between studies; Fried et al. report that women, similarly aged to those in the OPRA cohort, with CKD stage 3 or worse were not associated with an increased risk [23]; results confirmed in another longitudinal study [24]. Ensrud et al., conversely, reported that women with intermediate kidney function (stage 3a) had higher hip fracture risk, with an additionally higher risk in those with poor function (3b-5), although based on a smaller sample size and younger than in our study [8]. Other studies report that CKD stages 3 and 4 (intermediate/poor function) are associated with increased risk of hip fracture [5, 7], with up to a four-fold risk increase in the most severely impaired [25]. A recent population-based Dutch study in old adults report results comparable with ours [26]. Nonetheless, what we add with this study is kidney function estimated using cystC, proposed best in the elderly, and a large sample size of females, all of the same age. Two subsequent longitudinal studies have reported that BMD is of value in predicting fracture in CKD, with one of these studies including severe CKD and hemodialysis [27, 28]. Our study aims at further elucidating the complexity of risk prediction in the elderly by stratifying the time frame but also accounting for change over time. Kidney function was most predictive for fractures, both hip and osteoporotic, in the first few years after age 75, although not in the first 12 months, probably explained by the low number sustained in this short time period. No association

was seen in advanced age, possibly explained by a reduction of sample size due to mortality and loss to follow-up. In addition, and contrary to our expectations, no association between women with the worst kidney function and fracture risk was evident, possibly explained by the higher mortality [11].

Severe kidney disease is closely linked to disturbed mineral metabolism and consequently bone fragility. Our observation of an elevated risk of fracture even after adjustment for BMD supports an association between kidney function and bone quality. Furthermore, while reduced kidney function even in the absence of osteoporosis increased the risk of hip fracture, there was clearly an additive risk, with the highest fracture risk in those having both osteoporosis and reduced kidney function. That osteoporosis confers a higher fracture risk than a slight reduction of kidney function is not surprising, although it was only recently, KDIGO overturned its recommendation that routine BMD screening was unnecessary in CKD patients with evidence of CKD-MBD [29, 30]. Our results support this decision, indicating that bone density measurements provide important clinical information, despite the fact that the majority of women in this study most probably do not have a clinically validated diagnosis of CKD. Furthermore, also at earlier CKD stages, in those with mild to moderate reduction, BMD measurement might be of benefit.

Studies on reduced kidney function and osteoporosis-related fractures in older women are of importance since the conditions coexist in a large proportion of the elderly population, with numbers expected to increase [31]. Hence, our findings have implications not only for fracture prediction but for primary and secondary fracture prevention, mainly since drug administration relies on sufficient kidney function. Pharmacological treatment of patients with CKD 1–3, without evidence of CKD-MBD, does not differ from other patients,

but treating those with severely reduced kidney function remains problematic even with newer drugs [32].

Strengths and limitations

The study has limitations; firstly, contrary to our expectations, in our cohort, those with the most impaired kidney function did not have a higher risk of fracture, although, this is most likely due to a low number with very poor kidney function in these elderly women. Since only 3% have eGFR < 30 mL/min/1.73m² (CKD 4–5), this very small sub-group was not separately analyzed. Overall, however, the cohort is likely to well reflect a typical older population of community-dwelling women. Secondly, we also acknowledge that, while replicating the cross-sectional results in only those women who survived the entire 10-year follow-up, we may not have fully accounted for the influence of mortality. Thirdly, although this study was powered for differences in BMD, the age and sex of participants was chosen to capture maximum number of fractures during follow-up. Furthermore, the measurements of cysC and BMD at three consecutive timepoints enable fracture risk calculations across a variety of relevant time windows, although analyses including immediate and short fracture risk might not support multivariate modeling due to a low number of fractures. However, this is not true for the unadjusted data and the two most important confounders, age and sex, are already accounted for in this study since all study participants are women, identically aged. Fourth, participants might be healthier than those who declined [33] and more likely to have fractured [34], although this is a potential bias common to most studies. Lastly, as the OPRA cohort was designed as an osteoporosis study, urine albumin, important for CKD staging, was not a part of study protocol.

Table 4 Kidney function and osteoporosis; 5-year risk of hip and osteoporotic fracture from age 75

Fracture type	Reduced kidney function, without osteoporosis (n = 261)		Normal kidney function with osteoporosis (n = 161)		Reduced kidney function with osteoporosis (n = 94)	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
N fractures	11		15		11	
Hip	3.26 (1.13–9.39)	0.028	7.26 (2.64–19.99)	< 0.001	10.11 (3.51–29.14)	< 0.001
Adjusted*	3.08 (1.05–9.07)	0.041	6.47 (2.25–18.66)	0.001	9.42 (3.25–27.30)	< 0.001
N fractures	47		40		23	
Osteoporotic	1.71 (1.13–2.58)	0.012	2.41 (1.57–3.72)	< 0.001	2.66 (1.60–4.43)	< 0.001
Adjusted*	1.66 (1.08–2.54)	0.020	2.14 (1.34–3.40)	0.001	2.53 (1.52–4.23)	< 0.001

Reduced kidney function defined as intermediate and poor (stages 3a and 3b–5, eGFR ≤ 60 mL/min/1.73m²); Osteoporosis defined as FN T-score ≤ - 2.5

p values calculated using Cox Regression (reference category, normal kidney function, without osteoporosis, n = 379)

*Adjusted using model 1: weight, smoking (yes or no), and vitamin D levels

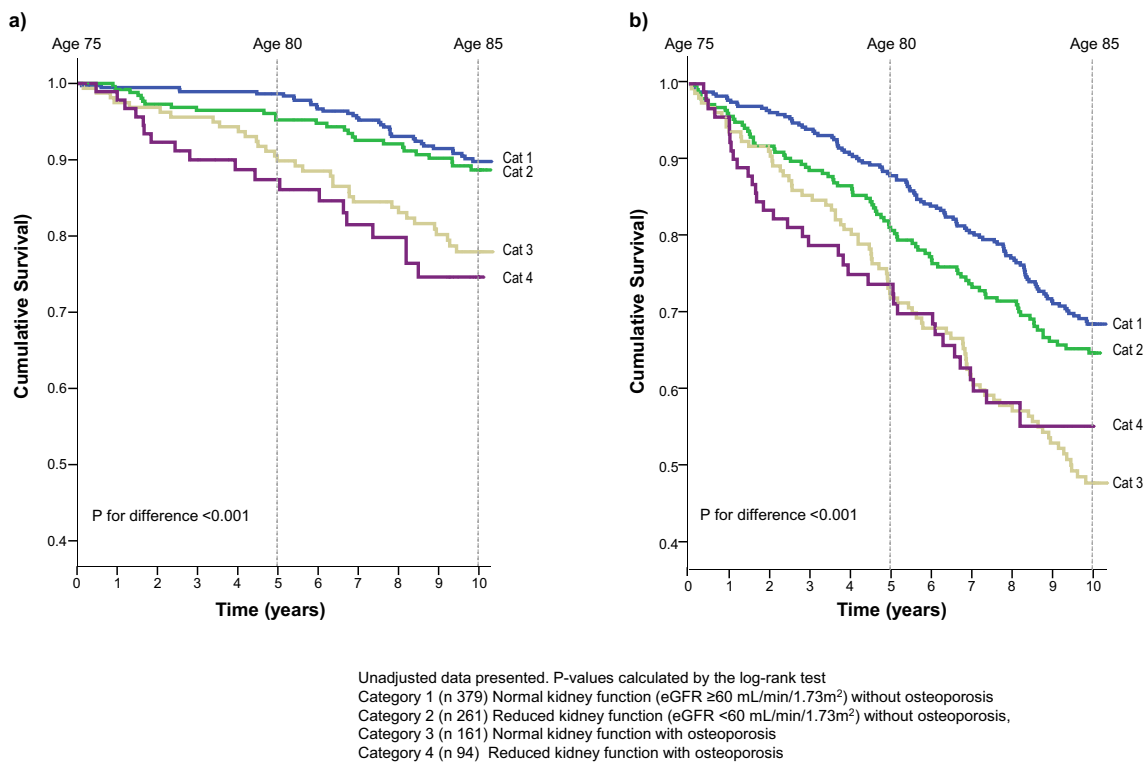


Fig. 3 Ten-year fracture-free survival curves for a the hip and b osteoporotic fracture based on combinations of kidney function (normal/reduced) and osteoporosis (with/without) at age 75

Strengths of this study include the single age of all participants at inclusion, meaning that corrections for age are unnecessary—at older ages, this is particularly relevant given differences between chronological and biological age. Importantly, the participants in this study are randomly selected from the population without any exclusion criteria and with a high participation rate. Hence, considered sufficiently representative of the community, i.e., of older Caucasian women. However, generalization with regard to other populations or ethnicities should be made cautiously. Another strength is the estimation of kidney function with cysC. This new marker of GFR is more trustworthy for GFR compared with creatinine, especially in the elderly [14, 30]. Furthermore, our prior detailed investigations of algorithms most appropriately estimating kidney function in older women provide the clinical foundation with inference for kidney function and bone health.

Conclusion

In older non-selected women, a mild to moderate reduction of kidney function even without a diagnosis of CKD is associated with an increased risk of hip and osteoporotic fracture, for up to 5 years, although not in women with the worst kidney function. This study also confirms the value of DXA assessment in the elderly with reduced kidney function. These findings suggest that the average older women with even

moderately reduced kidney function should be considered for bone health investigation.

Acknowledgments Thanks are extended to funders, the research nurses, and data management at the Clinical and Molecular Osteoporosis Research Unit, Malmö; and to all the women who kindly participated in the study. Thanks are also extended to Paul Gerdmann and Karl Obrant for data collection and to Lars Jephson and Jan-Åke Nilsson for statistical advice.

Funding information Open access funding provided by Lund University. This work was supported by grants from the Swedish Research Council (K2015-52X-14691-13-4), Forte (Grant 2007-2125), Greta and Johan Kock Foundation, A. Pahlsson Foundation, A. Osterlund Foundation, H Järnhardt foundation, King Gustav V 80-year fund, Thelma Zoegas Foundation, Swedish Rheumatism foundation, Skåne University Hospital Research Fund and the Research and Development Council of Region Skåne, Sweden.

Compliance with ethical standards

The study was performed in accordance with the Helsinki declaration and approved by the Lund University Ethical Review Board. Participants provided written informed consent.

Conflicts of interest None.

Open Access This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

- Kanis JA, Johnell O, Oden A, Sembo I, Redlund-Johnell I, Dawson A, De Laet C, Jonsson B (2000) Long-term risk of osteoporotic fracture in Malmö. *Osteoporos Int: J established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 11(8):669–674
- Lindeman RD, Tobin JD, Shock NW (1984) Association between blood pressure and the rate of decline in renal function with age. *Kidney Int* 26(6):861–868
- KDIGO (2009) clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease—Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 76: s1–s130. <https://doi.org/10.1038/ki.2009.188>
- KDIGO (2012) Clinical practice guideline for the evaluation and management of chronic kidney disease (2013). *Kidney Int Suppl* 3(1):19–63 and 73–90
- Ensrud KE, Parimi N, Cauley JA, Ishani A, Slinin Y, Hillier TA, Taylor BC, Steffes M, Cummings SR, Study of Osteoporotic Fractures G (2013) Cystatin C and risk of hip fractures in older women. *J Bone Miner Res* 28(6):1275–1282. <https://doi.org/10.1002/jbmr.1858>
- Kinsella S, Chavrimootoo S, Molloy MG, Eustace JA (2010) Moderate chronic kidney disease in women is associated with fracture occurrence independently of osteoporosis. *Nephron Clinical practice* 116(3):c256–c262. <https://doi.org/10.1159/000317207>
- LaCroix AZ, Lee JS, Wu L, Cauley JA, Shlipak MG, Ott SM, Robbins J, Curb JD, Leboff M, Bauer DC, Jackson RD, Kooperberg CL, Cummings SR, Women's Health Initiative O (2008) Cystatin-C, renal function, and incidence of hip fracture in postmenopausal women. *J Am Geriatr Soc* 56 (8):1434–1441. doi: <https://doi.org/10.1111/j.1532-5415.2008.01807.x>
- Ensrud KE, Lui LY, Taylor BC, Ishani A, Shlipak MG, Stone KL, Cauley JA, Jamal SA, Antonucci DM, Cummings SR (2007) Renal function and risk of hip and vertebral fractures in older women. *Arch Intern Med* 167(2):133–139. <https://doi.org/10.1001/archinte.167.2.133>
- Robertson L, Black C, Fluck N, Gordon S, Hollick R, Nguyen H, Prescott G, Marks A (2018) Hip fracture incidence and mortality in chronic kidney disease: the GLOMMS-II record linkage cohort study. *BMJ Open* 8(4):e020312. <https://doi.org/10.1136/bmjopen-2017-020312>
- Kim SM, Long J, Montez-Rath M, Leonard M, Chertow GM (2016) Hip fracture in patients with non-dialysis-requiring chronic kidney disease. *J Bone Miner Res: the Off J Am Soc Bone Miner Res* 31(10):1803–1809. <https://doi.org/10.1002/jbmr.2862>
- Malmgren L, McGuigan FE, Berglundh S, Westman K, Christensson A, Akesson K (2015) Declining estimated glomerular filtration rate and its association with mortality and comorbidity over 10 years in elderly women. *Nephron* 130(4):245–255. <https://doi.org/10.1159/000435790>
- Malmgren L, McGuigan F, Christensson A, Akesson KE (2017) Reduced kidney function is associated with BMD, bone loss and markers of mineral homeostasis in older women: a 10-year longitudinal study. *Osteoporos Int J established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 28(12):3463–3473. <https://doi.org/10.1007/s00198-017-4221-y>
- Gerdhem P, Ivaska KK, Alatalo SL, Halleen JM, Hellman J, Isaksson A, Pettersson K, Vaananen HK, Akesson K, Obrant KJ (2004) Biochemical markers of bone metabolism and prediction of fracture in elderly women. *J Bone Miner Res: Off J Am Soc Bone Miner Res* 19(3):386–393. <https://doi.org/10.1359/jbmr.0301244>
- Fliser D, Ritz E (2001) Serum cystatin C concentration as a marker of renal dysfunction in the elderly. *Am J Kidney Dis: Off J Natl Kidney Found* 37(1):79–83
- Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, Siscovick DS, Stehman-Breen C (2005) Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 352(20):2049–2060. <https://doi.org/10.1056/NEJMoa043161>
- Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS (2012) Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 367(1):20–29. <https://doi.org/10.1056/NEJMoa114248>
- Bucheber D, McGuigan F, Gerdhem P, Malm J, Ridderstrale M, Akesson K (2014) Vitamin D insufficiency over 5 years is associated with increased fracture risk—an observational cohort study of elderly women. *Osteoporos Int* 25(12):2767–2775. <https://doi.org/10.1007/s00198-014-2823-1>
- Jonsson B, Gardsell P, Johnell O, Redlund-Johnell I, Sernbo I (1994) Remembering fractures: fracture registration and proband recall in southern Sweden. *J Epidemiol Community Health* 48(5): 489–490. <https://doi.org/10.1136/jech.48.5.489>
- Lenora J, Akesson K, Gerdhem P (2010) Effect of precision on longitudinal follow-up of bone mineral density measurements in elderly women and men. *J Clin Densitometry: Off J Int Soc Clin Densitometry* 13(4):407–412. <https://doi.org/10.1016/j.jocd.2010.04.004>
- Tenne M, McGuigan F, Besjakov J, Gerdhem P, Akesson K (2013) Degenerative changes at the lumbar spine—implications for bone mineral density measurement in elderly women. *Osteoporos international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 24(4):1419–1428. <https://doi.org/10.1007/s00198-012-2048-0>
- Naylor KL, Garg AX, Zou G, Langsetmo L, Leslie WD, Fraser LA, Adachi JD, Morin S, Goltzman D, Lentle B, Jackson SA, Josse RG, Jamal SA (2015) Comparison of fracture risk prediction among individuals with reduced and normal kidney function. *Clin J Am Soc Nephrol: CJASN* 10(4):646–653. <https://doi.org/10.2215/cjn.06040614>
- West SL, Lok CE, Langsetmo L, Cheung AM, Szabo E, Pearce D, Fusaro M, Wald R, Weinstein J, Jamal SA (2015) Bone mineral density predicts fractures in chronic kidney disease. *J Bone Miner Res* 30(5):913–919. <https://doi.org/10.1002/jbmr.2406>
- Fried LF, Biggs ML, Shlipak MG, Seliger S, Kestenbaum B, Stehman-Breen C, Sarnak M, Siscovick D, Harris T, Cauley J, Newman AB, Robbins J (2007) Association of kidney function with incident hip fracture in older adults. *J Am Soc Nephrol: JASN* 18(1):282–286. <https://doi.org/10.1681/asn.2006050546>
- Jassal SK, von Muhlen D, Barrett-Connor E (2007) Measures of renal function, BMD, bone loss, and osteoporotic fracture in older adults: the Rancho Bernardo study. *J Bone Miner Res: Off J Am Soc Bone Miner Res* 22(2):203–210. <https://doi.org/10.1359/jbmr.061014>
- Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, Wong C, Stehman-Breen C (2000) Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int* 58(1):396–399. <https://doi.org/10.1046/j.1523-1755.2000.00178.x>
- Chen H, Lips P, Vervloet MG, van Schoor NM, de Jongh RT (2018) Association of renal function with bone mineral density and fracture risk in the Longitudinal Aging Amsterdam. *Osteoporos Int* 29(9): 2129–2138. <https://doi.org/10.1007/s00198-018-4592-8>
- Yenchev RH, Ix JH, Shlipak MG, Bauer DC, Rianon NJ, Kritchevsky SB, Harris TB, Newman AB, Cauley JA, Fried LF, Health A, Body Composition S (2012) Bone mineral density and fracture risk in older individuals with CKD. *Clin J Am Soc Nephrol* 7(7):1130–1136. <https://doi.org/10.2215/CJN.12871211>

28. Iimori S, Mori Y, Akita W, Kuyama T, Takada S, Asai T, Kuwahara M, Sasaki S, Tsukamoto Y (2012) Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients—a single-center cohort study. *Nephrol Dial Transplant* 27(1):345–351. <https://doi.org/10.1093/ndt/gfr317>
29. Isakova T, Nickolas TL, Denburg M, Yarlagadda S, Weiner DE, Gutierrez OM, Bansal V, Rosas SE, Nigwekar S, Yee J, Kramer H (2017) KDOQI US commentary on the 2017 KDIGO clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Am J Kidney Dis: Off J Natl Kidney Found* 70(6):737–751. <https://doi.org/10.1053/j.ajkd.2017.07.019>
30. Group KDIGOKC-MUW (2017) KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). *Kidney Int Suppl* 7:1–59
31. Nickolas TL, Leonard MB, Shane E (2008) Chronic kidney disease and bone fracture: a growing concern. *Kidney Int* 74(6):721–731. <https://doi.org/10.1038/ki.2008.264>
32. Miller PD (2014) Chronic kidney disease and the skeleton. *Bone research* 2:14044. <https://doi.org/10.1038/boneres.2014.44>
33. Wihlborg A, Akesson K, Gerdhem P (2014) External validity of a population-based study on osteoporosis and fracture. *Acta Orthop* 85(4):433–437. <https://doi.org/10.3109/17453674.2014.920987>
34. Gerdhem P, Akesson K (2007) Rates of fracture in participants and non-participants in the Osteoporosis Prospective Risk study. *J Bone Joint Surg (Br)* 89(12):1627–1631. <https://doi.org/10.1302/0301-620x.89b12.18946>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.