



The association between chronic kidney disease, falls, and fractures: a systematic review and meta-analysis

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Received: 14 March 2019 / Accepted: 4 October 2019 / Published online: 12 November 2019
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Abstract

Patients with chronic kidney disease (CKD) are more likely to experience falls and fractures due to renal osteodystrophy and the high prevalence of risk factors for falls. However, it is not well established how great the risk is for falls and fractures for the different stages of CKD compared to the general population. The objective of this systematic review and meta-analysis was to assess whether, and in which degree, CKD was associated with falls and fractures in adults. A systematic search in PubMed, Embase, CINAHL, and The Cochrane Library was performed on 7 September 2018. All retrospective, cross-sectional, and longitudinal studies of adults (18 years of older) that studied the association between CKD, fractures, and falls were included. Additional studies were identified by cross-referencing. A total of 39 publications were included, of which two publications assessed three types of outcome and four publications assessed two types of outcome. Ten studies focused on accidental falling; seventeen studies focused on hip, femur, and pelvis fractures; seven studies focused on vertebral fractures; and thirteen studies focused on any type of fracture without further specification. Generally, the risk of fractures increased when kidney function worsened, with the highest risks in the patients with stage 5 CKD or dialysis. This effect was most pronounced for hip fractures and any type of fractures. Furthermore, results on the association between CKD and accidental falling were contradictory. Compared to the general population, fractures are highly prevalent in patients with CKD. Besides more awareness of timely fracture risk assessment, there also should be more focus on fall prevention.

Keywords Accidental falls · Chronic kidney disease · Dialysis · Fracture

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00198-019-05190-5>) contains supplementary material, which is available to authorized users.

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Introduction

Worldwide, chronic kidney disease (CKD) is highly prevalent, with an estimated prevalence of 7% in stages 3 to 5 and with even higher rates in the elderly population [1]. Patients with CKD are prone to fractures due to renal osteodystrophy. This is a complex disease which is caused by a disturbance in metabolic and hormone levels (e.g., altered levels of calcium, phosphorus, parathyroid hormone, and vitamin D) that impairs bone quality and is characterized by abnormal bone remodeling [2, 3]. These bone abnormalities are seen in a majority of patients with CKD stage 3–5 and in all patients requiring dialysis [4]. Therefore, it is likely that patients with mild to moderate CKD already have a higher risk of fractures and that risk of fracture increases when kidney function decreases. Fractures in patients with CKD are a serious complication and are associated with a high morbidity, mortality [5], and economic burden [6, 7].

An important risk factor for fractures are falls [8]. Falls are a result of a complex interaction of factors such as muscle

weakness, neuropathy, polypharmacy, chronic illnesses, cognitive decline, impaired mobility, and frailty [9], of which are all highly prevalent in patients with CKD [10]. Therefore, it is likely that patients with CKD are also more prone to falls than patients without CKD. In addition to a high morbidity, mortality, and economic burden, falls can also lead to fear of falling, which can cause a decrease in physical activity and social isolation [11] and could thereby even further increase the risk of falling. Hence, although both falls and fractures seem to be important problems for patients with CKD, it is not well established how great the risk is for falls and fractures for the different stages of CKD compared to the general population.

More knowledge about the risk of falls and fractures could lead to better risk stratification, which could lead to better prevention strategies. Therefore, the objective of this systematic review is to assess whether, and in what degree, chronic kidney disease is associated with falls and fractures in adults.

Methods

Search strategy and selection criteria

We aimed to identify cross-sectional or cohort studies that investigated the association between chronic kidney disease, falls, and fractures, through a comprehensive search (from conception to September 7, 2018) of PubMed, Embase, CINAHL, and The Cochrane Library. We used the search terms *chronic kidney disease (dialysis patients included)*, *fracture*, and *falling*, with relevant synonyms. The complete search strategy is shown in Appendix 1. No limits were applied in the search.

Two authors (NG, GW) independently screened title and abstract, removed duplicate publications, and selected studies that assessed the association of CKD and fractures or falling. Studies were also included if association estimates could be calculated from prevalence/incidence from a CKD population compared to a non-CKD population. Animal studies, studies in children, studies in very specific populations (e.g., only patients with systemic lupus erythematosus, aluminum related bone disease), case reports, systematic reviews, conference abstracts, opinion papers, and studies not published in English were excluded. Considering intervention studies could possibly influence the outcome of falls or fractures, only intervention studies in which the placebo group was assessed were included in the study. The publication retrieval was completed by cross-reference checking in Web of Science for selected articles; citations of retrieved reviews, meta-analysis, and guidelines were also screened for potentially omitted studies. A similar selection procedure as described above was followed to check for eligibility of articles that were thereby retrieved. Initial disagreements on eligibility and selection of

articles were resolved by discussion and their inclusion is based on full consensus.

Data extraction

Data regarding study design and results were independently extracted by two investigators (NG and FO) for each eligible study. Items that were extracted are study design, patient selection, number of participants (dialysis, CKD), demographics (age, sex), method for estimated glomerular filtration rate (eGFR) calculation, as well as the outcomes in terms of association between CKD falling and fractures. If a study provided various measurements of eGFR, first choice was to extract data of the CKD-EPI based on serum creatinine. When this was not available, second choice was the MDRD based on serum creatinine, followed by the Cockcroft Gault (CG) (based on serum creatinine) and other measurements. Measurements of eGFR based on urinary creatinine were not included, as these made our studies less comparable. Furthermore, baseline characteristics were extracted for the whole population.

Quality assessment

The methodological quality of each of the studies was assessed independently by two reviewers (NG and FO), using the Newcastle-Ottawa quality assessment scale. This scale was adapted to create one scale for quality assessment of longitudinal studies, case-control studies, and cross-sectional studies (Appendix 2). Disagreements among the reviewers were discussed during a consensus meeting, and in case of persisting disagreement, the assistance of a third reviewer (MH) was enlisted.

Data synthesis and analysis

If baseline characteristics were not available for the whole population, these were calculated when possible. To increase comparability, we estimated unadjusted odds ratio (OR) or rate ratios using the reported number of participants or reported incidence rates for the studies in which only this information and no adjusted results were published. When multiple incidences were provided in the course of the study, the most recent incidence was used to calculate a rate ratio. Furthermore, to keep the studies as comparable as possible, when data was stratified by age, only data of all age categories of ≥ 65 years were included ($n = 2$ [12, 13]). To visualize the risks of falls and the various fracture types, the calculated and given association estimates were visualized in a graph. To enhance the clarity of this graph, we only included eGFR categories 60–89, 45–59, 30–44, 15–29, and < 15 .

For the meta-analysis, we summarized results for the studies that provided a hazard ratio (HR) or rate ratio for the hip

fracture and any type of fracture group using a random-effects model using the generic inverse variance method expressed as HR with 95% confidence intervals (95%CI). Heterogeneity was quantified by the I^2 statistic. All analyses were conducted using Review Manager 5.3. For the group of vertebral fractures and accidental falls the number of studies per different stage of CKD was considered too small and the studies too heterogeneous (different association estimates, different outcomes, e.g., all falls vs. only serious hospitalized fall incidents) to perform a meta-analysis.

Results

Characteristics of included studies

Our search identified 12,149 potential publications (6023 from Embase, 5490 from PubMed, 348 from CINAHL, and 288 from Cochrane). After removing 1890 duplicates and 10,220 studies for other reasons (Fig. 1), a total of 37 unique publications were included in this review. Cross reference checking yielded two additional publications.

The characteristics of the 39 included studies are summarized in Table 1. The first publication is from 2000 and the most recent from 2018. Most studies were conducted in the USA. The size of the study populations ranged from 173 to 4,099,342 (median 5601). Most studies included elderly

patients, with a median age over 65 years in most studies. Eight studies included only dialysis patients [13–20], all other studies included various stages of CKD. Ten studies focused on accidental falling [19, 21–29]; seventeen studies focused on hip, femur, and pelvis fractures [12–14, 17, 18, 20, 24, 30–39]; seven studies on vertebral fractures [12, 15, 22, 24, 31, 40, 41]; and thirteen studies focused on any type of fracture without further specification [12, 16, 22, 29, 42–50].

Quality assessment

Results of quality assessment can be found in Fig. 2 and Table 1. Reviewer agreement was over 95% for all aspects. The overall quality of included articles was good with a mean score of 6.1 out of 9 (standard deviation (SD) 1.2). Especially for the studies that assessed different types of fractures, many studies did not specify if they included or excluded patients with a previous fracture [13–15, 17, 18, 22, 24, 35–37, 40, 41, 46, 48, 50], and so risk of bias was often unclear regarding the definition of controls. This was also a concern with the non-response rate and rate of lost to follow-up: almost half of the studies did not report data on this. Furthermore, for the any type of fracture group, almost all studies used ICD codes without radiographic confirmation. Full details of the quality assessment can be found in Appendix 3.

Fig. 1 Flowchart diagram

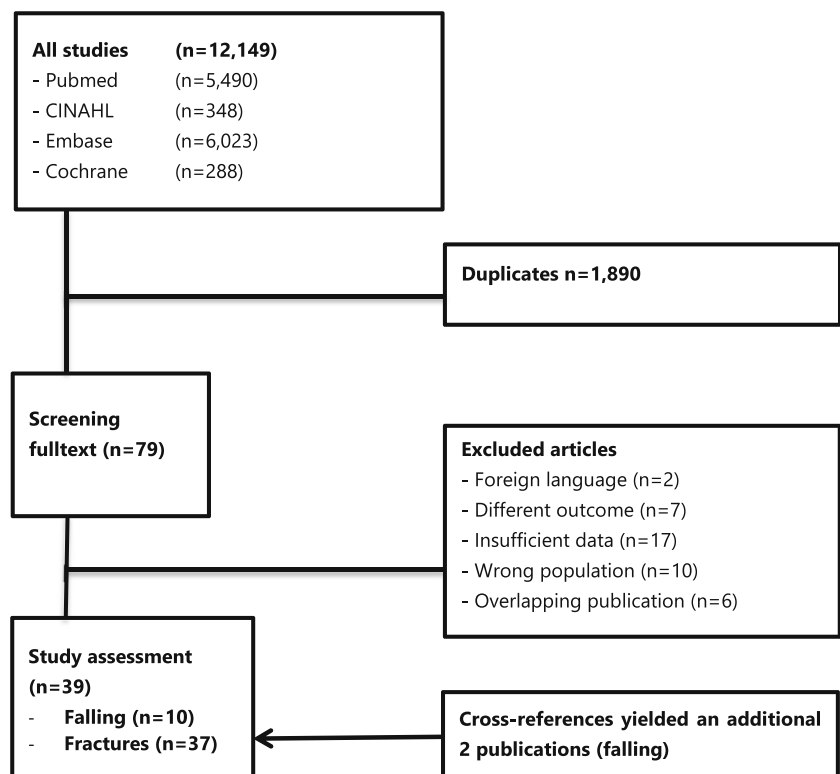


Table 1 Characteristics of the included studies

Study	Study design	Patient selection	Number of participants	Number of patients with eGFR < 60/ dialysis**	Age (median (± range))	% male	Me(dia)an follow-up time in years (range)	Overall score assessment (.../9)	Outcome			
									Accidental falls	Hip/femur +pelvis fractures	Vertebral fracture	Any type of fracture
Alem, 2000 [14]	RCS	US Renal Data System (USRDS)	?	326,464**	NR	56%	? (?–7)	4	X			
Arneson, 2013 [13]	RCS	Medicare, USA	1,267,416*	101,995**	≥ 66	46%*	? (?–1)	7	X			
Ateritiano, 2017 [15]	CS	Population-based cohort, USA	192	92**	65.9*	78%*	NA	8		X		
Bowling, 2016 [21]	PCS	Population-based cohort, USA (REGARDS)	8744	1604	≥ 65	51%	5.9 (?–9.9)	7	X			
Chen, 2018 [22]	PCS	Population-based cohort, The Netherlands (LASA)	1477	560*	75.8 ± 6.6	48%	? (?–6)	7/8	X		X	X
Coco, 2000 [18]	RCS	Outpatient dialysis unit (monocenter)	NR	1272	58 ± 0.4	49%	3.2 (?–10)	7	X			
Daya, 2016 [42]	PCS	Population-based (ARIC), USA	10,955	693	63.3*	44%*	13 (?–15)	7				X
Dooley, 2008 [30]	RS	Multicenter Veteran clinic, USA	33,091	13,632	67.5 (?)	100%	3 (?–7)	8	X			
Dukas, 2005 [23]	PCS	Multicenter study, Germany	186	NR	75.0 ± 4.1	48%*	? (?–0.7)	6	X			
Dukas, 2005 [24]	CS	Post hoc subanalysis of RCT	5313	NR	74.0 (?)	20%	NA	6/5	X	X		
Elliott, 2013 [12]	PCS	Population-based cohort, Canada	1,815,943	128,957	≥ 65	44%	4.4 (?–6)	5	X	X		X
Ensrud, 2007 [31]	CC	Population-based cohort, USA (SOF)	396	186	≥ 65	0%	5.9 (?)	6	X		X	
Ensrud, 2012 [43]	CC	Multicenter cohort study, USA (WHI-OS)	2190	NR	64.3*	0%	8.6 (?–12)	8				X
Ensrud, 2014 [32]	CC	Population-based cohort, USA (MrOS)	1602	388	73.8*	100%	7.9 (?–8)	8	X			
Fried, 2007 [33]	PCS	Population-based cohort, USA	5888	1190*	74.8*	42%*	7.1 (?)	7	X			
Hall, 2015 [25]	RCS	Multiple nursing homes, USA (RCT CONNECT for quality)	510	179*	77.2 ± 11.5	73%	0.2 (?–0.5)	7	X			
Hall, 2018 [44]	PCS	Multicenter Veteran clinic, USA	712,918	356,459	73.0*	100%	5.2 (?–10)	6				X
Hansen, 2016 [16]	RCS	Danish population + all patients receiving dialysis in Denmark	4,099,342	7566**	46*	49%	? (?–2)	6				X
Iwagami, 2018 [34]	RCS	Population-based cohort, England	484,698	242,349	75.4 ± 9.7	39%	4.2 (?–10)	7	X			
Kaji, 2010 [40]	CS	Outpatient clinic for metabolic bone disorders, Japan	659	85	64.5 ± 8.2	0%	NA	5			X	
Kim, 2016 [35]	RCS	Multicenter cohort, USA (NIS)	278,018	38,932	NR	31%*	? (?–1)	5	X			
Kinsella, 2010 [45]	CS	Monocenter study, Ireland	1702	347	61.7 ± 10.8	0%		4				X

Table 1 (continued)

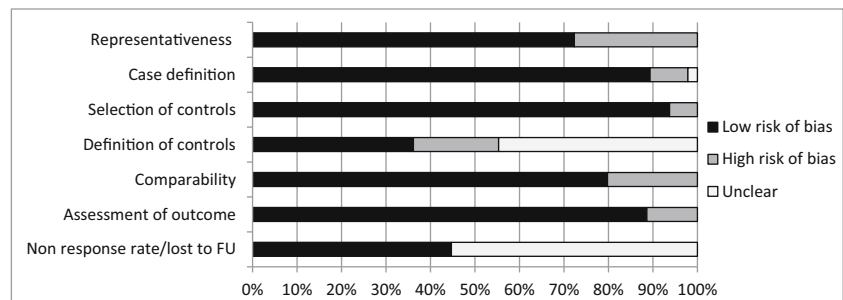
Study	Study design	Patient selection	Number of participants	Number of patients with eGFR < 60/ dialysis**	Age (me(dia)n (± range)	% male	Me(dia)n follow-up time in years (range)	Overall score quality assessment (.../9)	Outcome			
									Accidental falls	Hip/femur +pelvis fractures	Vertebral fracture	Any type of fracture
Kistler, 2018 [26]	CS	Behavioral risk factor surveillance system (BRFSS), USA	157,753	9116	≥ 65	44%	NA	6	X			
Kurajoh, 2018 [46]	CS	Multicenter study, Japan	555	181	76.8*	0%	NA	6				X
LaCroix, 2008 [39]	CC	Multicenter cohort study, USA (WHI-OS)	794	144	71 (?)	0%	7 (0.7–9.3)	9		X		
Liao, 2016 [47]	RCS	Population-based cohort, Taiwan (LHID2005)	11,312	1427	≥ 40	68%	2.6 (?–10)	6				X
Maravic, 2014 [17]	RCS	French national database	68,953	29,487**	82.1*	24%*	? (?–1)	5		X		
McCarthy, 2008 [50]	PCS	Multicenter cohort + population-based cohort, USA	427	85	68 ± 13.5	0%	14 (?–25)	7				X
Mishima, 2015 [41]	CS	Tertiary center, Japan	173	68	62.3 ± 12.2	57%	NA	4			X	
Naylor, 2014 [29]	PCS	Population-based cohort, Canada	679,114	107,841	> 65	45%*	? (?–3)	7	X			X
Naylor, 2015 [49]	PCS	Population-based cohort, Canada (CaMos)	2107	320	67.2*	29%	4.8 (?–5)	4				X
Nickolas, 2006 [36]	CS	Population-based cohort, USA (NHANES III)	6270	875	64.9*	48%*	NA	6		X		
Pérez-Sáez, 2015 [37]	RCS	Population-based cohort, Spain (SIDIAPO)	873,073	32,934	67.6	47%	3 (?–3)	6		X		
Račić, 2015 [19]	CS	Multiple HD centers, Bosnia and Herzegovina and Serbia + primary care center	406	106**	77.6*	61%	NA	4			X	
Rafiq, 2014 [27]	RS	Multiple GP databases, UK (QICKD)	135,433	NR	75.4 ± 7.6	44%	2.5 (?–5)	6	X			
Robertson, 2018 [38]	RCS	Single health region Scotland	39,630	19,882	63.3*	41%*	? (5.5–?)	7			X	
Rothenbacher, 2014 [28]	PCS	Population-based cohort, Ulm + Germany (ActiFE)	1385	196	75.6 ± 6.5	57%	1 (?–1)	8	X			
Wakasugi, 2013 [20]	RCS	All dialysis facilities in Japan	NR	128,141	NR	62%	? (?–1)	4			X	
Yenchek, 2012 [48]	PCS	Population-based cohort, USA (Health, aging, and body composition study)	2754	587	73.6 ± 2.9	49%*	11.3 (?)	7				X

PCS prospective cohort study, CS cross-sectional study, RCS retrospective cohort study, CC case-control study, NR not reported, NA not applicable, ? not reported

*Calculated

**Only dialysis patients included

Fig. 2 Quality assessment



Accidental falling

Results for accidental falling are shown in Table 2 and Fig. 3a. Ten studies assessed the association between CKD and accidental falling [19, 21–29]. Of these, five studies used an eGFR ≥ 60 as a reference category [19, 21, 25, 28], two studies an eGFR ≥ 65 [23, 24], one study an eGFR > 90 [27], one study the highest quartile (eGFR ≥ 74) [22], and one study compared used self-reported medical history of CKD [26]. Half of the included studies did not find an association between CKD and accidental falling [21, 22, 25, 27, 28], irrespective of CKD stage, reference category, and/or adjustment for potential confounders. The two studies that used an eGFR of ≥ 65 as reference both showed a significant association between a lower eGFR and falls with adjusted odds ratios ranging from 1.69 to 4.01 [23, 24]. An increasing risk of accidental falling was seen with decreasing kidney function in the two studies where risk ratios were calculated from prevalence/incidence (stage 3a risk ratio 1.55, stage 3b risk ratio 2.00, stage 4 risk ratio 2.39, stage 5 risk ratio 3.45 [29], and hemodialysis risk ratio 4.7 [19], Fig. 3a). In addition, one study addressed the association between self-reported medical history of CKD and falls and found a significant association (OR_{adj} 1.26, 95% CI 1.13–1.47) [26].

Hip fractures

Results for hip fractures are shown in Table 3 and Fig. 3b. Seventeen studies reported on the association between CKD and hip fractures [12–14, 17, 18, 20, 24, 30–39]. Fifteen studies used an eGFR ≥ 60 as a reference category [12–14, 17, 18, 20, 30, 32–38, 51], one study an eGFR ≥ 65 [24], and one study an eGFR > 90 [39]. Eleven out of seventeen studies found a higher risk of hip fractures for the different stages of CKD [12–14, 17, 18, 20, 34–38]. Three studies found an association for only the higher stages of CKD (eGFR < 30 [30], eGFR < 45 [31], and < 60 [39]) and hip fractures. Furthermore, three out of seventeen studies did not find an association between CKD and hip fractures [12, 32, 33]; although one study did show an increasing rate ratio when kidney function decreases, no association was seen between

CKD and hip fracture when adjusted for potential confounders [12]. Generally, risks were increased when kidney function decreased [12, 31, 38], with the highest fracture risks in stage 5/dialysis [13, 14, 17, 18, 20, 35] (Fig. 3b).

Vertebral fractures

Results for vertebral fractures are shown in Table 4 and Fig. 3c. Seven studies reported on vertebral fractures and CKD [12, 15, 22, 24, 31, 40, 41]. All but one study [24] used an eGFR of ≥ 60 as the reference category. Four out of seven studies found a higher risk of patients with CKD of developing vertebral fractures, compared to the non-CKD population [15, 24, 40, 41]. Furthermore, two other studies found a higher risk of vertebral fractures for patients with CKD, but when adjusted for potential confounders this risk was fully attenuated [12, 31]. This effect was not seen in the remaining study that did not found an association at all [22].

Any type of fracture

Results for any type of fracture are shown in Table 5 and Fig. 3d. Thirteen studies reported on incident fractures of any type and CKD [12, 16, 22, 29, 42–50]. Six studies used an eGFR ≥ 60 as reference category [12, 22, 29, 44, 48, 49], two studies a reference category of ≥ 90 [42, 43], one study a reference category of 75–89 [45], two studies did not specify their reference category (no CKD/general population) [16, 47], and two studies assessed the association between fractures in a continuous way [46, 50]. Eight out of thirteen studies found a higher risk of fractures when eGFR decreased < 60 ml/min/1.73 m² [16, 22, 29, 43–45, 48, 49]. Two studies found an increasing rate ratio, but when adjusted for potential confounders, this was fully attenuated [12, 42]. The three remaining studies that did not find an association studied very mild CKD (eGFR 60–90) [50], assessed eGFR in a continuous way [46] or did not specify their reference group [47]. In all included studies where multiple CKD stages were included, the risk of fractures increased when eGFR worsens [12, 22, 29, 43–45] (Fig. 3d).

Table 2 Study results for the association between accidental falling and chronic kidney disease

Study	eGFR method	Degree of kidney impairment					Adjusted (+/-)	Reference group
		< 15	15–29	30–44	< 45	45–59		
Bowling, 2016 [21]	CKD-EPI (creatinine)				HR 1.09 (0.86–1.37)‡	HR 0.91 (0.76–1.09)	+ ^{a,b,c,d,e,f}	≥ 60
Chen, 2018 [22]	MDRD (creatinine)						+ ^{a,b,c,d}	≥ 74
Dukas, 2005 [23]	CG (creatinine)						+ ^{a,c,d,e}	≥ 65
Dukas, 2005 [24]	CG (creatinine)						+ ^{a,c,e}	≥ 65
Hall, 2015 [25]	MDRD (creatinine)				Rate ratio 1.06 (0.85–1.32)	Rate ratio 0.97 (0.76–1.23)	+ ^{a,f}	≥ 60
Kistler, 2018 [26]	Self-report						+ ^{a,d,f}	Non-CKD
Naylor, 2014 [29]	CKD-EPI (creatinine)	♀ Risk ratio 3.45*	♀ Risk ratio 2.39*	♀ Risk ratio 2.00*		♀ Risk ratio 1.55*	–	≥ 60
Račić, 2015 [19]	Hemodialysis	Risk ratio 4.7*					–	Non-CKD
Rafiq, 2014 [27]	NHS codes						+ ^{a,b,d,e}	≥ 90
Rothenbacher, 2014 [28]	CKD-EPI (cystatin C)						–	≥ 60

CG Cockcroft-Gault formula, CKD-EPI Chronic Kidney Disease Epidemiology Collaboration, MDRD Modification of Diet in Renal Disease, OR odds ratio, HR hazard ratio

*Calculated from available data

‡Dialysis patients and/or stage 5 excluded

Adjustment

^aDemographics

^bToxications (e.g., alcohol, smoking status)

^cBMI, weight

^dComorbidity

^eUse of antihypertensive medication, psychoactive medication, antidepressants, sedatives, polypharmacy

^fImpaired mobility

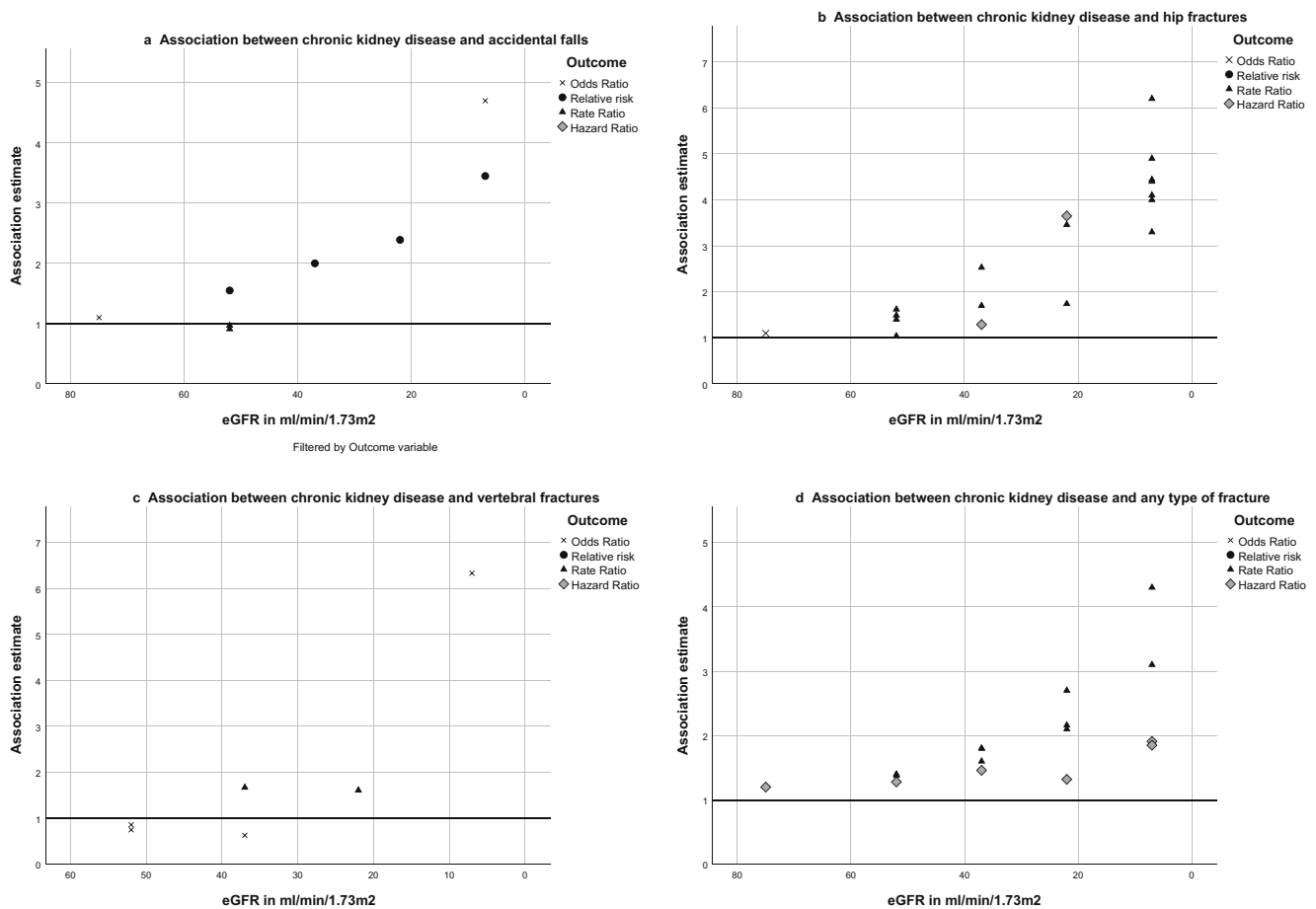


Fig. 3 a–d Association between chronic kidney disease, accidental falls (a), hip fractures (b), vertebral fractures (c), and all fractures (d)

Meta-analysis

For the hip fracture outcome, all studies that provided a hazard ratio or from which a rate ratio with 95%CI could be calculated were summarized in a meta-analysis (Fig. 4a). Subsequently, three studies were excluded because they only provided an odds ratio [24, 36, 39] and three studies were excluded because no 95%CI could be calculated [13, 17, 35]. All excluded studies found an association between CKD and hip fractures [13, 17, 24, 35, 36, 39]. All studies that were included into the meta-analysis assessed older adults (mean age of 63 years and older) [12, 14, 20, 30, 32–34, 37, 38]. Only in the largest study, which consisted of 1,815,943 patients, adjusted rate ratios were not reported [12]. There was a significant association between fractures and eGFR category < 60, 30–44, 15–29, and < 15. For the eGFR category of 45–59, there was a borderline association with a pooled HR of 1.36 (95%CI 0.99–1.86). There was a graded risk, with higher risk among the more severe stages of CKD. However, the heterogeneity among the estimates was large (in most subgroups $I^2 \geq 90\%$).

Also for the any type of fracture outcome, all studies that provided a hazard ratio or from which a rate ratios with 95%CI could be calculated are summarized in a meta-analysis (Fig.

4b). Two studies were excluded because they only provided odds ratios [45, 46], and two studies were excluded because they only provided risk ratios [48, 49]. As only one study assessed CKD in a continuous way with a hazard ratio as outcome [50], a meta-analysis for this outcome was not considered feasible. Half of the excluded studies did not find an association between mild stages of CKD and fractures [45, 46, 50]. In the studies that were included into the meta-analysis, mean age ranged from 46 [16] to 75.8 years [22]. Furthermore, two of the included studies rate ratios could not be adjusted for potential confounders [12, 29]. In the meta-analysis, there was a significant association between fractures and eGFR categories 45–59, 30–44, 15–29, and < 15. The risk was higher in more severe stages of CKD, with the highest risk in patients with an eGFR < 15 (pooled HR of 2.63 (95%CI 1.74–3.98). However, the heterogeneity was large, especially in the more severe stages of CKD (stage 4 and 5, I^2 94% and I^2 98%, respectively).

Discussion

In this systematic review, we found that a lower eGFR is associated with a higher fracture risk. This effect was the most

Table 3 Study results for the association between hip/femur fractures and chronic kidney disease

Study	eGFR method	Degree of kidney impairment					Adjusted (+/−)	Reference group
		< 15	15–29	< 30	30–44	< 45		
Alem, 2000 [14]	Dialysis	♂Rate ratio 4.44 (4.16–4.75) ♀Rate ratio 4.40 (4.16–4.64)						General population
Arneson, 2013 [13]	Hemodialysis	Rate ratio 4.0*						Non-ESKD
Coco, 2000 [18]	Dialysis	Rate ratio 17.4 (12.4–34.0)						General population
Dooley, 2008 [30]	MDRD (creatinine)		♂HR 3.65 (1.87–7.13)‡					General population
Dukas, 2005 [24]	CG (creatinine)					OR 1.57 (1.18–2.09)‡		General population
Elliott, 2013 [12]	CKD-EPI (creatinine)		Rate ratio 3.46 (3.13–3.83)*		Rate ratio 2.53 (2.38–2.69)*	Rate ratio 1.62 (1.54–1.71)*		≥ 60
Ensrud, 2007 [31]	MDRD (creatinine)			♀HR 1.58 (0.59–4.23)		♀HR 1.49 (0.93–2.38)		≥ 60
Ensrud, 2014 [32]	CKD-EPI (creatinine)					♂HR 0.92 (0.58–1.47)		≥ 60
Fried, 2007 [33]	MDRD (creatinine)					♂HR 0.97 (0.58–1.62) ♀HR 1.38 (0.99–1.94)		≥ 60
Iwagami, 2018 [34]	CKD-EPI (creatinine)			HR 1.72 (1.59–1.85)‡	HR 1.29 (1.24–1.36)	HR 1.04 (1.00–1.08)		≥ 60
Kim, 2016 [35]	ICD	Rate ratio 3.30*				Rate ratio 1.53*‡		Normal kidney function
LaCroix, 2008 [39]	Cystatin C [^] -1*76.7					♀OR 2.64 (1.41–4.97)	♀OR 1.10 (0.71–1.73)	≥ 90
Maravic, 2014 [17]	Dialysis	Rate ratio 4.1*						Non-dialysis
Nickolas, 2006 [36]	MDRD (creatinine)					OR 2.32 (1.13–4.74)‡		≥ 60
Pérez-Sáez, 2015 [37]	ICD					HR 1.16 (1.06–1.27)		≥ 60
	MDRD (creatinine)							≥ 60

Table 3 (continued)

Study	eGFR method	Degree of kidney impairment					Adjusted (+/-)	Reference group	
		< 15	15–29	< 30	30–44	< 45			45–59
Robertson, 2018 [38]			Rate ratio 1.74 (1.30–2.33)		Rate ratio 1.70 (1.38–2.09)		Rate ratio 1.40 (1.16–1.70)	Rate ratio 1.49 (1.24–1.79)	
Wakasugi, 2013 [20]	Dialysis		♂Rate ratio 6.2 (5.7–6.8) ♀Rate ratio 4.9 (4.6–5.3)						+ ^a General population

CG Cockcroft-Gault formula, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *MDRD* Modification of Diet in Renal Disease, *ESKD* end-stage kidney disease, *OR* odds ratio, *HIR* hazard ratio

*Calculated from available data

‡Dialysis patients and/or stage 5 excluded

Adjustment

^aDemographics (e.g., age, sex, race)

^bIntoxications (e.g., alcohol use, smoking status)

^cBMI, weight

^dComorbidity (e.g., diabetes, osteoporosis)

^eAdjusted for antiosteoporotic treatment (e.g., bisphosphonates) or exclusion of patients with antiosteoporotic drug use

^fUse of steroids, or exclusion of patients with steroid use

^gLaboratory values (e.g., calcium, phosphorus, PTH, 25-OHD)

^hBMD

Table 4 Study results for the association between vertebral fractures and chronic kidney disease

Study	eGFR method	Degree of kidney impairment				Adjusted (+/–)	Reference group
		< 15	15–29	30–44	< 45		
Vertebral fractures							
Atteritano, 2017 [15]	Hemodialysis	OR 6.33 (2.92–13.73-)*				+ ^a	Normal kidney function
Chen, 2018 [22]	MDRD (creatinine)			OR 0.63 (0.53–1.24)	OR 0.86 (0.56–1.32)	+ ^{a,b,c,d}	≥ 60
Dukas, 2005 [24]	CG (creatinine)					+ ^{a,b,c,e,f}	≥ 65
Elliott, 2013 [12]	CKD-EPI (creatinine)		Rate ratio 1.61 (1.37–1.89)*	Rate ratio 1.67 (1.54–1.81)*	Rate ratio 1.35 (1.27–1.44)*	–	≥ 60
Ensrud, 2007 [31]	MDRD (creatinine)				♀ OR 0.75 (0.45–1.23)	+ ^{a,c,h}	≥ 60
Kajii, 2010 [40]	MDRD (creatinine)				♀ OR 2.32 (1.45–3.71)*	– ^{e,f}	≥ 60
Mishima, 2015 [41]	Formula proposed by the Japanese Society of Nephrology				OR 2.48 (1.20–5.12)*‡	– ^{e,f}	≥ 60

CG Cockcroft-Gault formula, CKD-EPI Chronic Kidney Disease Epidemiology Collaboration, MDRD Modification of Diet in Renal Disease, OR odds ratio

*Calculated from available data

‡Dialysis patients and/or stage 5 excluded

Adjustment

^aDemographics (e.g., age, sex, race)

^bIntoxications (e.g., alcohol use, smoking status)

^cBMI, weight

^dComorbidity (e.g., diabetes, osteoporosis)

^eAdjusted for anti-osteoporotic treatment (e.g., bisphosphonates) or exclusion of patients with antiosteoporotic drug use

^fUse of steroids, or exclusion of patients with steroid use

[‡]Laboratory values (e.g., calcium, phosphorus, PTH, 25-OHD)

^bBMD

Table 5 Study results for the association between any type of fracture and chronic kidney disease

Study	eGFR method	Degree of kidney impairment					Adjusted (+/-)	Reference group
		< 15	15–29	30–44	45–59	Other		
Chen, 2018 [22]	MDRD (creatinine)			HR 1.46 (1.12–1.91)	HR 1.28 (1.12–1.46)		+ ^{a,b,c,d}	≥ 60
Daya, 2016 [42]	CKD-EPI (creatinine)			Rate ratio 1.80 (1.72–1.88)*	Rate ratio 1.38 (1.33–1.42)*	HR 0.89 (0.56–1.41)	+ ^{a,b,c,d,e,f}	≥ 90
Elliot, 2013 [12]	CKD-EPI (creatinine)		Rate ratio 2.16 (2.00–2.34)*				-	≥ 60
Ensrud, 2012 [43]	CKD-EPI (cystatin C)					♀ HR 2.46 (1.16–5.21)	+ ^{a,e}	≥ 90
Hall, 2018 [44]	MDRD	♂ HR 1.91 (1.45–2.50)	♂ HR 1.32 (1.16–1.49)			♀ HR 1.16 (0.85–1.58)	+ ^{a,b,c,d,e}	≥ 60
Hansen, 2016 [16]	Dialysis	HR 1.85 (1.75–1.95)					+ ^{a,d,e}	General population
Kinsella, 2010 [45]	MDRD (creatinine)					♀ OR 1.37 (1.0–1.89)	+ ^{a,e,f}	75–89
Kurajoh, 2018 [46]	Japanese formula for eGFR _{cr}					GFR < 75 ♀ OR 1.20 (0.93–1.55) Per 10 ml/min/1.73 m ² decrease: OR 0.96 (0.85–1.01)	+ ^{a,b,c,d}	NA
Liao, 2016 [47]	?					CKD HR 1.10 (0.95–1.27) Per 10 ml/min/1.73 m ² decrease: HR 0.92 (0.84–1.01)	+ ^{a,d,f}	No CKD
McCarthy, 2008 [50]	MDRD						+ ^{a,e}	NA
Naylor, 2014 [29]	CKD-EPI	♂ Rate ratio 4.3 (3.70–5.00) ♀ Rate ratio 3.1 (2.80–3.50)	♂ Rate ratio 2.7 (2.20–3.30) ♀ Rate ratio 2.1 (1.90–2.30)	♂ Rate ratio 1.8 (1.60–2.00) ♀ Rate ratio 1.6 (1.50–1.70)	♂ Rate ratio 1.3 (1.20–1.40) ♀ Rate ratio 1.40 (1.30–1.50)		-	≥ 60
Naylor, 2015 [49]	CKD-EPI (creatinine)					Risk ratio 1.86 (1.07–3.24)*	-	≥ 60
Yenchek, 2012 [48]	MDRD (creatinine)					Risk Ratio 1.26 (1.02–1.56)*	-	≥ 60

CG Cockcroft-Gault formula, CKD-EPI Chronic Kidney Disease Epidemiology Collaboration, MDRD Modification of Diet in Renal Disease, CKD chronic kidney disease

*Calculated from available data

‡Dialysis patients and/or stage 5 excluded

Adjustment

^a Demographics (e.g., age, sex, race)

^b Intoxications (e.g., alcohol use, smoking status)

^c BMI, weight

^d Comorbidity (e.g., diabetes, osteoporosis)

^e Adjusted for antiosteoporotic treatment (e.g., bisphosphonates) or exclusion of patients with antiosteoporotic drug use

^f Use of steroids, or exclusion of patients with steroid use

^g Laboratory values (e.g., calcium, phosphorus, PTH, 25-OHD)

^h BMD

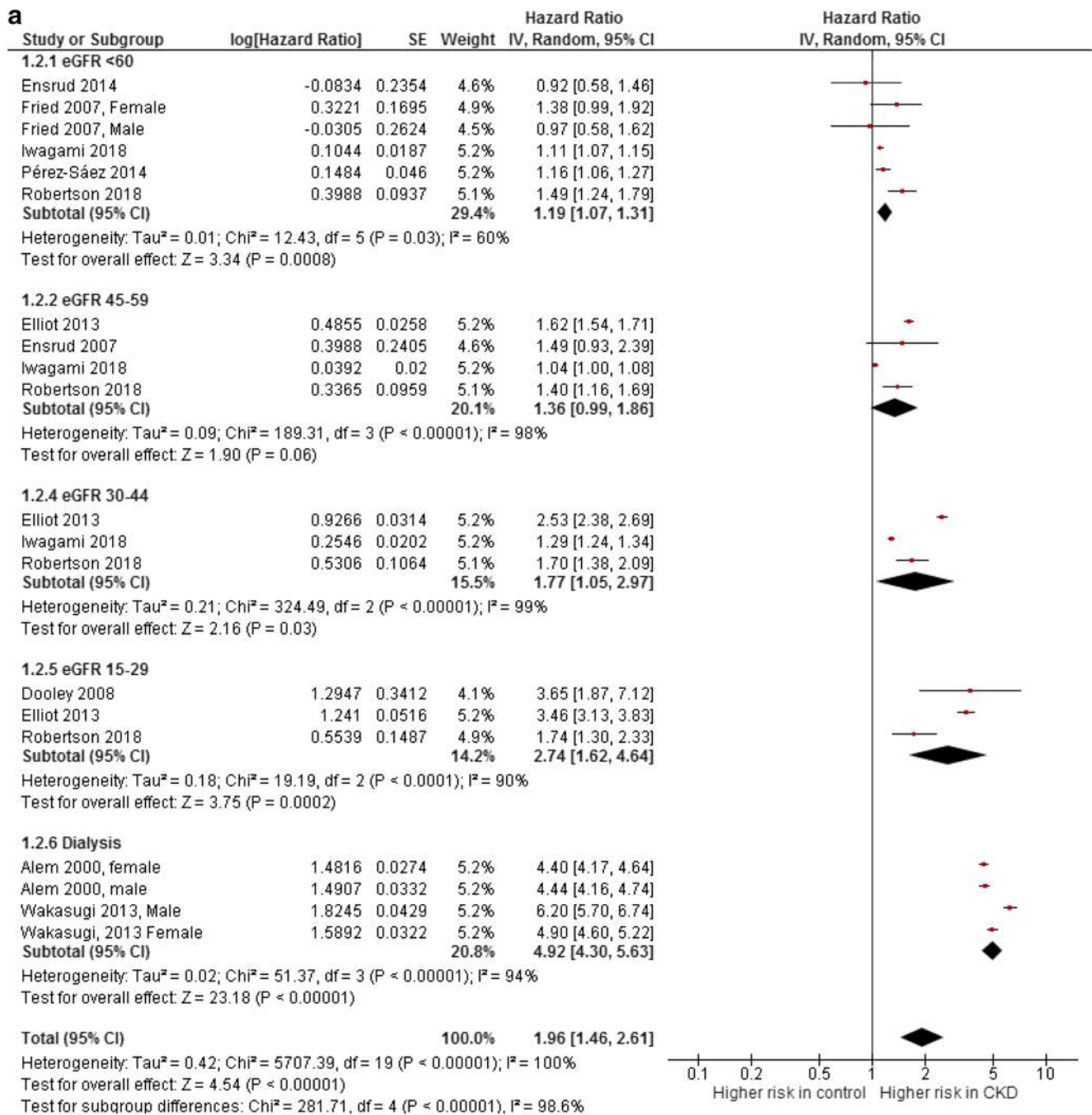


Fig. 4 a Associations of chronic kidney disease with incidence of hip fractures. **b** Associations of chronic kidney disease with any type of fracture

pronounced for the hip fractures and the any type of fracture group. Furthermore, the risk is higher when kidney function worsens, and starts approximately at an eGFR of < 60 (Fig. 3a–d and Fig. 4). For the association between a decreased eGFR and accidental falling, the evidence is contradictory.

The findings that we report on fractures support our hypothesis that a decreasing eGFR is associated with a higher fracture risk. Moreover, almost all studies that assessed patients with stage 5 found that CKD is an independent risk

factor for fractures with pooled hazard ratios of 4.9 for hip fractures and 2.6 for the any type of fracture group. This is in line with previous studies that showed that even in early stages of CKD, and in almost all patients with stage 5, an abnormal bone histology was found [52]. Although there were only a limited number of studies that assessed vertebral fractures, it is interesting that this risk seems to be lower compared to the hip and any type of fracture group. One possible explanation for these lower relative risks could be that half of the

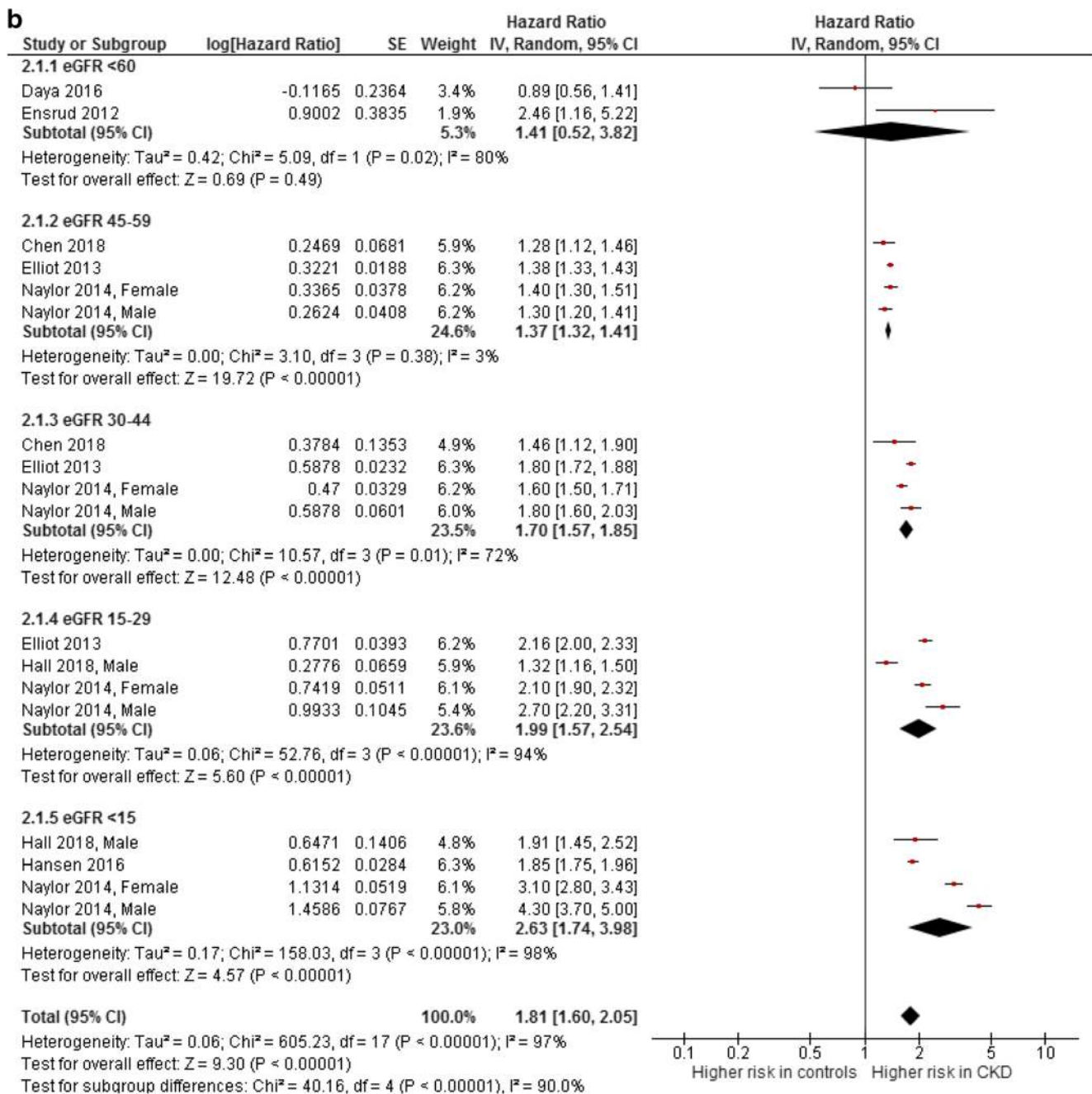


Fig. 4 (continued)

studies used ICD codes or medical history to diagnose vertebral fractures [12, 24, 31]. Prior research showed that approximately two thirds of vertebral fractures remain unnoticed as they are frequently asymptomatic [53]. Thus, it is likely that fractures are missed in studies that used ICD codes and/or medical history to diagnose vertebral fractures, and therefore, a potential difference between vertebral fractures in patients with CKD and patients without CKD.

In general, there was a graded risk for falls when kidney function worsens (Fig. 3a). However, half of our studies did not find an association between CKD and accidental falling.

One possible reason that some studies did not find an association between falls and CKD is that they adjusted their results for multiple confounders. There are several reasons why patients with CKD could fall more often compared to patients without CKD. First, CKD is frequently caused by hypertension and diabetes, which are both associated with falls [54, 55]. Second, CKD and treatment for optimization of CKD can lead to risk factors of falling. For example, due to inflammation and malnutrition, patients with CKD are more prone for muscle degeneration [56], which could lead to instability and falls. Furthermore, medication (e.g., ACE inhibitors) that is

frequently administered to patients with CKD could lead to postural hypotension, which is also a risk factor for falls. Third, CKD is more common in the elderly population, which is also an important risk factor [9]. Subsequently, this could mean that patients with CKD fall more often because of their risk profile, and not primarily because they have CKD.

Risks could also have been influenced by the type of measurement of eGFR. To keep our study results as comparable as possible, we chose to use the most frequently used measurements to estimate GFR (CKD-EPI, MDRD, and CG based on serum creatinine). However, serum creatinine is dependent on muscle mass, which could lead to a false-negatively low serum creatinine due to low muscle mass and therefore relatively “good” eGFR in the frail elderly [42]. This could potentially have led to a higher fracture rate in the better eGFR ranges. Another method to estimate eGFR in this population could be the use of cystatin C which is independent of muscle mass. For example, two studies did not find an association for eGFR based on creatinine, but did find an association between eGFR based on cystatin C and any type of fracture [42, 46]. On the other hand, another study that compared both methods did not find any difference for the association between CKD and hip fractures [32]. More research is needed to explore the differences in outcome when using cystatin C compared with serum creatinine.

As patients with CKD have much higher rates of fractures compared to the non-CKD population, it is very important to screen these patients timely for potential risk factors. For fractures, the updated Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends “BMD testing to assess fracture risk in patients with CKD stage 3a to 5 with evidence of CKD-BMD and/or risk factors for osteoporosis, if results will impact treatment decisions [57].” This could mean that in clinical practice, much more frequent BMD measurements should be done in patients with CKD, especially in the elderly with previous falls. Furthermore, as treatment of renal osteodystrophy is very complicated in the advanced stages of CKD due to the heterogeneity of the illness and the limited experience with different treatments, and most of the low-energy fractures in patients older than 50 years are caused by a fall [22, 58], it is also very important to prevent and lower the risks of falling as much as possible. Prior research has shown that most patients who experienced a fall did not mention this to their healthcare provider [59]; therefore, it is necessary for nephrologists and general practitioners to actively ask about previous falls in patients with CKD. At this moment, there is no clear recommendation from the KDIGO guidelines to screen for accidental falling or to start interventions in patients with high risk of fracture (or falls). This could be important as it can potentially prevent morbidity and even mortality, as various studies showed that multiple interventions are able to lower the risk of falling in patients with CKD [60–62].

This systematic review provides valuable information about the fracture and fall risk of patients with CKD, but it has several limitations. Included studies were heterogeneous, assessing different CKD stages, different eGFR methods, different definitions for falls and fractures, and different methods to measure the outcome. Therefore, a meta-analysis could not be performed for the outcome of vertebral fractures and accidental falls. Second, most studies were performed in elderly patients. Although we also presented some evidence for the younger patients, this evidence was scarce and our findings can possibly not be fully extrapolated to the younger CKD population. However, considering falls and fractures, elderly are most at risk and therefore identification in this population could lead to the highest benefit. Third, considering non-English manuscripts were excluded what could potentially have led to publication bias.

In conclusion, fractures are very common in the CKD population and the risk increases when kidney function worsens. Besides more awareness of timely fracture risk assessment, there also should be more focus on fall prevention.

Compliance with ethical standards

Conflicts of interest None.

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