Bone 148 (2021) 115960

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Estimated Glomerular Filtration Rate (eGFR) based on cystatin C was associated with increased risk of hip and proximal humerus fractures in women and decreased risk of hip fracture in men, whereas eGFR based on creatinine was not associated with fracture risk in both sexes: The Tromsø Study

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ARTICLE INFO

Keywords:
Chronic kidney disease
Creatinine
Cystatin C
Fracture
Women
Men

ABSTRACT

Purpose: Patients with end-stage kidney disease have an increased fracture risk. Whether mild to moderate reductions in kidney function is associated with increased fracture risk is uncertain. Results from previous studies may be confounded by muscle mass because of the use of creatinine-based estimates of the glomerular filtration rate (eGFRcre). We tested the hypothesis that lower eGFR within the normal range of kidney function based on serum cystatin C (eGFRcys) or both cystatin C and creatinine (eGFRcrecys) predict fractures better than eGFR based on creatinine (eGFRcre).

Methods: In the Tromsø Study 1994–95, a cohort of 3016 women and 2836 men aged 50–84 years had eGFRcre, eGFRcys and eGFRcrecys estimated using the Chronic Kidney Disease Epidemiology Collaboration equations. Hazard ratios (HRs) (95% confidence intervals) for fracture were calculated in Cox's proportional hazards models and adjusted for age, height, body mass index, bone mineral density, diastolic blood pressure, smoking, physical activity, previous fracture, diabetes and cardiovascular disease.

Results: During a median of 14.6 years follow-up, 232, 135 and 394 women and 118, 35 and 65 men suffered incident hip, proximal humerus and wrist fractures. In women, lower eGFRcre did not predict fracture, but the risk for hip and proximal humerus fracture increased per standard deviation (SD) lower eGFRcys (HRs 1.36 (1.16–1.60) and 1.33 (1.08–1.63)) and per SD lower eGFRcrecys (HRs 1.25 (1.08–1.45) and 1.30 (1.07–1.57)). In men, none of the eGFR estimates were related to increased fracture risk. In contrast, eGFRcys and eGFRcrecys were inversely associated with hip fracture risk (HRs 0.85 (0.73–0.99) and 0.82 (0.68–0.98)).

Conclusions: In women, each SD lower eGFRcys and eGFRcrecys increased the risk of hip and proximal humerus fracture by 25–36%, whereas eGFRcre did not. In men, none of the estimates of eGFR were related to increased fracture risk, and each SD lower eGFRcys and eGFRcrecys decreased the risk of hip fracture by 15–18%. The findings particularly apply to a cohort of generally healthy individuals with a normal kidney function. In future studies, the association of measured GFR using the gold standard method of iohexol clearance with fractures risk

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https://doi.org/10.1016/j.bone.2021.115960
Received 10 February 2021; Received in revised form 22 March 2021; Accepted 11 April 2021
Available online 14 April 2021

should be examined for causal inference. More clinical research is needed before robust clinical inferences can be made.

1. Introduction

Chronic kidney disease (CKD) affects approximately 10% of the adult population, and the incidence increases with advancing age [1]. In patients with CKD, fractures are associated with high morbidity, mortality and increased economic burden [2–5]. Patients with end-stage kidney disease have a higher fracture risk than the general population [6], but the risk for fractures in a general population with mild to moderate kidney function is unclear.

The relationship between kidney function and bone mineral density (BMD) is not well-defined. Reduced kidney function was not associated with lower femoral neck BMD in one study [7], and only in men in another study, which was partly explained by circulating parathyroid hormone (PTH) levels [8]. Others have reported reduced kidney function to be associated with low BMD of the total hip, but not of the spine [9].

Accurate assessment of kidney function requires cumbersome and costly measurement of glomerular filtration rate (GFR) using exogenous filtration markers, such as iohexol clearance [10]. Due to the lack of feasibility of these methods in clinical practice and large epidemiological studies, various equations have been developed to calculate validated estimates of GFR, based on endogenous biomarkers that are eliminated mainly by filtration through the glomeruli. In 2009, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) published an equation for eGFR based on serum creatinine (eGFRcre) and in 2012 an equation based on cystatin C (eGFRcys) and both (eGFRcrecys) [11,12]. Both eGFRcre and eGFRcys are influenced by non-GFR related factors that may confound the association between GFR and outcomes [13,14]. Importantly, eGFRcre is influenced by muscle mass, which may confound the association with fractures. A patient with large muscle mass for age and sex may have false low eGFRcre and low fracture risk. Conversely, a patient with sarcopenia may have false high eGFR and high fracture risk. Cystatin C is almost independent of age, sex and muscle mass, but may be influenced by other factors such as diabetes, smoking, obesity and inflammation [15]. In internal validation of models, equations that incorporated both creatinine and cystatin C showed a better ability to detect true GFR than equations based on each marker alone [13]. Moreover, the eGFRcrecys equation is less biased by non-GFR related factors [14,16].

Studies of community-dwelling older adults that have measured both eGFRcre and eGFRcys have reported that eGFRcys or eGFRcrecys, and not eGFRcre was associated with fracture risk, especially hip fracture risk [17–20]. However, the relationship between eGFRcre and fracture risk, may have been confounded by muscle mass, an important risk factor for fractures. Few population-based prospective studies have investigated the effect of kidney function on risk of fractures other than hip fractures [6,21]. In a systematic review and meta-analysis of the association between CKD, falls and fractures, most of the studies included elderly patients, with a median age over 65 years [6]. We expand upon this literature by focusing on a younger population, the vast majority of whom have normal kidney function and by studying not only hip fracture but also proximal humerus and wrist fractures.

The aims of this project were to investigate whether lower eGFR, calculated using creatinine, cystatin C and both (eGFRcre, eGFRcys, eGFRcre-cys), was associated with reduced BMD and increased fracture risk in women and men ≥50 years of age in the Tromsø Study. We tested the hypothesis that lower eGFRcys or eGFRcrecys within the normal range of kidney function is associated with reduced BMD and predict fractures better than eGFRcre in a general population with a high incidence of fracture.

2. Materials and methods

The Tromsø Study is a single-center, population-based health study in Northern Norway, with seven surveys conducted in 1974, 1979–80, 1986–87, 1994–95, 2001, 2007–08, and 2015–16 [22–25]. We used data from the fourth survey in 1994–95 (Tromsø 4) where all inhabitants in Tromsø over the age of 24 years were invited, and 27,158 subjects (72%) participated (Fig. 1). A total of 26,992 consented to medical research. After excluding 16,728 subjects below 50 years of age, 10,264 subjects 50–94 years of age remained. After excluding 4398 subjects with missing measurements of creatinine or cystatin C, five subjects who moved before Tromsø 4 and nine subjects with pathological fracture, 5852 subjects (3016 women and 2836 men) were left included in this cohort study. Of these, 123 subjects were missing valid BMD measurements at an extended examination [22]. All participants gave their informed written consent. The study is approved by the Regional Committee for Medical and Health Research Ethics and the Norwegian Data Inspectorate and is conducted in accordance with the World Medical Association Declaration of Helsinki.

At baseline, self-administered questionnaires were filled in. The participants reported whether they were currently smoking, a teetotaler and hours of moderate and hard physical activity during leisure time. A physical activity score was made by adding the hours/week of moderate and hard physical activity, giving the hours with hard activity double weight: score = moderate + 2 hard. Participants reported the use of blood pressure (BP) lowering drugs, oral corticosteroids and hormone replacement therapy (HRT), and whether they had diabetes, cardiovascular disease (CVD, angina, myocardial infarction and/or stroke), or a previous fracture of the hip and/or wrist. No participants reported to use bisphosphonates at baseline.

At baseline, height and weight were measured in light clothing without shoes, and body mass index (BMI) was calculated as weight divided by the square of height (kg/m^2). BMD was measured at the non-dominant distal forearm, with Single X-ray Absorptiometric (SXA)-devices (DTX-100 Osteometer Medi Tech, Inc., Hawthorne, California) and the coefficient of variation (CV) was 0.8% [26]. BMD was not measured at the hip, and a total body scan for assessment of muscle mass was not performed. Detailed description of the measurement methods, the strict quality control procedures for densitometry and long-term performance of the densitometers are previously published [22,24,27]. The systolic and diastolic BP was measured 3 times and we used the mean values from the second and third measurements. Non fasting blood samples were drawn and analyzed at the Department of Clinical Chemistry, University Hospital of North Norway, Tromsø [28]. Plasma creatinine was originally analyzed by a modified Jaffe reaction [29,30]. The plasma and serum samples were further stored at −70 °C. As the CKD-EPI equation used for estimation of eGFRcre is validated for enzymatic creatinine measurements, 111 plasma samples were thawed and reanalyzed with an enzymatic method (Modular P/Roche Diagnostics) in 2006. This is an isotope dilution mass spectrometry (IDMS) traceable assay, i.e. a standardized method. The plasma samples were randomly selected from the range of creatinine between 40 and 180, and reanalyzed creatinine values were fitted to a linear regression model, whereupon adjusted plasma creatinine values were calculated for all participants [29]. Cystatin C was analyzed in 2007 and 2009 from frozen serum in a Modular E analyzer (Roche Diagnostics, Mannheim, Germany) with turbidimetric immunoassay (Gentian AS, Moss, Norway), and intraassay CV was 4.0% [30]. The 52 samples with cystatin C values below the limit of detection (0.45 mg/L) were given a value midway between zero and the limit of detection (0.22 mg/L). Detailed descriptions of measurements of lipids, PTH and high-sensitive C-reactive

protein (hs-CRP) have been published [31,32]. The plasma creatinine and serum cystatin C levels were used to estimate GFR, according to the CKD-EPI equations [12].

All non-vertebral fractures that occurred during follow-up were identified from the radiographic archives of The University Hospital of North Norway in Tromsø between their participation in the 1994–95 survey and 1 January 2010 [33]. All non-vertebral fractures were registered here because this was the only provider of diagnostic radiology for fractures in Tromsø or within 250 km. The only exception would be fractures occurring while traveling with no radiographic control after returning. However, few patients with vertebral fractures are diagnosed at the hospital with an x-ray, and therefore vertebral fractures were not included in the x-ray-based registry. Of all the fractures, this study included osteoporotic fractures as fractures of the hip, proximal humerus and wrist. The validation of the fracture registration has been reported [34]. Follow-up time was assigned from the date of the baseline visit to the date of the first fracture, to death, when the participant moved or end of follow-up (1 January 2010), whichever occurred first. Analyses of fractures of the hip included the first hip fracture that happened during follow-up, with the same procedure for the first fractures of the proximal humerus and wrist fracture.

The SAS Software package, v9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses. The characteristics of the women and men are reported as mean and standard deviation (SD) for continuous variables and as number (n) and percentage (%) for categorical variables. The data from women and men were divided into quartiles according to eGFRcre, eGFRcys and eGFRcrecys. The associations of each of the kidney function estimates with BMD and fracture risk were assessed using eGFR as a continuous variable and as quartiles. Linear regression analysis was used to assess the association between eGFR and BMD, analysis of variance (ANOVA) to compare the groups (with the upper quartile as the reference) and adjusted for covariates. Linear regression analysis was used to test p for linear trends across the quartiles, by including the ordinal variable with 4 levels as an independent variable.

Cox's proportional hazards model was used to determine whether eGFR predicted fractures. To facilitate the comparison of the effect estimate of eGFRcre, eGFRcys and eGFRcrecys on fracture risk, we presented the hazard ratios (HRs) per SD difference in eGFR. Sensitivity analyses was performed for the fracture outcomes excluding participants with CKD defined as eGFR <60 ml/min/1.73 m^2. In addition, the HRs were quantified by including the group variables (dummies) with the upper quartile as the reference group. Finally, we examined whether women and men with CKD defined as eGFRcre, eGFRcys or eGFRcrecys <60 ml/min/1.73 m^2, had increased risk of fracture compared with those who had levels ≥60 ml/min/1.73 m^2. The proportionality assumptions of the models were verified by inspection of survival plots. Analyses were performed sex-stratified due to well-known differences in kidney function and fracture rates between women and men. Furthermore, interactions between sex and eGFRcre, eGFRcys and eGFRcrecys were tested in models of BMD and in models of hip fractures as endpoints. As age influence both eGFR and fracture risk we tested for interaction between age (< 65 vs. ≥65 years) and all the estimates of eGFR in models of hip fractures. The analysis were adjusted for age, height, BMI, distal forearm BMD, current smoking (yes/no), alcohol intake (teetotaler, yes/no), the use of HRT (yes/no), the use of oral corticosteroids (yes/no), physical activity score, a history of previous fracture (yes/no), diabetes (yes/no), and CVD (yes/no), the use of any BP lowering drugs (yes/no) and diastolic BP, the calciotropic hormone PTH and inflammatory marker hs-CRP in both sexes, all known to be associated with kidney function and fracture risk [35–38]. In the final models we kept included the significant covariates, which differed between sexes. The covariates were added one by one to explore the reasons why some associations changed from non-significant to significant. PTH and hs-CRP were log-transformed due to skewed distribution and were included in the analysis to explore biological mechanisms. *P*-values <0.05 were considered as statistically significant.

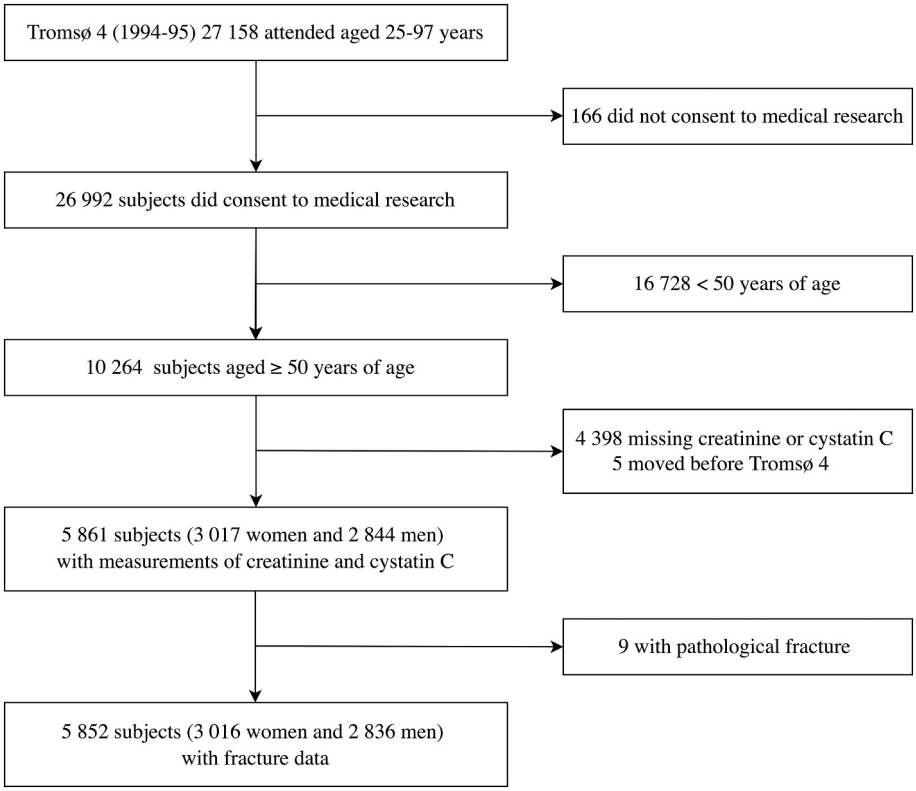

Fig. 1. Participants from the Tromsø 4 study in 1994–95.

3. Results

At baseline, mean age (range) was 63.5 years (50–84) in women and 62.8 years (50–84) in men (Table 1). Mean ± SD eGFRcre, eGFRcys and eGFRcrecys was 89.6 ± 11, 87.4 ± 18.4 and 89.5 ± 15.3 (ml/min/1.73 m^2) in women and 91.1 ± 12.0, 91.6 ± 20.2 and 92.8 ± 15.9 (ml/min/1.73 m^2) in men. The number and proportion of women with CKD defined as eGFRcre, eGFRcys and eGFRcrecys <60 ml/min/1.73 m^2 were 73 (2.4%), 216 (7.2%) and 99 (3.3%) and corresponding number and proportion of men were 65 (2.3%), 155 (5.5%) and 88 (3.1%). The number of women and men with missing values for some variables are shown (Table 1).

In models of BMD, there was a marginal interaction between sex and eGFRcre ($p = 0.074$), but not between sex and eGFRcys ($p = 0.598$) or sex and eGFRcrecys ($p = 0.729$). In women, higher eGFRcre and eGFRcrecys were associated with lower BMD after adjustment for covariates ($\beta = -0.44$, $p < 0.001$ and $\beta = -0.25$, $p = 0.002$, Supplementary Table 1). In adjusted models, women in the lowest vs. upper quartile of eGFRcre had a mean BMD of 393 vs. 382 mg/cm^2, while those in the lowest vs. upper quartile of eGFRcrecys had a mean BMD of 390 vs.383 mg/cm^2 (Table 2). In men, higher eGFRcre was associated with lower BMD after adjustment for covariates ($\beta = -0.37$, $p = 0.001$). In the adjusted model, men in the lowest vs. upper quartile of eGFRcre had a mean BMD of 540 vs. 529 mg/cm^2 (Table 2). In both sexes, eGFRcys was not associated with BMD after adjustment for covariates.

During a median of 14.6 years follow-up (range 0.02–15.3), and 34,851 person-years, 232 (7.7%), 135 (4.5%) and 394 (13.1%) of 3016 women suffered an incident hip, proximal humerus and wrist fracture, and the fracture rates were 6.1, 3.5 and 10.8 per 1000 person-years (Table 3 and Supplementary Tables 2–4). During 33,442 person-years, 118 (4.2%), 35 (1.2%) and 65 (2.3%) of 2836 men suffered an incident hip, proximal humerus and wrist fracture, and the fracture rates were 3.5, 1.0 and 1.9 per 1000 person-years.

In models of hip fractures, there was no interaction between sex and eGFRcre, but interactions between sex and eGFRcys ($p < 0.001$) and sex and eGFRcrecys ($p = 0.003$). In both sexes, lower eGFRcre was not associated with increased risk of any fracture type (Table 3). In women, the risk for hip and proximal humerus fracture increased per SD lower eGFRcys, HRs (95% confidence interval) were 1.36 (1.16–1.60) and 1.33 (1.08–1.63), and lower eGFRcrecys HRs were 1.25 (1.08–1.45) and 1.30 (1.07–1.57). In men, the risk of hip fracture decreased per SD lower eGFRcys and eGFRcrecys and changed from non-significant to significant in multivariable models (HRs 0.85 (0.73–0.99) and 0.82 (0.68–0.98)). No single covariate explained this change, which was explained by the combination of height, smoking and BMD. The change in association with eGFRcrecys was explained by height. Adjustment for PTH and hs-CRP did not change any of the results. In models of hip fractures, there was an interaction between age (<65 vs. ≥65 years) and eGFRcys in women ($p = 0.049$), but no other interaction between age and any estimates of eGFR in both sexes. Of 1652 women <65 years, 49 had hip fractures, HR for hip fracture was 1.74 (1.25–2.41), and of 1364 women ≥65 years, 183 had hip fractures and HR was 1.29 (1.07–1.54) in the full models. In sensitivity analysis, excluding participants with CKD according to eGFR value, hip fracture risk increased per SD lower eGFRcys (HR 1.25 (1.01–1.54)) in women and decreased per SD lower eGFRcre, eGFRcys and eGFRcrecys in men (HRs 0.73 (0.56–0.97), 0.82 (0.69–0.96) and 0.74 (0.62–0.88)) (Table 4).

The relationships of eGFR with fractures were linear in nature and there was no evidence of a threshold (Supplementary Tables 2–4). Women with eGFRcys in the lowest quartile had an increased risk of hip fracture compared with those in the upper quartile of eGFRcys (HR 2.09; 95% CI 1.15–3.78) (Supplementary Table 3). Men with eGFRcys in the lowest quartile had a reduced risk of hip fracture compared with those in the upper quartile of eGFRcys (HR 0.57; 95% CI 0.33–0.99). Otherwise, there was no significant increased risk of any type of fracture across quartiles for eGFRcre, eGFRcys or eGFRcrecys in both sexes.

Finally, women but not men with CKD defined as eGFRcys or eGFRcrecys <60 ml/min/1.73 m^2 had increased risk for hip and proximal humerus fracture. This was not the case when CKD was defined as eGFRcre <60 ml/min/1.73 m^2 (Supplementary Table 5). The HRs for these types of fractures were ranging from 1.64 to 3.16 after adjustment for all the covariates in women with eGFRcys or eGFRcrecys <60 ml/min/1.73 m^2.

Exclusion of 298 (9.9%) women using HRT and 146 individuals (82 women and 64 men) with high-energy trauma involved due to e.g. traffic accidents, did not change the results.

Table 1
Baseline characteristics of 3016 women and 2836 men in the Tromsø Study.

	Women		Men	
	Missing		Missing	
Age (years)	0	63.5 ± 6.3	0	62.8 ± 6.5
Height (cm)	6	161 ± 6.1	3	175 ± 6.8
Weight (kg)	6	68.0 ± 12.0	3	79.7 ± 12.1
Body mass index (BMI) (kg/m^2)	6	26.2 ± 4.5	3	26.1 ± 3.4
Distal forearm bone mineral density (mg/cm^2)	68	388 ± 67	55	533 ± 67
Systolic blood pressure (mm Hg)	35	142 ± 22.7	5	141 ± 19.9
Diastolic blood pressure (mm Hg)	35	79.9 ± 12.6	5	82 ± 11.4
Creatinine (μmol/L)	0	61.3 ± 11.4	0	76.1 ± 17.5
Cystatin C (mg/L)	0	0.87 ± 0.18	0	0.89 ± 0.20
eGFRcre from creatinine (ml/min/1.73 m^2)	0	89.6 ± 11.8	0	91.1 ± 12.0
eGFRcys from cystatin C (ml/min/1.73 m^2)	0	87.4 ± 18.4	0	91.6 ± 20.2
eGFRcrecys from creatinine and cystatic C(ml/min/1.73 m^2)	0	89.5 ± 15.3	0	92.8 ± 15.9
Total cholesterol (mmol/L)	1	7.1 ± 1.3	0	6.5 ± 1.2
High density lipoprotein cholesterol (mmol/L)	5	1.7 ± 0.4	6	1.4 ± 0.4
Triglycerides (mmol/L)	1	1.5 ± 0.9	0	1.6 ± 1.0
Physical activity score[a]	2	2.8 ± 2.1	7	3.6 ± 2.5
Currently smoking, n (%)	0	878 (29.1)	0	887 (31.3)
Teetotaler, n (%)	6	890 (29.6)	2	400 (14.1)
History of previous fracture, n (%)	0	544 (18.0)	0	299 (10.5)
History of diabetes, n (%)	14	105 (3.5)	11	98 (3.5)
History of cardiovascular disease[b], n (%)	0	359 (11.9)	0	578 (20.4)
Blood pressure lowering drug use, n (%)	0	598 (19.8)	0	589 (20.8)
Oral corticosteroid use, n (%)	0	43 (1.4)	0	29 (1.0)
Hormone replacement therapy use, n (%)	0	298 (9.9)		

Values are mean ± SD or n (%). Number of missing varied for some of the variables.
eGFR = estimating glomerular filtration rate.
[a] Hours of moderate activity + 2 times hours of hard activity.
[b] History of angina, myocardial infarction and/or stroke.

4. Discussion

In this Norwegian population-based cohort, lower eGFR based on cystatin C as well as the combination of cystatin C and creatinine predicted fracture of the hip and proximal humerus, whereas eGFR based on

Table 2
Mean (95% CI) bone mineral density (BMD) of the distal forearm (mg/cm^2) by quartiles of estimates of glomerular filtration rate (ml/min/1.73 m^2) calculated based on creatinine (eGFRcre), cystatin C (eGFRcys) and both (eGFRcrecys) by sex. The Tromsø Study 1994–95.

	Women		Men	
	Mean BMD (95% CI)[a]	Mean BMD (95% CI)[b]	Mean BMD (95% CI)[a]	Mean BMD (95% CI)[c]
	n = 2948	n = 2942	n = 2781	n = 2767
eGFRcre (ml/min/1.73 m^2)				
<84.8	396 (391–400)	393 (388–397)	544 (539–549)	540 (535–546)
84.8–92.6	392 (388–397)	392 (387–396)	539 (534–544)	536 (531–541)
92.7–98.3	383 (379–387)	384 (380–388)	527 (522–532)	529 (524–533)
>98.3	379 (374–384)	382 (377–387)	525 (520–530)	529 (524–534)
P for trend	<0.001	<0.001	<0.001	<0.001
eGFRcys (ml/min/1.73 m^2)				
<78.1	389 (384–393)	386 (382–390)	531 (525–536)	530 (525–536)
78.1–91.0	390 (386–394)	391 (387–395)	536 (531–541)	536 (531–540)
91.1–102	386 (382–390)	387 (383–391)	531 (526–536)	530 (25–535)
>102	386 (381–392)	387 (382–393)	535 (530–539)	536 (531–540)
P for trend	0.320	0.925	0.570	0.378
eGFRcrecys (ml/min/1.73 m^2)				
<82.0	392 (388–396)	390 (386–394)	534 (529–540)	532 (527–537)
82.0–92.4	390 (386–395)	390 (386–394)	537 (532–541)	536 (532–541)
92.4–101	386 (382–391)	388 (384–392)	531 (526–536)	531 (526–535)
>101	381 (376–386)	383 (377–387)	532 (527–536)	534 (530–538)
P for trend	<0.001	0.041	0.282	0.969

[a] Adjusted for age using analyses of variance.
[b] Adjusted for age, body mass index (BMI), height, smoking, physical activity, history of cardiovascular disease, use of hormone replacement therapy and corticosteroid in women.
[c] Adjusted for age, BMI, height, diastolic blood pressure, smoking, physical activity, and use of any blood pressure lowering drugs in men.

creatinine did not predict fracture in women. In men none of the estimates of eGFR were related to increased fracture risk. In contrast, eGFRcys and eGFRcrecys were inversely associated with hip fracture risk in men. As the number of participants with abnormal kidney function was small in this cohort, the findings particularly apply to a cohort of generally healthy individuals with a normal kidney function. At baseline, higher eGFRcre, but not eGFRcys was associated with a lower distal forearm BMD in both women and men, which is a new finding.

In epidemiological studies, the relationship between kidney function and BMD is inconsistently reported and varies by skeletal site [8,39]. A population based study reported that decreased kidney function was related to lower femoral neck BMD in men, but not women [8]. This relationship was partly explained by higher PTH levels. Two studies reported no differences in hip BMD across quartiles of eGFRcys in women or men [19,20]. To our knowledge, no previous study has reported such a paradoxical negative association between eGFRcre and distal forearm BMD as we did. This cohort, had predominately normal kidney function according to the eGFR, and only 2–7% of the participants had eGFR <60 ml/min/1.73 m^2, which could explain the results. The intriguing findings that higher eGFRcre and not eGFRcys was associated with lower BMD, is almost certainly explained by confounding from muscle mass because it is likely that individuals with lower BMD have less muscle mass and falsely higher eGFRcre. This would further highlight why creatinine is not an optimal measure of kidney function. Moreover, bone quality may be compromised with reduced kidney function without low BMD [40].

Previous studies on the relationship between kidney function and fracture risk have had some limitations [6]. Different methods have been used for assessment of kidney function such as the four variable MDRD equation to calculate eGFR based on creatinine [17], the CKD-EPI equation to calculate eGFR based on creatinine [8] and based on cystatin C [18]. A majority of the studies examined the association between eGFR and the risk of hip fracture only, and most studies used eGFR based on creatinine [6]. However, the studies that have used both creatinine and cystatin C to calculate eGFR according to the CKD-EPI equations, reported consistently that eGFRcys or eGFRcrecys, and not eGFRcre, was associated with hip fracture risk [6,19,20,41,42]. Other studies have included individuals with a mean age of 75–80 years where 25–33% had eGFRcys <60 ml/min/1.73 m^2 [6,8,19,43], whereas the current study was population-based and included relatively healthy individuals with a lower mean age of about 63 years and only 5–7% with eGFRcys <60 ml/min/1.73 m^2.

In the current study, the association between lower eGFRcys and risk of fracture was sex specific. In women, results were consistent and robust as eGFRcys predicted fracture before and after adjustment for BMD and other covariates, and also in analysis with CKD defined as eGFRcys <60 ml/min/1.73 m^2. The increased risk of fractures in women with lower eGFRcys, confirms the findings reported by Ensrud et al., that older women with higher cystatin C, but not higher creatinine, had an increased risk of hip fracture independent of other risk factors [19]. In another study by Ensrud et el., postmenopausal women with mild kidney dysfunction assessed with eGFRcys had increased risk of non-vertebral fracture [18]. Ensrud et al. also reported that men with lower eGFRcys had a 1.6 fold increased risk of hip fracture, but this was explained largely by other traditional risk factors [20]. As in this study, they reported that lower eGFRcre and eGFRcrecys were not associated with a risk of hip fracture in men. Our results showed an apparent protective effect of decreased eGFRcys on the risk for hip fractures in men. As this finding was independent of BMI, PTH and CRP, it was less likely confounded by obesity, secondary hyperparathyroidism or inflammation. The associations were weak and must be interpreted cautiously, however, the associations were confirmed in the sensitivity analysis.

There was no association detected between eGFRcre and fracture risk in both sexes. Creatinine is dependent on muscle mass, which is an important determinant of fracture risk. Frail individuals with lower muscle mass may therefore have a falsely high eGFRcre compared to individuals with higher muscle mass. In the current cohort, the cystatin C based eGFR yielded a higher proportion of eGFR <60 ml/min/1.73 m^2 than the creatinine-based eGFR. This might reflect the independence of cystatin C with muscle mass in older adults [44]. This could also explain why eGFR based on cystatin C was superior to eGFR based on creatinine in predicting fracture risk in women in this study of a population with normal range of kidney function.

Although cystatin C based eGFR is less dependent on muscle mass it is generally not superior to creatinine in assessment of GFR [12,13].

Table 3
Risk of hip, proximal humerus, or wrist fracture by eGFR based on creatinine, cystatin C and both, by sex.

Fracture site	Women			Men		
	Fracture n	HR (95% CI)[a] $n = 3016$	HR (95% CI)[b] $n = 2948$	Fracture n	HR (95% CI)[a] $n = 2836$	HR (95% CI)[c] $n = 2779$
Per 1 SD lower eGFRcre						
Hip	232	1.06 (0.93–1.22)	1.06 (0.91–1.23)	118	0.81 (0.65–1.03)	0.85 (0.67–1.07)
Proximal humerus	135	1.13 (0.95–1.35)	1.20 (1.00–1.45)	35	1.01 (0.69–1.47)	1.03 (0.72–1.48)
Wrist	394	0.92 (0.82–1.03)	0.93 (0.83–1.05)	65	0.82 (0.60–1.13)	0.87 (0.63–1.19)
Per 1 SD lower eGFRcys						
Hip	232	1.33 (1.14–1.55)	1.36 (1.16–1.60)	118	0.91 (0.77–1.07)	0.85 (0.73–0.99)
Proximal humerus	135	1.31 (1.07–1.62)	1.33 (1.08–1.63)	35	1.13 (0.79–1.62)	0.99 (0.71–1.39)
Wrist	394	0.96 (0.86–1.07)	1.00 (0.89–1.13)	65	1.16 (0.89–1.53)	1.12 (0.85–1.48)
Per 1 SD lower eGFRcrecys						
Hip	232	1.22 (1.06–1.41)	1.25 (1.08–1.45)	118	0.86 (0.71–1.03)	0.82 (0.68–0.98)
Proximal humerus	135	1.26 (1.04–1.52)	1.30 (1.07–1.57)	35	1.08 (0.75–1.55)	1.01 (0.71–1.45)
Wrist	394	0.93 (0.83–1.04)	0.98 (0.87–1.10)	65	1.06 (0.81–1.39)	1.05 (0.79–1.38)

SD unit for estimates of glomerular filtration rate based on creatinine (eGFRcre), cystatin C (eGFRcys) and both (eGFRcrecys) were 11.9, 19.4 and 15.7 ml/min/1.73 m^2, respectively.

[a] Hazard ratio (HR) with 95% confidence interval (CI) adjusted for age using Cox's proportional hazards model.

[b] Adjusted for age, height, body mass index (BMI), bone mineral density (BMD), smoking, history of previous fracture and diabetes, high-sensitive C-reactive protein and use of corticosteroid and any blood pressure lowering drugs in women.

[c] Adjusted for age, height, BMI, BMD, smoking, history of previous fracture, diabetes and cardiovascular disease, and use of any blood pressure lowering drugs in men.

Moreover, eGFRcys is reported to be associated with smoking, low physical activity, high triglycerides, high LDL cholesterol, low HDL cholesterol and obesity after adjustment for measured GFR (mGFR), using iohexol clearance, a gold standard for assessment of kidney function, suggesting that those associations could not be explained by kidney function alone [10]. Low-grade inflammation is reported associated with fracture risk [45,46]. The prediction of fracture risk by eGFRcys in the present study is unlikely to be confounded by low-grade inflammation because this was independent of hs-CRP. However, biomarkers for inflammation other than hs-CRP also correlate with cystatin C [14,19]. Although lower eGFRcys and eGFRcrecys increased the risk of hip and proximal humerus fracture in women independent of many covariates, residual confounding may exist. The associations of eGFR with fracture risk are multifactorial and complex. One reason why none of the eGFR estimates were associated with wrist fractures in both sexes in this cohort, might be that wrist fractures are common in younger and healthier individuals than hip and proximal humerus fractures that are common in older frail adults.

This study adds to the growing evidence that eGFRcys predicts fractures in women [6]. Whether eGFRcre predicts fractures remains less clear, and suggests that fracture risk evaluation should rather use eGFRcys or eGFRcrecys as a marker of kidney function. For clinicians it is of relevance that eGFRcre, the most commonly used estimate of kidney function in clinical routine was not related to risk of fracture in both sexes. At least for women, a measure of eGFRcys, even within the normal range, may be of benefit for assessment of fracture risk, while we do not know yet if this is the case for men. The question whether a causal association exists between slightly reduced GFR and increased fracture risk, can only be answered by examining whether the gold standard for GFR measurement (iohexol clearance) predict fractures. Although measured GFR using iohexol clearance will not be feasible in clinical practice, its associations with fractures risk should be examined in both sexes in well-powered research studies to achieve a better understanding of the pathophysiology and causal inference.

Table 4
Sensitivity analysis of risk of hip, proximal humerus, or wrist fracture by eGFR based on creatinine, cystatin C and both in women and men after excluding participants with eGFR <60 ml/min/1.73 m^2.

Fracture site	Women			Men		
	Fracture n	HR (95% CI)[a]	HR (95% CI)[b]	Fracture n	HR (95% CI)[a]	HR (95% CI)[c]
Per 1 SD lower eGFRcre		$n = 2943$	$n = 2878$		$n = 2771$	$n = 2717$
Hip	223	1.03 (0.87–1.23)	1.04 (0.87–1.24)	115	0.71 (0.54–0.93)	0.73 (0.56–0.97)
Proximal humerus	131	1.16 (0.93–1.43)	1.23 (1.00–1.53)	33	0.81 (0.50–1.33)	0.90 (0.56–1.44)
Wrist	386	0.91 (0.79–1.04)	0.91 (0.80–1.05)	63	0.72 (0.49–1.04)	0.76 (0.52–1.10)
Per 1 SD lower eGFRcys		$n = 2800$	$n = 2738$		$n = 2681$	$n = 2629$
Hip	195	1.19 (0.97–1.46)	1.25 (1.01–1.54)	109	0.86 (0.73–1.02)	0.82 (0.69–0.96)
Proximal humerus	117	1.15 (0.89–1.49)	1.19 (0.92–1.53)	31	0.96 (0.66–1.40)	0.91 (0.63–1.30)
Wrist	368	0.96 (0.84–1.08)	0.98 (0.86–1.12)	62	1.25 (0.90–1.73)	1.25 (0.89–1.76)
Per 1 SD lower eGFRcrecys		$n = 2917$	$n = 2853$		$n = 2748$	$n = 2694$
Hip	212	1.12 (0.94–1.33)	1.16 (0.97–1.39)	112	0.77 (0.64–0.93)	0.74 (0.62–0.88)
Proximal humerus	123	1.10 (0.87–1.37)	1.16 (0.92–1.45)	33	0.95 (0.63–1.41)	0.92 (0.62–1.37)
Wrist	394	0.93 (0.83–1.04)	0.97 (0.85–1.10)	64	1.10 (0.91–1.50)	1.09 (0.80–1.49)

SD unit for estimates of glomerular filtration rate based on creatinine (eGFRcre), cystatin C (eGFRcys) and both (eGFRcrecys) were 11.9, 19.4 and 15.7 ml/min/1.73 m^2, respectively.

[a] Hazard ratio (HR) with 95% confidence interval (CI) adjusted for age using Cox's proportional hazards model.

[b] Adjusted for age, height, body mass index (BMI), bone mineral density (BMD), smoking, history of previous fracture and diabetes, high-sensitive C-reactive protein and use of corticosteroid and any blood pressure lowering drugs in women.

[c] Adjusted for age, height, BMI, BMD, smoking, history of previous fracture, diabetes and cardiovascular disease, and use of any blood pressure lowering drugs in men.

The strengths of this study are its prospective design including a large sample of women and men from a general population with a high attendance rate and inclusion of incident fractures based on a validated fracture registry. Another strength is that we used both creatinine and cystatin C to calculate eGFR in a normal population. The sensitivity analysis confirming that lower eGFRcys was associated with increased risk of hip fracture in women and decreased risk of hip fracture in men, indicate that the results are valid for individuals with eGFRcys in the normal range and were not driven by a few participants with manifest CKD. Limitations of this study include low power (particular in men), residual confounding by unmeasured risk factors, such as falls, lean body mass, hip BMD and bone turnover markers, which could influence our findings. Moreover, as discussed above, all estimates of kidney function may be confounded, and analysis has not taken into account mortality as a competing risk. Our results should be interpreted cautiously.

In conclusion, lower eGFR based on cystatin C was associated with increased risk of hip and proximal humerus fractures in women, whereas eGFR based on creatinine was not. In men, none of the eGFR estimates were related to increased fracture risk. However, lower eGFR based on cystatin C and the combination of cystatin C and creatinine were inversely associated with hip fracture risk. The findings particularly apply to relatively healthy individuals with a normal kidney function. We infer that fracture risk evaluation related to kidney function may be best assessed using eGFR based on cystatin C, or the combination of creatinine and cystatin C, as a marker of kidney function in clinical practice, at least in women. Further work is needed to assess whether this is the case in men, before robust clinical inferences can be made.

Funding

The study received no funding.

CRediT authorship contribution statement

Study concept and design: SKN, MDS, ÅB. Statistical analysis ÅB. Data interpretation and critical revision of the manuscript for the intellectual content, writing of the report and approval of the final version: SKN, MDS, TM, FIN, CA, TTB, BOE, RMJ, ÅB. ÅB takes responsibility for the integrity of the data analyses.

Declaration of competing interest

RMJ: Has received consultant fees from Astra Zeneca, Novo Nordisk, MSD, Eli Lilly and The Norwegian Diabetes Association. All the authors state they have no other disclosures.

Acknowledgments

This work was not supported by any funding. The Tromsø Study headed by Sameline Grimsgaard provided access to data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2021.115960.

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