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Degree of Albuminuria is Associated With Increased Risk of Fragility Fractures Independent of Estimated GFR

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Introduction: Fragility fractures are common in persons with chronic kidney disease (CKD); however, the association between fragility fractures and albuminuria is not well-studied. The primary objective of this study is to determine the association of albuminuria with incident risk of fragility fractures. The secondary objective is to examine the risk of fragility fracture by estimated glomerular filtration rate (eGFR) and Kidney Disease Improving Global Outcomes (KDIGO) risk categories.

Methods: Community dwelling adults residing in Alberta, Canada who had at least 1 creatinine and albuminuria measurement between April 1, 2008 and March 31, 2019 participated in the study ($N = 2.72$ million). Incident fragility fractures were identified using Canadian Chronic Disease Surveillance Systems Osteoporosis Working Group algorithms. Albuminuria was categorized as none/mild (albumin-to-creatinine ratio [ACR] <30 mg/g, protein-to-creatinine ratio [PCR] <150 mg/g, trace/negative dipstick); moderate (ACR 30–300 mg/g, PCR 150–500 mg/g, 1+ dipstick) or severe (ACR >300 mg/g, PCR >500 mg/g, ≥2+ dipstick). Multivariable analysis controlled for 42 variables.

Results: Patients with severe albuminuria had an increased risk of hip fracture (odds ratio [OR] = 1.37; 95% confidence interval [CI] 1.28, 1.47]), vertebral fracture (OR = 1.31; 95% CI 1.21, 1.41) and any-type fracture (OR = 1.22; 95% CI 1.17, 1.28) compared with patients with none/mild albuminuria. Patients in the most severe KDIGO risk category had an increased risk of hip fracture (OR = 1.22; 95% CI 1.16, 1.29), vertebral fracture (OR = 1.18; 95% CI 1.09, 1.26) and any type of fracture (OR = 1.25; 95% CI 1.21, 1.30).

Conclusion: This study demonstrates the important role of albuminuria as a risk factor for fragility fractures in CKD and may help inform risk stratification and prevention strategies in this high-risk population category.

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Albuminuria and eGFR represent distinct aspects of kidney function. According to the KDIGO guidelines, eGFR is widely accepted as the best index of excretory kidney function and is generally used to classify and prognosticate kidney disease.[1] Albuminuria is a marker of kidney damage, reflecting increased glomerular permeability and inflammation. The "KDIGO Risk Categories" incorporates both the degree of albuminuria and eGFR to characterize kidney disease that is associated with future risk of kidney failure, cardiovascular events, and mortality.

Fragility fractures are common in advanced CKD, though the exact mechanisms contributing to the increased risk are difficult to elucidate due to the complex physiology of CKD.[2,3] To determine the relationship between fragility fractures and CKD, most studies use eGFR as the independent variable. A small number of studies have used albuminuria to predict fracture risk and suggest a possible link between albuminuria and fragility fractures. Limitations in this existing body of literature include a lack of large population-based studies, composite outcomes (i.e., specific individual fracture sites are not delineated),[4–6]

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and reporting of surrogate outcomes such as bone mineral density without reporting on the clinically important outcomes of fractures.[7,8]

The objective of this study is to examine the independent association between degrees of albuminuria and incident fragility fractures at 5 individual skeletal sites and fracture at any site, in a large population-based cohort in Alberta, Canada. Secondary outcomes include risk of fragility fracture by stage of eGFR and by KDIGO risk categories.

METHODS

This retrospective cohort study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[9] The institutional review boards at the University of Alberta (Pro00053469) and University of Calgary (REB16-1575) approved this study and waived the requirement for participants to provide consent due to the large sample size.

Data Sources and Cohort

We used the Alberta Kidney Disease Network database, consisting of patient registry, physician claims, hospitalizations, and ambulatory care utilization data from all adults registered with Alberta Health (the provincial health ministry), linked with provincial clinical laboratories, pharmaceutical information network (drugs dispensation) and vital statistics**.** This database has been widely used[10-12] because of its population-based coverage of a geographically defined area, including demographic characteristics, health services utilization, and clinical outcomes. Additional information on the database is available elsewhere, including the validation of selected data elements.[13] All Alberta residents are eligible for insurance coverage by Alberta Health with >99% participation. All laboratory values of Alberta's population and all the outpatient-dispensed prescriptions are captured. Variables included from the database include the following: adjusted for albuminuria, eGFR, time period, age, biological sex, rural status, most materially deprived neighborhood quintile, previous fracture, prescriptions (specifically steroid, bisphosphonate, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and calcium channel blocker), and morbidities (alcohol misuse, myocardial infarction, rheumatoid arthritis, asthma, atrial fibrillation, cancer, chronic liver disease, severe constipation, dementia, depression, diabetes mellitus, epilepsy, gout, heart failure, hypertension, hypothyroid, inflammatory bowel disease, irritable bowel syndrome, multiple sclerosis, osteoporosis, chronic pain, Parkinson's disease, peptic ulcer, peripheral artery disease, psoriasis, chronic pulmonary disease, schizophrenia, stroke, and transient ischemic attack). The database was used to assemble cohorts of adults with at least 1 outpatient serum creatinine measurement who resided in Alberta, Canada between April 1, 2008 and March 31, 2019. The index date for the primary analysis was the first serum creatinine within 6 months of an albuminuria measurement after or on April 1, 2008, the day of first contact with Alberta Health, or their 18th birthday, whichever was latest. We followed participants until death, out-migration, end of study (March 2019), or when their eGFR measurement reduced to below 15 ml/min per 1.73 m^2, whichever was earliest. Follow-up was stopped if the eGFR reduced to below 15 ml/min per 1.73 m^2 due to the strong association with metabolic bone disease and the increased risk of fragility fractures at low eGFR thresholds.[14,15] Participants with kidney failure, defined as an eGFR <15 ml/min per 1.73 m^2 were censored (Supplementary Figure S1) because subjects with kidney failure are likely systematically different.[14,15] A total of 469,859 patients were excluded due to a eGFR <15 ml/min per 1.73 m^2.

Assessment of Kidney Function and Albuminuria

Kidney function was estimated for each participant in the study using the median of all outpatient eGFR measurements taken within 6-month intervals. The KDIGO staging was also updated every 6 months with the available eGFR and albuminuria measurements. Median eGFR was categorized based on the KDIGO criteria as ≥90, 60 to 89.9, 45 to 59.9, 30 to 44.9 and 15 to 29.9 ml/min per 1.73 m^2.[16,17] Outpatient albuminuria was categorized as none/mild (ACR <30 mg/g, PCR <150 mg/g, negative/trace dipstick]; moderate (ACR 30–300 mg/g, PCR 150–500 mg/g, 1+ dipstick), or severe (ACR >300 mg/g; PCR >500 mg/g; 2+, 3+, 4+ dipstick).[18] The albuminuria variable was expressed as a 3-level ordinal variable and the median was obtained for all 6-month intervals. Measures of eGFR and albuminuria were used to assign KDIGO risk categories: low, moderate, high, and very high.[1]

Fragility Fractures

Participants were evaluated for the following fragility fractures: wrist or forearm, spine, hip, humerus, and pelvis or any fracture from this list, using administrative algorithms by the Canadian Chronic Disease Surveillance System Osteoporosis Working Group for osteoporosis and osteoporosis-related fracture.[19] A new fracture at the same site would not be included until a year after the previous fracture. A composite outcome of a fracture at any site was included as the primary outcome.

Morbidities, Prescriptions, and Other Characteristics

Morbidities were defined using a previously published framework with validated algorithms as applied to Canadian physician claims, hospitalizations, and ambulatory care data, each of which had positive predictive values ≥70% as compared to a gold standard measure such as chart review. Detailed methods for classifying comorbidity status and the specific algorithms used are found elsewhere.[19-21] Each participant was classified with respect to the presence or absence of these 28 chronic conditions (lookback extended as far as April 1994 when records were available) for each 6-month interval.[22] Information on key drugs dispensed was also collected for each 6-month interval and included bisphosphonates, oral glucocorticoids (steroids), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers. Glucocorticoid use was restricted to oral prescriptions, reassessed every 6 months. Duration and quantity were not assessed.

Duration and quantity were not assessed. Use was assessed for each 6-month interval. We used administrative data to identify age, biological sex, and rural residence location.[23] We included the Pampalon index of material deprivation created by Alberta Health Services.[24] It categorizes participants at the postal code level into 5 strata of socioeconomic inequalities in health care services and population health with 5 representing the most deprived neighborhoods.

Statistical Analyses

All analyses were performed with Stata MP 17·0 (www.stata.com); and baseline descriptive statistics were reported as counts and percentages, or medians and interquartile ranges, as appropriate. We used ordered logistic regression to test for trends across albuminuria categories.

Random-intercept generalized linear models (binomial family and a logistic link) were used to determine the associations of fractures with eGFR and albuminuria, or in an additional model with KDIGO risk categories. Participants were modeled as a random effect. The sequence of time intervals was modeled as a fixed linear effect. We treated all covariates as 6-month time-varying covariates. An exposure term was included because each participant's last time interval was often less than 6 months.

We adjusted for past fracture (lookback extended as far as April 1994 when records were available), age, biological sex, neighborhood material deprivation quintile, rural/urban residence, the 5 medications, and the 28 morbidities. The threshold P for statistical significance was set at 0.05. We reported baseline (first 6-month interval) descriptive statistics as counts and percentages, or medians and interquartile ranges. The number of events reported, along with fully adjusted ORs and 95% CIs.

A few variables had missing values across the 6-month intervals: material deprivation quintile (6.8%), rural/urban residence (1.2%), eGFR (62.5%), and albuminuria (70.1%). However, 83% of participants had more than 1 measure of eGFR and 77.1% had more than 1 measure of albuminuria over the observation period. For the purposes of modeling, a missing material deprivation index was represented with an indicator variable, rural/urban residence was assumed to be the most frequent value (urban), and the last value was carried forward for missing eGFR and albuminuria.

Sensitivity Analyses

We performed several sensitivity analyses. First, we considered an interaction between eGFR category and albuminuria. This was to determine whether the effect of albuminuria was due to its close association with eGFR or whether it had an independent effect. Second, we included participants who had never had albuminuria assessed. Missing albuminuria was modeled with an indicator variable. Given that the majority of participants were without a measured albuminuria within each 6-month interval (>70%), this was performed to determine if patients who had an albuminuria measured represented a different population (i.e., more likely to have diabetes mellitus). Third, we included participants with quantitative assessments (i.e., excluding urine dip-test data) of albuminuria only as the nonquantitative tests (urinalysis) may misclassify albuminuria depending on the specific gravity of the urine sample. Fourth, we did a subgroup analysis on diabetes status, because diabetes itself is an independent risk factor for fracture. The KDIGO categories were added to determine if the results differed when both eGFR and albuminuria were considered concurrently. Fifth, we considered a cohort that had never been treated with any bisphosphonates and oral glucocorticoids; both medications impact the status of bone turnover and the risk for fracture. Lastly, we considered age-sex groups using all 2-way interaction terms among age groups (18–64, 65–79, and ≥80 years) and sex with albuminuria and eGFR categories. Unadjusted rates and ORs with corresponding 95% CIs are reported for these age-sex groups.

RESULTS

We identified 3,360,756 potential participants from the database of community dwelling adults aged 18 and over, who were registered with Alberta Health, with at least 1 measurement of eGFR between April 1, 2008 and

Table 1. Characteristics of participants by albuminuria

Patient characteristics	Albuminuria[a] (*N* [%] or Median [interquartile range])		
	None/mild	Moderate	Severe
N	2,561,977 (94.0)	127,223 (4.7)	35,826 (1.3)
Age, yr	45 [33, 57]	47 [32, 63]	52 [35, 67]
Male	1,179,606 (46.0)	65,003 (51.1)	20,145 (56.2)
Most deprived	517,512 (22.2)	29,658 (26.1)	8827 (28.0)
Rural	220,584 (9.0)	16,561 (13.6)	5273 (15.4)
Osteoporosis	151,584 (5.9)	8114 (6.4)	2405 (6.7)
Past fracture	66,782 (2.6)	4521 (3.6)	1532 (4.3)
Number of morbidities	1 [0, 2]	1 [0, 3]	2 [1, 3]
Steroid use	80,828 (3.2)	6008 (4.7)	2391 (6.7)
Bisphosphonate use	81,536 (3.2)	4302 (3.4)	1323 (3.7)
Estimated glomerular filtration rate, ml/min per 1.73 m^2			
≥90	1,589,278 (62.0)	69,936 (55.0)	15,294 (42.7)
60–89	858,163 (33.5)	41,555 (32.7)	11,229 (31.3)
45–59	84,270 (3.3)	9236 (7.3)	4044 (11.3)
30–44	25,479 (1.0)	4776 (3.8)	3216 (9.0)
15–29	4787 (0.2)	1720 (1.4)	2043 (5.7)

ACR, albumin-to-creatinine ratio; PCR, protein-to-creatinine ratio.
[a]Albuminuria: None/mild (ACR <30 mg/g, PCR <150 mg/g, negative/trace dipstick); Moderate (ACR 30–300 mg/g, PCR 150–500 mg/g, 1+ dipstick) or Severe (ACR >300 mg/g, PCR >500 mg/g, 2+, 3+, 4+ dipstick).

March 31, 2019. Participants were followed-up with for a median of 7.6 years (range 1 day–11.2 years).

A total 165,871 patients were excluded due to an eGFR below 15 ml/min per 1.73 m^2 and 469,869 were excluded due to a lack of albuminuria assessment. The final number of participants in the primary analysis was 2,725,026. The multivariable analysis, controlling for 42 covariates described earlier were used to calculate fracture risk and presented as OR. There were 78,123 (2.9%) participants who experienced at least 1 fracture during follow-up. The rate of fracture was 4.9 fractures per 1000 patient-years.

Almost all participants (94%) had no or mild albuminuria, 4.7% had moderate degree of albuminuria and a minority (1.3%) had severe albuminuria. Participants with severe albuminuria were older (median age 52 years vs. 43 years in the none/mild albuminuria group), more likely to be male and live in a rural residence, have more prior fractures, had more glucocorticoids and bisphosphate use and more likely to have a lower eGFR (see Table 1).

Albuminuria and Incident Fracture Risk

Albuminuria did not modify the association between eGFR and any fractures (interaction term $P = 0.22$); therefore, the results of the model was without an interaction term (Figures 1 and 2). There was a graded association between the risk of fracture at any site and greater severity of albuminuria (severe vs. normal/mild; OR 1.22; 95% CI 1.17, 1.28; and moderate vs. normal/mild OR 1.18; 95% CI 1.15, 1.21; Figure 1). Results were similar for hip, spine, and humerus. A graded association with severity of albuminuria was not seen for pelvic or wrist fractures although risk for both fracture types was greater in those with moderate albuminuria only (pelvis moderate vs. normal/mild; OR 1.25; 95% CI 1.16, 1.35; and wrist/forearm OR 1.05; 95% CI 1.00,1.10) (See Figure 1).

Age and sex group analyses (Supplementary Table S1) showed greater fracture risk with increasing age and with females (vs. males); the differences within age-sex groups across albuminuria categories were similar to the overall pooled average.

eGFR and Incident Fracture Risk

The risk of fragility fracture across eGFR category was U-shaped with participants with eGFR between 45 and 59 ml/min per 1.73 m^2 having the lowest risk of any fracture (OR 0.94, 95% CI 0.92, 0.9; vs. eGFR 60–89 ml/min per 1.73 m^2 [referent group]; Figure 2). This was generally true for all types of fractures with the possible exception of wrist/forearm and spine. There was an increased risk of fracture in the eGFR ≥90 ml/min per 1.73 m^2 category compared to the referent group 60 to 89 ml/min per 1.73 m^2 across all fracture groups (any fracture OR 1.21 95% CI 1.19, 1.24) with the exception of wrist/forearm. At the other end of the U-shape, eGFR 15–29 ml/min per 1.73 m^2 was also significant for any fracture but this was driven largely by pelvic fractures (any fracture OR 1.17 [95% CI 1.11, 1.23]; pelvis OR 1.30 [95% CI 1.14, 1.48]) (See Figure 2).

KDIGO Risk Categories and Incident Fracture Risk

The relationship between fracture risk and KDIGO risk categories demonstrated a graded risk of fracture by severity of KDIGO risk category for most fracture sites. For fracture of any site, there was an increased risk by KDIGO risk category compared to the reference (moderate risk OR 1.03 [95% CI 1.01, 1.05], high risk OR 1.12 [95% CI 1.09, 1.16] and very high-risk category OR 1.25 [95% CI 1.21, 1.30]). A similar trend was seen for spine, pelvic, and hip fracture. Wrist fracture had a graded negative association, and humerus had no association (See Figure 3).

Sensitivity Analysis

Further sensitivity analyses were performed for any fracture (Table 2). The conclusions did not change substantively when participants with missing albuminuria were included in the model, nor when glucocorticoid users were excluded from the model. In subgroup analysis, participants with and without diabetes had similar findings. Lastly, when only participants with quantitative albuminuria values were analyzed, the associations between fragility fractures and albuminuria were similar and numerically larger

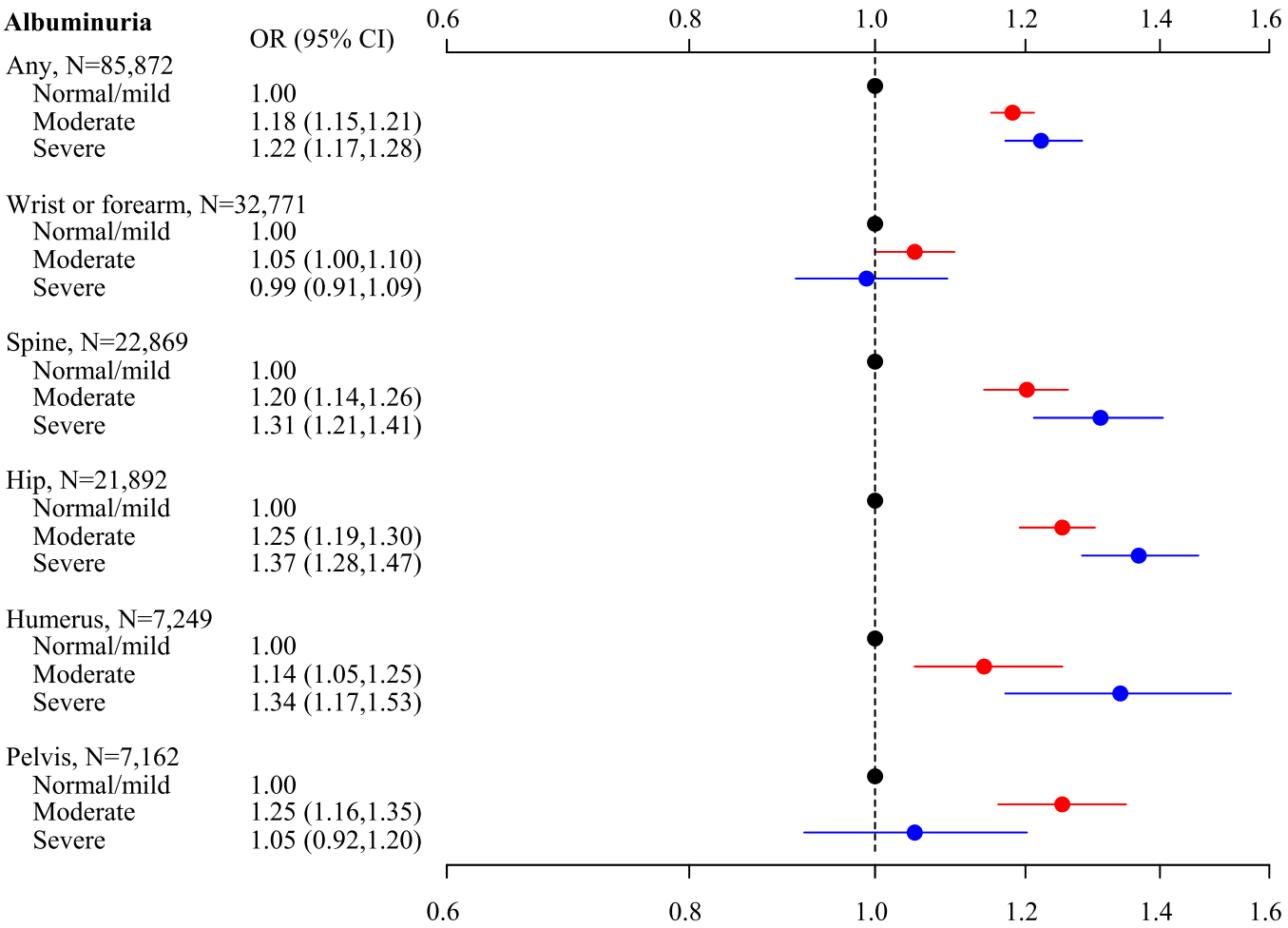

Figure 1. More severe albuminuria is associated with increased fracture risk at most sites. Adjusted for albuminuria, eGFR, time period, age, biological sex, rural status, most materially deprived neighborhood quintile, previous fracture, 5 prescriptions, and 28 morbidities. Odds ratios with 95% confidence intervals are presented. A maximum of 1 fracture was allowed for any one time period, which is why the number of site-specific fractures adds to more than the any-fracture total. CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

(e.g., the OR for severe albuminuria was 1.48 [95% CI 1.34, 1.62]).

DISCUSSION

To our knowledge, this is the first large, population-based study to describe an independent association between severity of albuminuria and incident fragility fracture. In addition, it is the first study we are aware of which describes the relationship between KDIGO risk categories and risk of fragility fracture. Thirdly, a novel U-shaped association was found between fragility fracture and eGFR and fracture at any site.

Albuminuria

Albuminuria and fragility fracture have been examined in a small number of cohort studies, including 3 population studies, 2 demonstrating a graded risk of hip fracture with increasing severity of albuminuria,[25,26] and a third which showed the same relationship with hospitalization for fracture. We found a consistent risk with both men and women, whereas earlier studies had suggested this relationship was found in women but not in men.[6] A subsequent study in men showed an association between albuminuria and decline in bone mineral density at the hip, but not incident fractures; this may have been a result of inadequate statistical power because the small subset with macroalbuminuria had high rates of fracture.[5] A study in older adults also found that lower bone mineral density was correlated with severity of albuminuria.[7] In summary, our results are congruent with the published literature demonstrating a strong association between albuminuria and fracture risk, in both sexes, independent of eGFR, across multiple fracture sites including hip, pelvis, and vertebrae and any type of fracture (i.e., fracture at any of these sites).

Wrist fracture had the weakest association with albuminuria (OR 1.05 for moderate albuminuria only), compared with the other fracture sites. Using composite outcomes can conceal nuances in the data and may mask the null effect of certain fracture sites. Our data demonstrates that the risk of fracture and albuminuria is consistent across all fracture sites, and

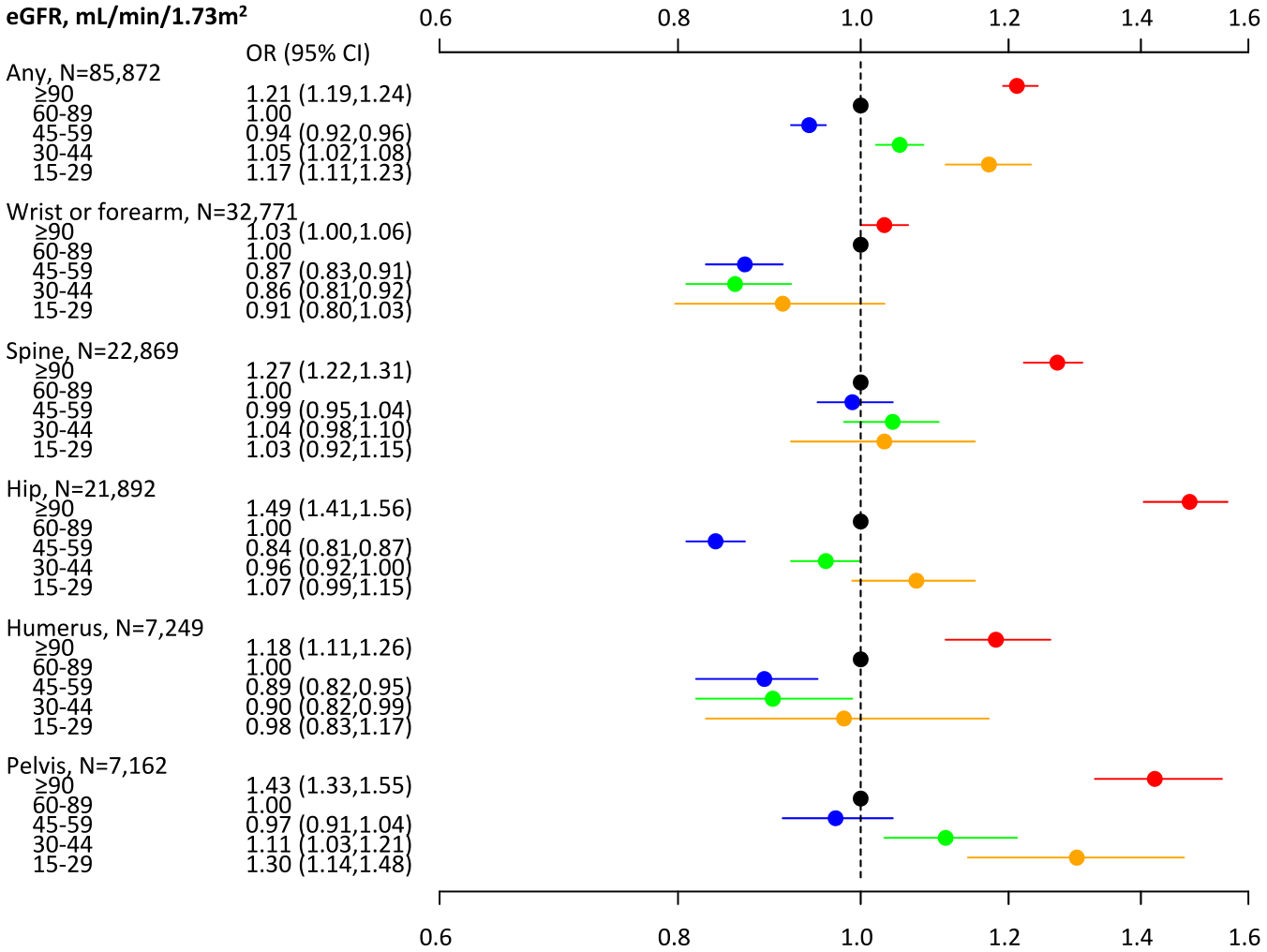

Figure 2. U-shaped Relationship between eGFR and fracture risk for any type, hip and pelvis. Adjusted for albuminuria, eGFR, time period, age, biological sex, rural status, most materially deprived neighborhood quintile, previous fracture, 5 prescriptions, and 28 morbidities. Odds ratios with 95% confidence intervals are presented. A maximum of 1 fracture was allowed for any one time period, which is why the number of site-specific fractures adds to more than the any-fracture total. CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

strongest in the hip. Collecting data on variables such as weight, previous history of falls, and fragility score could help elucidate the stronger association between hip and fracture compared with wrist. However, because this data is not available, it is considered a limitation of the study.

This study also adds to the literature, because it is the largest cohort and controlled for many variables that were missing in previous studies.

Glomerular Filtration Rate

Our data demonstrated a U-shaped association between eGFR and risk of fragility fracture, with the highest risks of fracture incurred at eGFR ≥90 ml/min per 1.73 m^2 and eGFR 15 to 29 ml/min per 1.73 m^2. A sensitivity analysis demonstrated this relationship was also observed using serum creatinine (data not shown).[27]

Although the relationship between stage of CKD (based on eGFR measures only) and fracture risk has been studied extensively in the literature, there are no clear patterns that emerge apart from an increased risk of hip fracture risk in ESKD.[28] Although there may be some agreement that a lower eGFR is likely a risk factor for fragility fracture, there are not enough data available to determine if this is a linear graded relationship. Limitations of the existing literature include study selection, which limits generalizability (i.e., type 2 diabetes, or patients with osteoporosis)[29–31]; variation in the definition of "normal kidney function" (i.e., eGFR ≥90 ml/min per 1.73 m^2, 60–89 ml/min per 1.73 m^2 or <65 ml/min per 1.73 m^2)[29–34]; or collapsing eGFR categories due to the proportionately fewer patients in the lower eGFR groups.[14,31,35] In addition, many studies do not include patients with an eGFR ≥90 ml/min per 1.73 m^2.[29,32,36] Lastly, studies that examine fracture risk over a relatively short period (i.e., <5 years) may underestimate the risk because fracture outcomes occur over the longer term (i.e., over 10 years).[32]

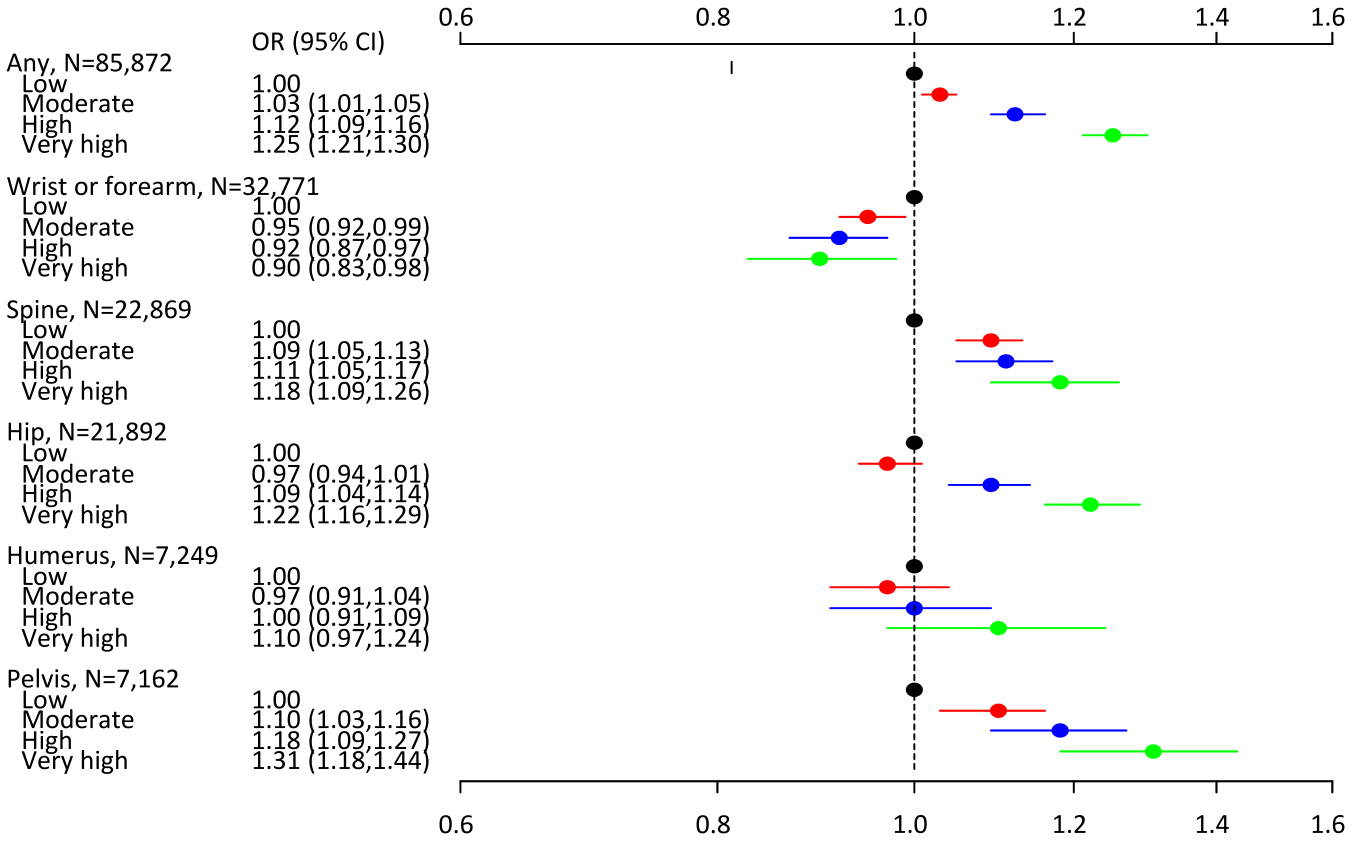

Figure 3. More severe KDIGO category is associated with increased fracture risk. Adjusted for KDIGO category, time period, age, biological sex, rural status, most materially deprived neighborhood quintile, previous fracture, 5 prescriptions, and 28 morbidities. Odds ratios with 95% confidence intervals are presented. A maximum of 1 fracture was allowed for any one time period which is why the number of site-specific fractures adds to more than the any-fracture total. CI, confidence interval; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; OR, odds ratio.

Our study attempted to address many of these limitations. The large population cohort allowed for distinct categories of eGFR; 42 covariates were controlled for, including previous fracture, bisphosphonate use and glucocorticoid use, and the population was a large cohort of community dwelling adults. Although other studies have examined risk of fracture in the eGFR ≥90 ml/min per 1.73 m^2 group,[34] the U-shape association has only been reported in a single article that we are aware of, which was published on the same population cohort (with fewer members) almost 10 years ago.[27] As suggested by the previous authors, this phenomenon may relate to the overestimation of eGFR in patients with low muscle mass and chronic illness, which are both risk factors for falls and fractures. In addition, evidence suggests that in the initial stages of type 1 and type 2 diabetes, there is a supraphysiologic elevation of eGFR as an adaptation in reduction in the functional nephron mass or due to the increase in glomerular hydraulic pressure[37]; thus, the increased risk theoretically accounted for the disproportionate number of patients with diabetes in the eGFR ≥90 ml/min per 1.73 m^2 group. However, in the sensitivity analysis, there was no difference in fracture risk in patients with and without diabetes.

KDIGO Categories and Incident Fragility Fracture

Our study is the first to evaluate KDIGO risk categories to determine an association with fracture risk. The results demonstrated that there was a graded relationship with more severe KDIGO category and risk of fracture in the spine, hip and pelvis, and fracture at either site, mirroring the pattern observed with albuminuria and fracture. This is consistent a study by Kim *et al.*[26] that found that a lower GFR and higher albuminuria had a synergistic effect in increasing the risk of hip fracture among patients with CKD. We suggest that using both albuminuria and eGFR is useful as a marker of fragility fractures, in addition to using eGFR and albuminuria independently.

Mechanisms to Explain the Risk of Fragility Fracture and Albuminuria

There are a few hypotheses purported to explain the association between albuminuria and fragility fracture. The first relates to endothelial dysfunction and

Table 2. Associations of any fracture with time-varying albuminuria and eGFR: primary and sensitivity analyses

Characteristic	Primary	Sensitivity: missing albuminuria	Sensitivity: quantitative albuminuria	Diabetes	No diabetes	No steroid use anytime during follow-up
Half-year time periods	39,015,399	47,331,714	9,782,939	5,411,213	33,604,186	29,424,132
Participants	2,725,026	3,194,885	835,737	409,613	2,461,163	2,140,568
Events	85,872	101,393	27,372	18,467	67,405	57,189
Albuminuria						
Normal/mild	1.00	1.00	1.00	1.00	1.00	1.00
Moderate	1.18 (1.15, 1.21)	1.18 (1.15, 1.21)	1.31 (1.24, 1.39)	1.14 (1.09, 1.19)	1.20 (1.17, 1.24)	1.16 (1.13, 1.20)
Severe	1.22 (1.17, 1.28)	1.21 (1.16, 1.26)	1.48 (1.34, 1.62)	1.24 (1.17, 1.33)	1.21 (1.15, 1.29)	1.18 (1.12, 1.24)
Missing	-	1.17 (1.15, 1.19)	-	-	-	-
eGFR, ml/min per 1.73 m^2						
≥90	1.21 (1.19, 1.24)	1.21 (1.19, 1.23)	1.27 (1.18, 1.37)	1.23 (1.17, 1.29)	1.21 (1.18, 1.24)	1.18 (1.15, 1.21)
60–89	1.00	1.00	1.00	1.00	1.00	1.00
45–59	0.94 (0.92, 0.96)	0.95 (0.93, 0.97)	0.98 (0.91, 1.05)	0.92 (0.89, 0.97)	0.94 (0.91, 0.96)	0.93 (0.91, 0.96)
30–44	1.05 (1.02, 1.08)	1.09 (1.06, 1.12)	1.04 (0.95, 1.13)	1.05 (1.00, 1.11)	1.05 (1.01, 1.09)	1.08 (1.04, 1.12)
15–29	1.17 (1.11, 1.23)	1.20 (1.14, 1.26)	1.26 (1.12, 1.42)	1.21 (1.12, 1.31)	1.12 (1.04, 1.20)	1.22 (1.14, 1.30)

eGFR, estimated glomerular filtration rate.
Adjusted for albuminuria, eGFR, time period, age, biological sex, rural status, most materially deprived neighborhood quintile, previous fracture, prescriptions (specifically steroid, bisphosphonate, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and calcium channel blocker), and morbidities (alcohol misuse, myocardial infarction, rheumatoid arthritis, asthma, atrial fibrillation, cancer, chronic liver disease, severe constipation, dementia, depression, diabetes mellitus, epilepsy, gout, heart failure, hypertension, hypothyroid, inflammatory bowel disease, irritable bowel syndrome, multiple sclerosis, osteoporosis, chronic pain, Parkinson's disease, peptic ulcer, peripheral artery disease, psoriasis, chronic pulmonary disease, schizophrenia, stroke, and transient ischemic attack). There was a random effect for participants.
Odds ratios with 95% confidence intervals are presented. A maximum of 1 fracture was allowed for any one time period which is why the number of site-specific fractures adds to more than the any-fracture total.

vascular perfusion. In the glomerular basement membrane, endothelial dysfunction can modify glomerular barrier permeability, leading to increased albuminuria in the urine.[8] Albuminuria, as marker of endothelial dysfunction, may impact bone perfusion and reduce the rate of remodeling, leading to a loss of bone mineral density and increase risk of fracture.[5,25]

A second hypothesis is that albuminuria may be a marker of decreased bone quality due to its association with inflammation. Oxidative stress and inflammation are known to affect bone quality, as in conditions such as diabetes mellitus, rheumatoid arthritis, and multiple myeloma. In diabetes mellitus, albuminuria is associated with increased serum levels of advanced glycation end productions (i.e., hemoglobin A1C), which weakens the cross-links between collagen fibrils, resulting in a loss of bone plasticity and strength.[38]

Lastly, albuminuria may be related to changes in mineral metabolism in the kidney, as suggested by a few small studies. Higher albuminuria has been associated with increased parathyroid hormone levels, independent of eGFR, and whereas parathyroid hormone has anabolic and catabolic effects on bone, the catabolic effects appear to be dominant in states of persistent parathyroid hormone elevation.[39] A study in patients with IgA nephropathy demonstrated an elevation in FGF23 associated with higher rates of albuminuria, which may interfere with the tubular excretion of phosphate, leading to FGF23 resistance.[40]

While the exact mechanism remains to be elucidated, our study provides strong evidence that albuminuria impacts risk of fragility fractures.

Strengths and Limitations

There are many strengths of the study. The study cohort is a population-based design of community dwelling adults across demographics and results are thereby highly generalizable. In addition, these participants were followed-up with for 11 years, which allowed for statistical power and control of numerous variables making the results highly reliable; and a sensitivity analysis did not change the outcomes. A time-varying approach was used to adjust for changes in albuminuria and creatinine over time.

We did not include biochemical markers of bone health such as calcium, phosphate, parathyroid hormone, or vitamin D metabolites. However, only a small proportion of participants had stage 4 CKD, we would not expect disturbances in calcium metabolism and metabolic bone disease to have a large effect on the fracture outcome. In addition, we are not able to fully explain the reason for the U-shaped curve seen with the extremes of kidney stages and fragility fracture. We hypothesize the risk is likely due to residual confounding and inaccurate estimates of eGFR at low levels (i.e., low muscle mass, and low creatinine), which could lead to overestimation of eGFR. However, we do not have anthropometric data such as height weight and body mass index.

Furthermore, fracture data included pathologic fractures because they represent a small proportion of

all fractures, and their exclusion can lead to underestimation of the fracture burden due to osteoporosis. However, it is possible that including these fractures overestimates the true osteoporotic fracture burden. Incident vertebral fractures are likely underrepresented in this data set. Hospital and physician data are not reliable at diagnosing these types of fractures and are a limitation to this study, as well as others that use secondary data sets to detect fracture risk.[19]

Lastly, because this was a population study, there were risk factors known to contribute to fractures that were not measured, including falls, menopausal status, smoking, and parental history of hip fractures.

In conclusion, this population-based study of over 2.7 million community dwelling adults with and without CKD found that albuminuria is strongly associated with incident fracture risk at either site, hip, humerus, pelvic fracture and spinal fracture, with more severe albuminuria having a stronger effect; a graded association with fractures and KDIGO risk categories was also observed for most fracture sites and a U-shaped association was found for any type fracture, hip and pelvis, with highest risk at eGFR $\geq$90 ml/min per 1.73 m^2 and 15 to 29 ml/min per 1.73 m^2.

We propose that albuminuria may be a prognostic indicator for incident fracture risk in the population with CKD, and that the KDIGO risk categories which combine albuminuria and eGFR can be used to prognosticate fracture risk. These findings underscore the importance of using albuminuria in addition to eGFR when evaluating metabolic bone health and fracture risk.

DISCLOSURE

SK is Director of the Real World Evidence Consortium that conducts investigator initiated, industry funded research; this work is unrelated to this submission. SK is supported by the Kidney Health Research Chair and the Division of Nephrology at the University of Alberta. PS holds the Charles A Allard Chair in Diabetes Research. All other authors have declared no conflicting interests.

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Data Availability Statement

We are not able to make our dataset available to other researchers due to our contractual arrangements with the provincial health ministry (Alberta Health), who is the data custodian. Researchers may make requests to obtain a similar dataset at https://sporresources.researchalberta.ca.

AUTHOR CONTRIBUTIONS

SK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. SCH, PS, and AKB conceived the study; SCH, NW, AKB, PS, and SK designed the study; SCH and NW wrote the first draft of the manuscript; and NW performed the statistical analysis. All authors critically reviewed, revised, and approved the final manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Associations of any fracture with time-varying albuminuria and eGFR by age and sex groups.

Figure S1. Participant flow.

STROBE Checklist.

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