ORIGINAL ARTICLE

Proteinuria screening and risk of bone fracture: a retrospective cohort study using a nationwide population-based database

Akira Okada[1], Akira Honda[2], Hideaki Watanabe[3], Yusuke Sasabuchi[4], Shotaro Aso[4], Kayo Ikeda Kurakawa[1], Masaomi Nangaku [5], Toshimasa Yamauchi[6], Hideo Yasunaga[3], Hirotaka Chikuda[2], Takashi Kadowaki[1,6,7] and Satoko Yamaguchi [1]

[1]Department of Prevention of Diabetes and Lifestyle-Related Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [2]Orthopaedic Surgery, Gunma University Graduate School of Medicine, Gunma, Japan, [3]Department of Clinical Epidemiology and Health Economics, The University of Tokyo, Tokyo, Japan, [4]Department of Real World Evidence, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [5]Division of Nephrology and Endocrinology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [6]Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Japan and [7]Toranomon Hospital, Tokyo, Japan

Correspondence to: Satoko Yamaguchi; E-mail: syamaguc@m.u-tokyo.ac.jp

ABSTRACT

Background and hypothesis. Proteinuria is associated with an increased risk of kidney function deterioration, cardiovascular disease, or cancer. Previous reports suggesting an association between kidney dysfunction and bone fracture may be confounded by concomitant proteinuria and were inconsistent regarding the association between proteinuria and bone fracture. Therefore, we aimed to evaluate the association using a large administrative claims database in Japan.

Methods. Using the DeSC database, we retrospectively identified individuals with laboratory data including urine dipstick test between August 2014 and February 2021. We evaluated the association between proteinuria and vertebral or hip fracture using multivariable Cox regression analyses adjusted for various background factors including kidney function. We also performed subgroup analyses stratified by sex and kidney function and sensitivity analyses with Fine & Gray models considering death as a competing risk.
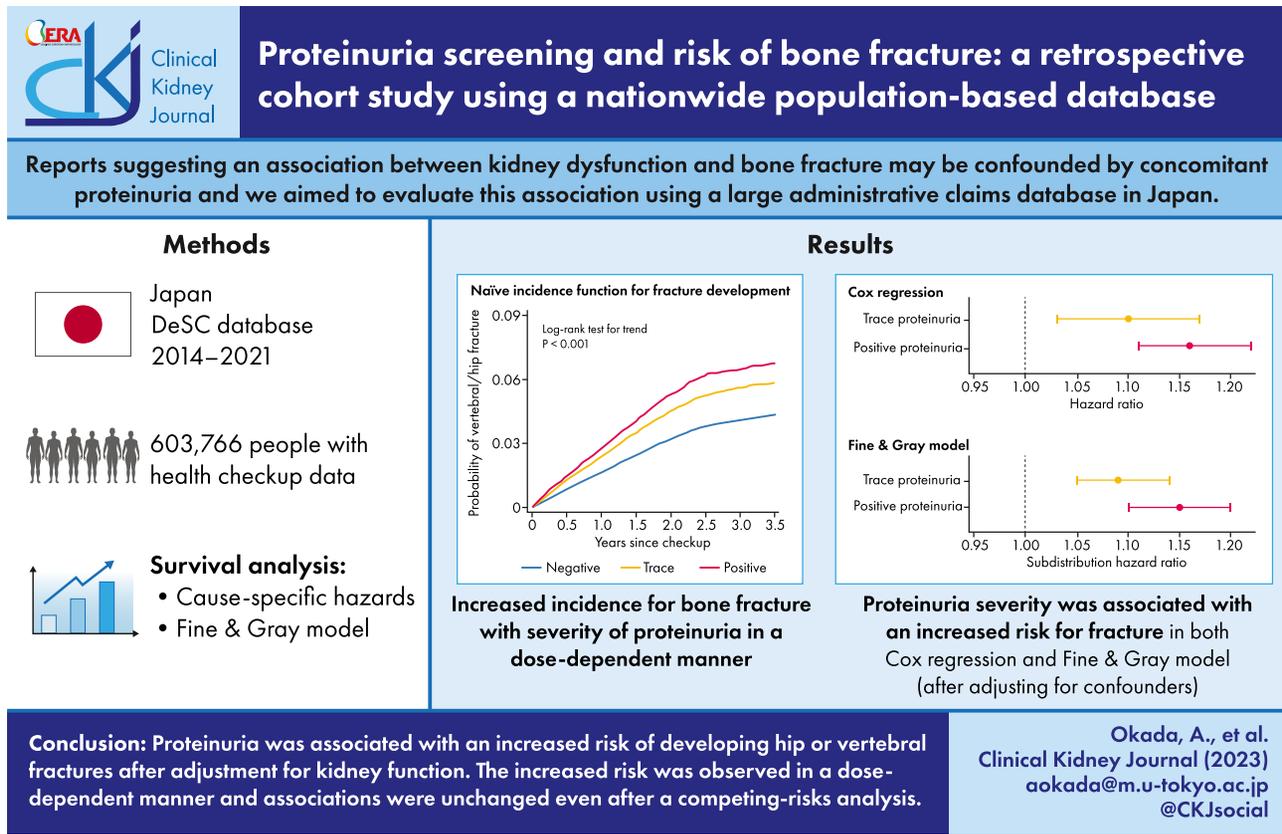
Results. We identified 603 766 individuals and observed 21 195 fractures. With reference to the negative proteinuria group, the hazard ratio for hip or vertebral fracture was 1.10 [95% confidence interval (CI), 1.05–1.14] and 1.16 (95%CI, 1.11–1.22) in the trace and positive proteinuria group, respectively, in the Cox regression analysis. The subgroup analyses showed similar trends. The Fine & Gray model showed a subdistribution hazard ratio of 1.09 (95%CI, 1.05–1.14) in the trace proteinuria group and 1.15 (95% CI, 1.10–1.20) in the positive proteinuria group.

Conclusions. Proteinuria was associated with an increased risk of developing hip or vertebral fractures after adjustment for kidney function. Our results highlight the clinical importance of checking proteinuria for predicting bone fractures.

GRAPHICAL ABSTRACT

Proteinuria screening and risk of bone fracture: a retrospective cohort study using a nationwide population-based database

Reports suggesting an association between kidney dysfunction and bone fracture may be confounded by concomitant proteinuria and we aimed to evaluate this association using a large administrative claims database in Japan.

Methods

Japan
DeSC database
2014–2021

603,766 people with health checkup data

Survival analysis:
- Cause-specific hazards
- Fine & Gray model

Results

Increased incidence for bone fracture with severity of proteinuria in a dose-dependent manner

Proteinuria severity was associated with an increased risk for fracture in both Cox regression and Fine & Gray model (after adjusting for confounders)

Conclusion: Proteinuria was associated with an increased risk of developing hip or vertebral fractures after adjustment for kidney function. The increased risk was observed in a dose-dependent manner and associations were unchanged even after a competing-risks analysis.

Okada, A., et al.
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aokada@m.u-tokyo.ac.jp
@CKJsocial

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KEY LEARNING POINTS

What was known:
- Proteinuria is known as an independent risk factor for not only kidney function deterioration or cardiovascular disease development but also cancer or anaemia.
- Previous reports suggesting an association between kidney dysfunction and bone fracture may be confounded by concomitant proteinuria.
- It remains unknown whether there is an independent association between proteinuria and bone fracture after adjustment for kidney function.

This study adds:
- The severity of proteinuria is associated with an increased risk for bone fracture in a dose-dependent manner.
- With reference to the negative proteinuria group, the hazard ratio for hip or vertebral fracture was 1.10 in the trace proteinuria group and 1.16 in the positive proteinuria group in the Cox regression analysis.
- The association between proteinuria and bone fracture was consistent in an age- and sex-stratified analysis and competing-risks analysis.

Potential impact:
- Proteinuria was independently associated with an increased risk of developing hip or vertebral fractures after adjustment for kidney function.
- Semi-quantitative assessment of proteinuria may help detect a potential risk of fractures and would be useful in risk stratification for the subsequent development of fractures.

INTRODUCTION

Proteinuria is a main component of chronic kidney disease (CKD) and plays an important role in the development of cardiovascular disease and deterioration of kidney function [1]. Furthermore, proteinuria has recently been shown to be associated with an increased risk for the development of other diseases such as cancer or anaemia [2, 3], and screening for proteinuria with the urine dipstick test has increasing importance in public health and clinical settings.

Bone fracture in older individuals with CKD affects activities of daily living and prognosis [4, 5]. Comorbid vertebral fracture was shown to be a prognostic factor in individuals with CKD [5]. Accumulated evidence suggests that risk factors for bone fracture include age, female sex, smoking, glucocorticoid use, osteoporosis, and comorbidity of CKD [6, 7]. Several studies reported that a decrease in estimated glomerular filtration rate (eGFR) was associated with an increased risk of bone fracture [6, 8], while others showed no such association after multivariable adjustment [9, 10].

Positive proteinuria has been suggested as a possible risk factor for the development of bone fractures [11, 12], but the association between proteinuria and bone fractures remains controversial. Previous studies have shown that proteinuria was independently associated with bone fracture in older female people [11], but not in older male people [11, 13]. One previous study also demonstrated that adjusting for kidney function nearly eliminated the association, especially in male individuals [11]. Because positive proteinuria is usually concomitant with decreased eGFR [14], the association between proteinuria and bone fracture after adjustment for kidney dysfunction remains to be elucidated. In addition, bone fracture is associated with higher mortality in older people or people with CKD; thus, it is necessary to consider death as a competing risk [15–17]. Only one study considered death as a competing risk in a competing risk analysis to evaluate the risk of hip fracture [17] but the study did not consider proteinuria or kidney function as risk factors.

Therefore, the present study aimed to examine the association between proteinuria and vertebral or hip fracture after adjusting for multiple confounders including kidney dysfunction, and using competing risk models among older people or people with decreased kidney function.

MATERIALS AND METHODS

Data source

We used the DeSC database (DeSC Healthcare, Inc., Tokyo, Japan). Details of the DeSC database have been described elsewhere [18]. Briefly, the database contains administrative claims data submitted to health insurers by clinics, hospitals, and pharmacies from August 2014 to February 2021. This database encompasses three insurers: the association/union-administered health insurance for salaried employees in large companies; the National Health Insurance for self-employed individuals, retired individuals, and their dependents; and the Advanced Elderly Medical Service System for all individuals aged 75 or older [18]. The database also contains information on annual health checkups for approximately 30% of the entire population. Health checkup data included information on patient demographics (including age, sex, height, weight, and blood pressure measurement), clinical laboratory tests, and questionnaires on lifestyle factors (e.g. smoking history and medical history of cerebrovascular or cardiovascular disease).

In the claims data, the recorded diagnoses were based on the International Classification of Diseases, 10th Revision (ICD-10) codes, and drug specifications were based on the World Health Organization Anatomical Therapeutic Chemical Classification System (WHO-ATC) codes.

Inclusion/exclusion criteria

Individuals who satisfied the following criteria were included in the study: those undergoing the first health checkup with data on weight, proteinuria, and serum creatinine levels; those with a look-back period of 4 months; and those with information on death or survival. We excluded patients with a history of dialysis or kidney transplantation before the checkup, missing data on body mass index (BMI) or blood pressure, or a history of bone fracture or surgery for hip or vertebral fracture within four months before the checkup.

Study outcomes and variables

The primary outcome was a composite of hip fracture (ICD-10 codes S7200, S7210, and S7220) and vertebral fracture (S2200, S2210, S3200, S3210, S3270, T0210, and T080). Secondary outcomes focused on each fracture (hip or vertebral).

We obtained the following information from the health checkup data: sex; BMI; eGFR; and history of stroke and cardiovascular disease. We also obtained information on comorbidities of osteoporosis (ICD-10 codes, M80-82), malignancy (C or D0), and diabetes (E10-14) from the claims data in the 3 months prior to the checkup. The Charlson Comorbidity Index (CCI) was evaluated [19]. We also collected the information on prescription history of anti-diabetes agents (WHO-ATC codes, A10), anti-dyslipidemia agents (C10), anti-hypertensives (C02-04, C07-09), anti-dementia drugs (N06D), and systemic corticosteroids (H02AB). We also obtained the prescription history of drugs for osteoporosis and those potentially related to bone fractures available in Japan: selective oestrogen receptor modulator (G03XC01 and G03XC02); anti-receptor activator of nuclear factor-kappaB ligand antibody (M05BX04); hormone replacement therapy (G03CA03, G03CA04, G03CA57, G03CC06, G03EA02, G03FA01, G03FA02, G03FA10, G03FA11, G03FA17, G03FB01, G03FB05, G03FB09, and L02AA03); teriparatide (H05AA02); romosozumab (M05BX06); vitamin D3 (A11CC); calcium preparation (A12AA); bisphosphonates (M05BA0); nonsteroidal anti-inflammatory drugs (M01A); anti-rheumatoid agents (M01C); anti-neoplasm agents (L); antiacids (A02A); histamine-2 blockers (A02BA); and proton pump inhibitors (A02BC).

BMI was categorised into underweight (<18.5 kg/m^2), normal weight ($18.5–<25.0$ kg/m^2), and overweight/obesity (≥25.0 kg/m^2). This categorization is because the Japanese population has an increased risk of non-communicable diseases such as diabetes and cardiovascular disease at BMI ≥25.0 kg/m^2, and individuals with ≥30.0 kg/m^2 account for only 2% of the population in Japan [20, 21]. According to the definition of the Japanese Society of Hypertension, blood pressure was classified as follows: normal blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg), Grade 1 hypertension (systolic blood pressure 140–159 mmHg or diastolic blood pressure 90–99 mmHg), Grade 2 hypertension (systolic blood pressure 160–179 mmHg or diastolic blood pressure 100–109 mmHg), and Grade 3 hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mm Hg) [22].
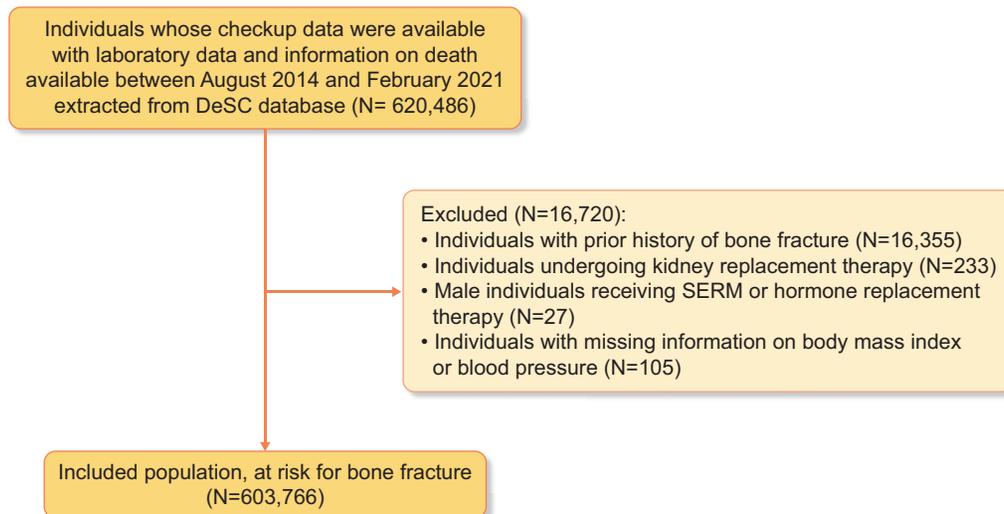
Figure 1: Flow chart of patient selection.

Statistical analysis

The background characteristics of the eligible population were summarized based on proteinuria status (negative/trace/positive). Patient characteristics were then compared across the groups using the chi-square test for categorical variables and analysis of variance for continuous variables.

Individuals were followed up from the baseline checkup until the earliest date of bone fracture, death, or censoring. Cause-specific hazard ratios (HRs) were estimated using a multivariable Cox regression model. A sensitivity analysis was performed, considering death as a competing risk, using a subdistribution hazard model and the Fine & Gray method [23]. While the former is suitable for etiological assessment, the latter is suitable for event prediction [24]. We also conducted three sensitivity analyses. In the first analysis, we calculated the hazard ratio for fracture events after adjusting for multiple variables, utilizing the urinary albumin-creatinine ratio (ACR) predicted by the conversion equation, which incorporated information from dipstick test results, sex, and comorbidities [25]. In this analysis, we treated the predicted urinary ACR as a non-linear variable and applied a restricted cubic spline model with three knots. In the second and third sensitivity analyses, we classified the entire population into two groups based on whether individuals exhibited positive proteinuria on the dipstick test or had a predicted urinary ACR of ≥300 mg/gCre, respectively.

The results of all analyses were obtained after adjustment for age; sex; BMI; blood pressure; smoking/drinking status; eGFR category; HbA1c; history of stroke and cardiovascular disease; Charlson comorbidity index; osteoporosis (diagnosis or drug administration); diabetes (diagnosis or drug administration); dementia (diagnosis or drug administration); rheumatoid arthritis; and prescription history of the following drugs: antihypertensives, antidyslipidemic agents, systemic corticosteroids, selective oestrogen receptor modulator, anti-receptor activator of nuclear factor-kappaB ligand antibody, hormone replacement therapy, teriparatide, romosozumab; vitamin D3, calcium preparation, bisphosphonates, nonsteroidal anti-inflammatory drugs, anti-rheumatoid agents, anti-neoplasm agents, antiacids, histamine-2 blockers, and proton pump

inhibitors. Subgroup analyses stratified by sex and eGFR (cutoff value of 45 ml/min/1.73 m^2) were performed. The cutoff for eGFR was determined by balancing the sample size and the degree of kidney dysfunction (moderately to severely decreased or worse) [26]. In these stratified analyses, competing risk analyses were also performed because some specific populations may have been affected by a competing risk of death.

Statistical significance was set at $P < 0.05$. All analyses were performed using Stata version 17 software (StataCorp, College Station, TX, USA). This study was approved by the Institutional Review Board of The University of Tokyo (approval number: 2021010NI). The requirement for informed consent was waived due to the anonymity of the data.

RESULTS

Study population

Fig. 1 illustrates the patient selection process. We identified 620 486 individuals who met the inclusion criteria between August 2014 and February 2021. We excluded those with a history of bone fracture ($n = 16 355$), those undergoing kidney replacement therapy ($n = 233$), those receiving hormone replacement therapy among male individuals ($n = 27$), or those with missing values for BMI or blood pressure ($n = 105$). Thus, we obtained 603 766 individuals for analysis.

Table 1 presents the population demographics. Those with proteinuria were older; more likely to be male; and had higher BMI, more comorbidities, and lower eGFR. Overall, 21 195 individuals developed bone fractures and 10 346 died (Table S1, see online supplementary material). Individuals who died or developed a bone fracture were more likely to have proteinuria, be older, and have a lower BMI and higher CCI.

Overall incidence and naive incidence and cumulative incidence functions

During the follow-up period ($n = 1 335 563$ person-years at risk), 21 195 individuals (15.9 per 1000 person-years, with 95% CI, 15.7–16.1) developed bone fractures. The lowest event rate for fracture was observed in the negative proteinuria group [14.5 (95%

Table 1. Characteristics of eligible patients categorized by proteinuria status

		Negative N = 490 724	Trace N = 66 358	Positive N = 46 684	P-value
Age (years)		75.0 (66.0–79.0)	77.0 (70.0–82.0)	78.0 (73.0–83.0)	<0.001
Male sex		202 617 (41.3%)	31 895 (48.1%)	26 039 (55.8%)	<0.001
Body mass index (kg/m^2)		22.6 (20.6–24.8)	23.0 (20.8–25.2)	23.5 (21.2–25.9)	<0.001
BMI category (kg/m^2)	<18.5	36 620 (7.5%)	5081 (7.7%)	3340 (7.2%)	<0.001
	18.5–<25.0	336 719 (68.6%)	43 077 (64.9%)	27 470 (58.8%)	
	≥25.0	117 385 (23.9%)	18 200 (27.4%)	15 874 (34.0%)	
Blood pressure category[b]	Normal	337 585 (68.8%)	43 262 (65.2%)	26 762 (57.3%)	<0.001
	Grade 1 hypertension	119 151 (24.3%)	17 558 (26.5%)	14 203 (30.4%)	
	Grade 2 hypertension	28 433 (5.8%)	4552 (6.9%)	4471 (9.6%)	
	Grade 3 hypertension	5539 (1.1%)	984 (1.5%)	1243 (2.7%)	
	Missing	16 (0.0%)	2 (0.0%)	5 (0.0%)	
Smoking status	Non/past smoker	425 614 (86.7%)	55 516 (83.7%)	38 484 (82.4%)	<0.001
	Current smoker	45 550 (9.3%)	6569 (9.9%)	5164 (11.1%)	
	Missing	19 560 (4.0%)	4273 (6.4%)	3036 (6.5%)	
Drinking frequency	Rarely or Never	249 793 (50.9%)	32 525 (49.0%)	22 998 (49.3%)	<0.001
	Occasionally	81 302 (16.6%)	9960 (15.0%)	6689 (14.3%)	
	Regularly	89 941 (18.3%)	12 744 (19.2%)	9299 (19.9%)	
	Missing	69 688 (14.2%)	11 129 (16.8%)	7698 (16.5%)	
Estimated glomerular filtration rate (ml/min/1.73 m^2)		67.2 (58.4–76.7)	64.3 (54.8–74.4)	58.9 (47.6–70.4)	<0.001
Estimated glomerular filtration rate category (ml/min/1.73 m^2)	≥60	347 869 (70.9%)	41 122 (62.0%)	22 147 (47.4%)	<0.001
	45–59	119 247 (24.3%)	19 353 (29.2%)	14 830 (31.8%)	
	30–44	21 372 (4.4%)	5139 (7.7%)	7183 (15.4%)	
	15–29	2071 (0.4%)	694 (1.0%)	2182 (4.7%)	
	<15	165 (0.0%)	50 (0.1%)	342 (0.7%)	
HbA1c (%)[a]		5.6 (5.4–5.9)	5.7 (5.4–6.0)	5.8 (5.5–6.2)	<0.001
HbA1c category (%), NGSP	<5.7	295 406 (60.2%)	37 171 (56.0%)	22 944 (49.1%)	<0.001
	5.7 –6.4	145 150 (29.6%)	19 868 (29.9%)	14 025 (30.0%)	
	6.5 –7.9	37 157 (7.6%)	6849 (10.3%)	7189 (15.4%)	
	≥8.0	5041 (1.0%)	1369 (2.1%)	1944 (4.2%)	
	Missing	7970 (1.6%)	1101 (1.7%)	582 (1.2%)	
Charlson Comorbidity Index		0.0 (0.0–2.0)	0.0 (0.0–2.0)	1.0 (0.0–2.0)	<0.001
Diabetes		100 497 (20.5%)	17 323 (26.1%)	17 048 (36.5%)	<0.001
Dementia		13 346 (2.7%)	3302 (5.0%)	3057 (6.5%)	<0.001
Rheumatoid arthritis		10 494 (2.1%)	1555 (2.3%)	1083 (2.3%)	<0.001
Osteoporosis		96 454 (19.7%)	14 815 (22.3%)	9859 (21.1%)	<0.001
History of ischemic heart disease	Without cardiovascular disease history	418 437 (85.3%)	53 198 (80.2%)	35 887 (76.9%)	<0.001
	With cardiovascular disease history	38 643 (7.9%)	6250 (9.4%)	6038 (12.9%)	
	Missing	33 644 (6.9%)	6910 (10.4%)	4759 (10.2%)	
History of stroke	Without cerebrovascular disease history	436 914 (89.0%)	55 862 (84.2%)	38 405 (82.3%)	<0.001
	With cerebrovascular disease history	20 225 (4.1%)	3615 (5.4%)	3526 (7.6%)	
	Missing	33 585 (6.8%)	6881 (10.4%)	4753 (10.2%)	
Antihypertensive prescription		219 059 (44.6%)	36 724 (55.3%)	32 288 (69.2%)	<0.001
Antidyslipidemic prescription		157 180 (32.0%)	24 125 (36.4%)	19 128 (41.0%)	<0.001
Systemic corticosteroids		41 990 (8.6%)	5652 (8.5%)	4079 (8.7%)	0.37
Prescription of bisphosphonates		23 456 (4.8%)	3714 (5.6%)	2415 (5.2%)	<0.001
Vitamin D3 prescription		47 521 (9.7%)	7257 (10.9%)	4458 (9.5%)	<0.001
Prescription of selective estrogen receptor modulators		11 409 (2.3%)	1407 (2.1%)	789 (1.7%)	<0.001
Prescription of calcium preparation		4466 (0.9%)	669 (1.0%)	409 (0.9%)	0.028
Prescription of anti-RANKL antibody		3763 (0.8%)	644 (1.0%)	372 (0.8%)	<0.001
Prescription of teriparatide		1303 (0.3%)	202 (0.3%)	120 (0.3%)	0.17

Table 1. Continued

	Negative N = 490 724	Trace N = 66 358	Positive N = 46 684	P-value
Prescription of romosozumab	205 (0.0%)	34 (0.1%)	23 (0.0%)	0.45
Hormone replacement therapy	3098 (0.6%)	391 (0.6%)	205 (0.4%)	<0.001
Prescription of NSAIDs	122 033 (24.9%)	17 379 (26.2%)	12 649 (27.1%)	<0.001
Prescription of anti-rheumatoid agents	1061 (0.2%)	150 (0.2%)	99 (0.2%)	0.85
Prescription of anti-neoplastic agents	10 568 (2.2%)	1532 (2.3%)	1304 (2.8%)	<0.001
Antacid prescription	64 658 (13.2%)	10 565 (15.9%)	7661 (16.4%)	<0.001
Histamine-2 blocker prescription	31 460 (6.4%)	4799 (7.2%)	3777 (8.1%)	<0.001
Proton pump inhibitor prescription	82 450 (16.8%)	13 809 (20.8%)	11 280 (24.2%)	<0.001
Bone fracture during follow-up	16 067 (3.3%)	2845 (4.3%)	2283 (4.9%)	<0.001
Death before bone fracture during follow-up	7687 (1.6%)	1710 (2.6%)	2097 (4.5%)	<0.001

Data are presented as median (IQR) for continuous variables and *n* (%) for categorical variables.

IQR, interquartile range; NGSP, National Glycohemoglobin Standardization Program; NSAIDs, nonsteroidal anti-inflammatory drugs; RANKL, receptor activator of nuclear factor-kappa beta.

[a]Data are presented for individuals with available HbA1c values (N = 594 113)

[b]Blood pressure categorization is as follows: normal blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg), Grade 1 hypertension (systolic blood pressure 140–159 mmHg or diastolic blood pressure 90–99 mmHg), Grade 2 hypertension (systolic blood pressure 160–179 mmHg or diastolic blood pressure 100–109 mmHg), and Grade 3 hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mm Hg)

CI, 14.3–14.7) per 1000 person-years], followed by the trace proteinuria group [21.0 (95% CI, 20.2–21.8) per 1000 person-years], and the positive proteinuria group [25.0 (95% CI, 24.0–26.1) per 1000 person-years].

The overall incident rate for vertebral fracture was 13.1 (95% CI, 12.9–13.3) per 1000 person-years. When comparing incidence rates among individuals based on proteinuria status, the lowest event rate for vertebral fracture was observed in the negative proteinuria group [12.2 (95% CI, 12.0–12.4) per 1000 person-years], followed by the trace proteinuria group [16.8 (95% CI. 16.2–17.5) per 1000 person-years], and the positive proteinuria group [19.0 (95% CI, 18.2–19.9) per 1000 person-years].

The overall incident rate for hip fracture was 3.1 (95% CI, 3.0–3.2) per 1000 person-years. Analyses stratified by proteinuria status showed that the lowest event rate for hip fracture was observed in the negative proteinuria group [2.6 (95% CI, 2.5–2.7) per 1000 person-years], followed by the trace proteinuria group [4.7 (95% CI, 4.3–5.1) per 1000 person-years], and the positive proteinuria group [6.6 (95% CI, 6.1–7.1) per 1000 person-years].

When death was considered as a competing risk, the adjustment for competing risks did not collectively change the graph (Fig. S1, see online supplementary material).

Hazard ratios for proteinuria

After multivariable adjustment for variables such as kidney function and administered medications, the HR for bone fracture events was 1.10 (95% CI, 1.05–1.14) for the trace proteinuria group and 1.16 (95% CI, 1.11–1.22) for the positive proteinuria group (Table 2; Table S2, see online supplementary material). The HRs of variables, except for proteinuria categories for bone fracture, are shown in Table S2 (see online supplementary material). Known risk factors for bone fracture such as higher age, female sex, lower BMI, and systemic corticosteroid use were associated with an increased risk of bone fracture, while severely decreased kidney function or kidney failure (i.e. eGFR <30 ml/min/1.73 m^2) was not independently associated.

Subdistribution HRs for bone fracture were also calculated using the Fine & Gray method. The subdistribution HR of positive proteinuria for fracture was similar to that obtained using Cox regression analysis [1.15 (95% CI, 1.10–1.20)] in the multivariable adjustment model (Table 2).

In the sensitivity analysis where we used continuous predicted urinary ACR, we observed a monotonic association between increased ACR and the risk of fracture events (Fig. 2). For instance, individuals with predicted ACR values of 30 and 300 mg/gCre had hazard ratios of 1.12 (95% CI, 1.08–1.16) and 1.23 (95% CI, 1.15–1.30), respectively. When assessing the risk associated with positive proteinuria compared to negative or trace proteinuria, the hazard ratio for fracture events was 1.14 (95% CI, 1.09–1.20). Furthermore, when defining positive proteinuria as a predicted urinary ACR of ≥300 mg/gCre, the hazard ratio for fracture events was 1.10 (95% CI, 1.00–1.21).

Stratified analyses

The results of the stratified analyses are presented in Table 3. Sex-stratified analysis showed that the HRs for positive proteinuria compared with negative proteinuria were significantly associated with an increased occurrence of fracture after multivariable adjustment in both sexes. In both kidney function groups in the analysis stratified by kidney function, HRs for positive proteinuria compared with negative proteinuria were significantly associated with an increased incidence of fracture after multivariable adjustment.

DISCUSSION

In the present cohort study using a nationwide epidemiological database, we found that proteinuria was associated with an increased risk of developing fracture. Our findings are mostly consistent not only in the stratified analysis but also in the competing risk analysis after multivariate adjustment. This study is the first to report that proteinuria is associated with an increased risk of bone fracture in either sex.

Previous studies on the association between proteinuria and fracture have been limited owing to small sample sizes. For example, in a cohort study focusing on the risk of fracture among males, albuminuria was not significantly associated with an increased risk of vertebral fracture in a multivariate model with adjustment for kidney dysfunction [13]. This study showed an

Table 2. The hazard ratios for fracture events after multivariable adjustment

	Urinary protein category	Negative	Trace			Positive		
Outcome	Model	HR	HR	95% CI	P value	HR	95% CI	P value
Vertebral or hip fracture	Cox regression	Reference	1.10	(1.05,1.14)	<0.001	1.16	(1.11,1.22)	<0.001
Vertebral fracture	Cox regression	Reference	1.07	(1.03,1.12)	0.002	1.11	(1.05,1.17)	<0.001
Hip fracture	Cox regression	Reference	1.21	(1.11,1.32)	<0.001	1.36	(1.25,1.49)	<0.001
Vertebral or hip fracture	Fine & Gray model	Reference	1.09	(1.05,1.14)	<0.001	1.15	(1.10,1.20)	<0.001

CI, confidence interval; HR, hazard ratio.
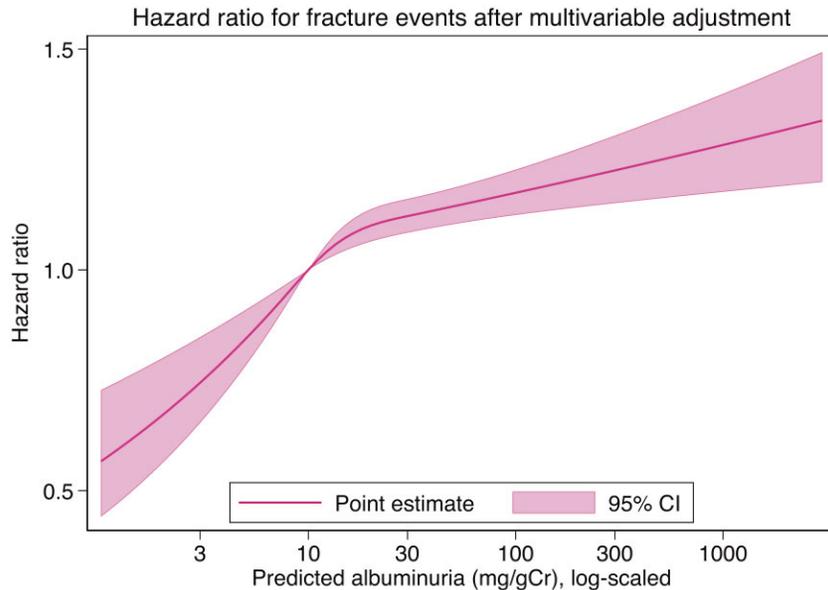
Figure 2: Hazard ratio for fracture events in relation to predicted albumin-creatinine ratios. CI, confidence interval.

Table 3. The hazard ratios for bone fracture after multivariable adjustment in the stratified analyses

			Negative	Trace			Positive		
Category	Method	Strata	HR	HR	95% CI	P value	HR	95% CI	P value
Sex	Cox regression	Female	Reference	1.12	(1.07,1.17)	<0.001	1.16	(1.10,1.22)	<0.001
		Male	Reference	1.05	(0.97,1.13)	0.26	1.19	(1.10,1.29)	<0.001
	Fine & Gray model	Female	Reference	1.11	(1.06,1.17)	<0.001	1.14	(1.08,1.21)	<0.001
		Male	Reference	1.04	(0.96,1.13)	0.31	1.17	(1.08,1.27)	<0.001
eGFR	Cox regression	≥45 ml/min/1.73 m^2	Reference	1.10	(1.05,1.14)	<0.001	1.15	(1.09,1.21)	<0.001
		<45 ml/min/1.73 m^2	Reference	1.07	(0.96,1.21)	0.22	1.18	(1.07,1.31)	0.001
	Fine & Gray model	≥45 ml/min/1.73 m^2	Reference	1.09	(1.05,1.14)	<0.001	1.14	(1.08,1.20)	<0.001
		<45 ml/min/1.73 m^2	Reference	1.07	(0.95,1.20)	0.26	1.17	(1.06,1.30)	0.002

CI, confidence interval; HR, hazard ratio.

insignificant association between macroalbuminuria and vertebral fracture (HR, 1.26; 95% CI, 0.39–4.00), which may have been attributed to the small sample size [13]. Our study revealed a consistent result among the male participants, probably due to the much larger sample size (3000 in the previous study vs. 300 000 in the current study).

Some studies have suggested that low kidney function is a risk factor for hip fracture, whereas others have not. For example, multivariable adjustment negated the association between the risk of bone fracture and decreased eGFR [9, 10]. Studies showing an association between the risk of bone fracture and decreased eGFR failed to adjust for the presence of proteinuria as a covariate [6, 8]. The proportion of patients with severe proteinuria may have been higher in those with lower GFR than in those with higher eGFR [14], and the association between low eGFR and increased fracture risk may have been confounded by the presence of proteinuria.

The incidence of bone fracture in this study was comparable to those reported in previous studies. Our study obtained an incidence of vertebral fracture of 13.1 per 1000 person-years

(median age of 76 years), which was comparable to 12.8–24.5 per 1000 person-years among people aged 70–79 years in a population-based study [27]. Two reports from Asia described a similar incidence, a report from Korea yielded 11.8–12.4 per 1000 person-years among people aged 75–79 years [28], and an article from Hong Kong reported an incidence of 4.5–12.1 per 1000 person-years among people aged 75–79 years [29]. Regarding hip fracture, the incidence was reported to be approximately 2–3 per 1000 person-years among people aged 70–79 years in another population-based study in Japan [30] and 3.5–5.3 per 1000 person-years among people aged 75–79 years in Hong Kong [29]. These numbers are similar to the incidence (3.1 per 1000 person-years) obtained in the present study.

There are several possible mechanisms underlying the association between proteinuria and bone fracture. First, proteinuria has been associated with an increased risk of decreased bone mineral density independent of kidney function [31]. Second, proteinuria has been reported to be associated with frailty and decreased cognitive function after multivariable adjustment for factors including kidney function [32, 33]. Albuminuria and eGFR were independently associated with cardiovascular outcomes in a meta-analysis [34]. Although most remain unknown, possible mechanisms may include impaired suppression of phosphate re-absorption via decreased Klotho expression and decreased FGF-23 signalling [35]. Further studies are needed to reveal the pathophysiology behind the association between proteinuria and bone fracture.

Our study has several limitations. First, due to the nature of the database, we could not obtain information regarding menopausal status, bone metabolism markers such as 25(OH)-vitamin D, plasma FGF-23, and parathyroid hormone levels, daily calcium intakes (aside from medications), or the mechanism of fractures (e.g. whether the fracture was traumatic). These unmeasured variables may have served as confounding factors. Second, although participant inclusion might have involved a smaller selection bias than in ordinary cohort studies, older people who are hospitalised or with very low activities of daily living may have been excluded due to the lack of the opportunity to undergo health checkups. Third, we could not adjust for bone density due to the lack of such data. Finally, we obtained information on urinary protein using the dipstick test but not by quantitative albuminuria testing. This is because we used data from mass screening, in which dipstick measurement has a cost advantage over quantitative measurement for the assessment of albuminuria [34]. Considering that the correlation between dipstick-defined proteinuria and quantitative albuminuria measurement was validated [25] and a dose-relationship (negative/trace/positive proteinuria) was observed among most strata in our analyses, the results of our study should be considered robust. Moreover, the predicted urinary ACR was associated with an elevated risk of bone fracture, providing further evidence for a dose-dependent relationship between proteinuria and the risk of bone fracture.

In conclusion, positive proteinuria was associated with a higher risk of fracture development, compared with negative proteinuria in the general population, using a large-scale database. Moreover, semi-quantitative assessment of proteinuria may help detect a potential risk of fracture and, therefore, would be useful in risk stratification for a subsequent development of fracture.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

AUTHORS' CONTRIBUTIONS

Study design: A.O. and A.H.; data acquisition: H.Y.; statistical analyses: A.O., A.H., Y.S., S.A., S.Y., H.C., and H.Y.; data interpretation: H.W., K.I.K., M.N., T.Y., H.Y., H.C., T.K., and S.Y.; supervision: S.Y., M.N., T.Y., H.Y., H.C., and T.K.; funding acquisition: H.Y. Each author contributed important intellectual content during manuscript drafting or revision, agreed to be personally accountable for the individual's own contributions, and ensured that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, were appropriately investigated and resolved, including documentation in the literature, if appropriate.

DATA AVAILABILITY STATEMENT

The data underlying this article were provided by DeSC Healthcare, Inc. under licence. Data will be shared on request to the corresponding author with permission of DeSC Healthcare, Inc.

CONFLICT OF INTEREST STATEMENT

None declared.

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