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A Study of Renal Insufficiency and the Risk of Developing Three Types of Fractures, with Results from Cross-Sectional Analysis and Mendelian Randomization

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Abstract: This study aims to explore the correlation between renal insufficiency and three common types of fractures. An observational study was conducted using NHANES data from 1999 to 2010 (20,292 participants, weighted to 145,742,649 people). After weighted multivariate adjusted logistic regression analysis, it was found that renal insufficiency is a risk factor for the three types of fractures, and the negative correlation remains significant after adjusting for covariates. Mendelian randomization analysis showed that renal insufficiency has a causal relationship only with wrist fractures (IVW: OR = 1.0003, CI = 1.00004 - 1.00050, p = 0.02). The conclusion indicates a significant correlation and partial causal relationship between the two, and it is necessary to pay attention to the fracture risk of patients with renal insufficiency, explore the related mechanisms, and conduct in-depth research.

1. Introduction

Recent international epidemiological studies show kidney disease mortality and morbidity are rising, becoming the seventh leading global death risk factor, prompting calls to address kidney disease and comorbidities[1-2]. Clinically, renal dysfunction, defined via serum creatinine, clearance, and glomerular filtration rate, is termed renal insufficiency[3]. Previous studies focused on renal insufficiency causes like nephritis, obesity, and diabetes[4-5], but research on its systemic damage, especially bone health links, is limited and conflicting. Some studies note renal insufficiency impacts nutrient metabolism, affecting bone health[6],hemodialysis patients face higher hip fracture risk[7].

Yet, a six-year Amsterdam study found no link between reduced kidney function and vertebral fractures[8].A 1.8-million-person survey saw no increased fracture risk with eGFR <60 ml/min[9]. A cross-sectional studies found no kidney disease stage-hip fracture association[10]. Current literature lacks definitive evidence on renal insufficiency and fracture risks, with unresolved debates. This study uses large database analysis, adjusting covariates, to clarify links with three common fractures, then validates via MR and GWAS data to explore genetic correlation and causality, aiming to provide theoretical and genetic support for understanding their biological underpinnings.

2. Methods

2.1 NHANES Database Cross-Sectional Study

Using the U.S. NHANES database (1999–2010, biennial surveys[11]), "renal insufficiency" (exposure) was defined via questionnaire: "Ever told you had weak/failing kidneys" (excluding stones/infections; responses: Yes/No/Refuse/Don't know/Missing), for participants ≥20 years. Outcome variables were three common fractures (hip/wrist/spine), identified via the question: "Has a doctor ever told you of a broken/fractured hip/wrist/spine?" (with the same response options and age inclusion criteria as specified). The study included demographic factors (age, gender, ethnicity, BMI, education level, marital status, poverty index) and clinical variables (hypertension, history of diabetes, smoking/drinking status, serum uric acid level).

2.2 Mendelian randomization

MR utilized GWAS data from the IEU Open GWAS project (University of Bristol[12], with single nucleotide polymorphisms (SNPs) associated with renal insufficiency and fractures selected for analysis. MR is based on three key assumptions regarding these SNPs: (1) they correlate strongly with the exposure; (2) they are independent of confounding factors; (3) they affect the outcome only through the exposure[13].

2.3 Statistical Analysis

NHANES data, weighted for complex sampling, underwent baseline characterization, univariate analysis, and multivariate-adjusted logistic regression (calculating ORs and 95% CIs). Stratified analyses explored effect modifiers. MR analyses used inverse variance weighting (IVW) as primary method, supplemented by MR-Egger, weighted median[14].SNPs were filtered (clumping: $r^2<0.001$, 10,000 kb distance), with sensitivity checks (MR-PRESSO for outliers/horizontal pleiotropy, leave-one-out tests[15]). Bidirectional MR assessed reverse causality. All analyses used R software; $p<0.05$ was statistically significant.

3. Results

3.1 Cross-Sectional Analysis Findings

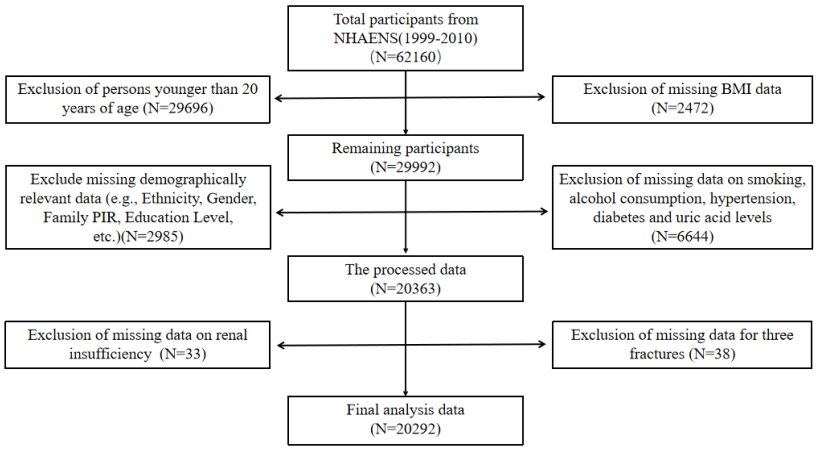

Figure 1: Data acquisition process for cross-sectional study of NHANES database.

After screening 62,160 initial participants from 1999–2010 NHANES cycles (excluding those <20 years, with missing data), 20,292 participants were included (weighted to represent 145,742,649 Americans; flow chart in Figure 1). Baseline data (TABLE 1) showed 1,974, 469, and 263 cases of wrist, spine, and hip fractures, respectively. Hip fracture patients had the highest mean age (56.69 ± 1.11 years), followed by spine (50.13 ± 0.83) and wrist (46.32 ± 0.43) fractures. Compared to non-fracture groups, all fracture groups had lower poverty-income ratios (PIR), higher uric acid levels, greater male predominance, and significant differences in alcohol consumption, smoking status, and renal insufficiency. BMI showed no significant differences across groups. Age and hypertension status were significant predictors in spine/hip fracture groups, while ethnicity showed highly significant differences and sex distribution varied markedly."

Table 1: Baseline table Incorporating Fractures from the NHANES Database Overall and in the Three Fracture Groups

Character	Wrist Fracture (1974)			Spine Fracture (469)			Hip Fracture (263)		
	No	Yes	P value	No	Yes	P value	No	Yes	P value
Age(years) (mean±SD)	45.99(0.25)	46.32(0.43)	0.44	45.92(0.24)	50.13 (0.83)	< 0.0001	45.91 (0.24)	56.69 (1.11)	<0.0001
PIR (mean±SD)	3.14(0.03)	3.11(0.06)	0.53	3.14(0.03)	3.00(0.10)	0.12	3.14 (0.03)	2.79 (0.14)	0.02
BMI(kg/m^2) (mean±SD)	28.41(0.08)	28.20(0.20)	0.27	28.38(0.08)	28.86(0.30)	0.1	28.39 (0.08)	27.95 (0.58)	0.44
Uric Acid(umol/L) (mean±SD)	322.90 (0.92)	328.26 (1.96)	0.02	323.28 (0.85)	331.63(4.08)	0.04	323.31 (0.84)	340.24 (6.45)	0.01
Sex (n,%)			< 0.0001			0.01			0.27
Female	8773(49.48)	820(41.05)		9410(48.74)	183 (41.50)		9482 (48.60)	111 (44.79)	
Male	9545(50.52)	1154(58.95)		10413 (51.26)	286 (58.50)		10547 (51.40)	152 (55.21)	
Ethnicity (n,%)			< 0.0001			< 0.0001			0.09
Mexican American	3648(7.64)	242(4.08)		3820(7.32)	70(4.47)		3850 (7.27)	40(5.42)	
Non-Hispanic Black	3405(9.86)	214(5.06)		3584(9.49)	35(3.27)		3577 (9.33)	42(9.79)	
Non-Hispanic White	9476(73.28)	1374(84.49)		10526 (74.24)	324 (84.91)		10684 (74.45)	166 (79.98)	
Other	1789(9.23)	144(6.37)		1893(8.95)	40(7.36)		1918 (8.96)	15(4.81)	
Marital (n,%)			0.33			0.15			<0.001
Married	10331 (59.12)	1052(57.07)		11122 (58.94)	261 (57.16)		11251 (58.97)	132 (51.75)	
NeverMarried	4132(22.98)	456(23.99)		4498(23.15)	90 (20.76)		4549 (23.15)	39 (17.71)	
Separated	3855(17.90)	466(18.95)		4203(17.90)	118 (22.08)		4229 (17.88)	92 (30.53)	
Education Level (n,%)			0.2			0.63			<0.0001
<9th Grade	2137(5.33)	169(4.30)		2252(5.21)	54(5.48)		2267 (5.19)	39(7.45)	
9-12th Grade	7251(36.80)	774(36.87)		7831(36.75)	194 (38.93)		7895 (36.65)	130 (51.24)	
College Graduate or above	8930(57.87)	1031(58.84)		9740(58.04)	221 (55.59)		9867 (58.15)	94 (41.31)	
Alcohol (n,%)			< 0.001			< 0.0001			0.001
No	15234 (84.33)	1558(80.27)		16451 (84.10)	341 (75.71)		16589 (83.99)	203 (74.58)	
Yes	3084(15.67)	416(19.73)		3372(15.90)	128 (24.29)		3440 (16.01)	60 (25.42)	
Smoke (n,%)			< 0.0001			< 0.001			<0.001
No	8638(47.80)	756(39.31)		9239(47.12)	155 (37.34)		9303 (47.03)	91 (32.17)	
Yes	9680(52.20)	1218(60.69)		10584	314		10726	172	

				(52.88)	(62.66)		(52.97)	(67.83)	
Diabetes (n,%)			0.15			0.12			0.003
No	16205 (91.67)	1778(92.82)		17587(91.85)	396 (89.59)		17764 (91.85)	219 (86.10)	
Yes	2113(8.33)	196(7.18)		2236(8.15)	73 (10.41)		2265 (8.15)	44 (13.90)	
Hypertension (n,%)			0.06			< 0.001			<0.001
No	12453 (72.08)	1275(69.58)		13455 (72.05)	273(62.40)		13580 (71.96)	148 (57.76)	
Yes	5865(27.92)	699(30.42)		6368(27.95)	196(37.60)		6449 (28.04)	115 (42.24)	
Kidney Disease (n,%)			0.02			0.003			<0.0001
No	17898 (98.31)	1909(97.57)		19360 (98.27)	447 (96.56)		19562 (98.29)	245 (92.83)	
Yes	420(1.69)	65(2.43)		463(1.73)	22(3.44)		467(1.71)	18 (7.17)	

3.2 Associations between Renal Function and Fracture Risk

Univariate analysis (Table 2) showed kidney disease, smoking, alcohol consumption, and elevated uric acid increased risk for all three fractures. Multivariate logistic regression (Table 3) included Model 1 (unadjusted), Model 2 (adjusted for demographics: age, sex, ethnicity, poverty index, education, marital status, BMI), and Model 3 (adjusted for all covariates). All models confirmed renal insufficiency as a significant risk factor for all three fractures.

Table 2: Each of the three groups was subjected to a one-way analysis of variance based on the included variables, with an OR greater than 1 representing fracture promotion and a p-value <0.05 representing statistical significance.

Character	OR(95% CI) Wrist	P value	OR(95% CI) Spine	P value	OR(95% CI) Hip	P value
Age(years)	1.001(0.998,1.005)	0.439	1.016(1.010,1.022)	<0.0001	1.040(1.032,1.048)	<0.0001
PIR	0.988(0.952,1.026)	0.533	0.947(0.885,1.013)	0.114	0.875(0.786,0.974)	0.015
BMI(kg/㎡)	0.995(0.985,1.004)	0.282	1.011(0.998,1.024)	0.085	0.989(0.960,1.019)	0.458
Uric Acid(umol/L)	1.001(1.000,1.001)	0.015	1.001(1.000,1.002)	0.039	1.002(1.001,1.004)	0.007
Sex						
Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.407(1.259,1.572)	<0.0001	1.341(1.081,1.663)	0.008	1.165(0.884,1.537)	0.275
Ethnicity						
Mexican American	Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic Black	0.962(0.781,1.184)	0.710	0.564(0.361,0.880)	0.012	1.408(0.821,2.416)	0.211
Non-Hispanic White	2.160(1.828,2.552)	<0.0001	1.874(1.417,2.477)	<0.0001	1.441(0.927,2.238)	0.103
Other	1.294(0.990,1.692)	0.059	1.346(0.803,2.254)	0.256	0.720(0.315,1.647)	0.433
Marital						
Married	Ref	Ref	Ref	Ref	Ref	Ref
NeverMarried	1.081(0.941,1.243)	0.268	0.924(0.713,1.199)	0.549	0.872(0.539,1.411)	0.573
Separated	1.097(0.946,1.271)	0.216	1.271(0.928,1.742)	0.133	1.946(1.364,2.776)	<0.001
Education Level						
<9th Grade	Ref	Ref	Ref	Ref	Ref	Ref
9-12th Grade	1.243(0.959,1.612)	0.100	1.008(0.655,1.549)	0.972	0.974(0.597,1.591)	0.917
College Graduate or above	1.262(0.980,1.624)	0.070	0.911(0.584,1.422)	0.678	0.495(0.306,0.803)	0.005
Alcohol						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.323(1.153,1.519)	<0.001	1.697(1.327,2.169)	<0.0001	1.788(1.259,2.540)	0.001
Smoke						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.414(1.239,1.614)	<0.0001	1.495(1.181,1.893)	0.001	1.872(1.301,2.693)	<0.001
Diabetes						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.851(0.682,1.062)	0.152	1.310(0.934,1.838)	0.116	1.820(1.224,2.707)	0.004
Hypertension						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.129(0.995,1.280)	0.059	1.554(1.239,1.948)	<0.001	1.877(1.347,2.615)	<0.001
Kidney Disease						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.448(1.072,1.955)	0.016	2.026(1.278,3.211)	0.003	4.429(2.244,8.745)	<0.0001

Subgroup analyses stratified by age (20–39, 39–58, >58 years), BMI (<18.5, 18.5–23.9, >23.9 kg/m²), poverty index (≤1.57, 1.57–3.63, 3.63–5.0), and uric acid (<420, ≥420 μmol/L). For wrist fractures, renal insufficiency was a risk factor except in other ethnic groups, never-married individuals, and normal BMI groups, with significant interactions for gender and marital status ($p < 0.05$). Spine fracture subgroups showed no interactions. Hip fracture subgroups had significant interactions for age, marital status, and poverty, indicating varying risk relationships across subgroups.

Table 3: To study the effect of renal insufficiency on three types of fractures.

Model 1: unadjusted model						
Model 2: adjusted for demographics						
Model 3: adjusted for all included covariates						
Character	Wrist Fracture		Spine Fracture		Hip Fracture	
	OR(95% CI)	P value	OR(95% CI)	P value	OR(95% CI)	P value
Kidney Disease	Model 1		Model 1		Model 1	
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.448(1.072,1.955)	0.016	2.026(1.278,3.211)	0.003	4.429(2.244,8.745)	<0.0001
Kidney Disease	Model 2		Model 2		Model 2	
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.493(1.088,2.050)	0.014	1.732(1.070,2.802)	0.026	3.092(1.518,6.301)	0.002
Kidney Disease	Model 3		Model 3		Model 3	
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.463(1.068,2.003)	0.018	1.638(1.007,2.665)	0.047	2.816(1.404,5.646)	0.004

3.3 MR Results

Following NHANES cross-sectional analysis confirming renal insufficiency as a risk factor for three fractures after full adjustment, causal exploration was conducted (Figure 2). From IEU database, 5 renal insufficiency-related and 6 fracture-related (wrist, spine, hip) GWAS datasets were included (Table 4).

Table 4: GWAS data included in the two-sample MR study associated with renal insufficiency and three fractures.

GWAS ID	Year	Trait	Sample size	Number of SNPs	Population
ukb-b-6633	2018	Renal/Kidney Disease	462933	9851867	European
ebi-a-GCST90018822	2021	Renal/Kidney Disease	482858	24185976	European
ebi-a-GCST90018790	2021	Renal/Kidney Disease	482266	24187658	European
ukb-e-585_AFR	2020	Renal/Kidney Disease	6548	15503910	African American or Afro-Caribbean
ebi-a-GCST90010147	2020	Renal/Kidney Disease	1301	18166693	European
ebi-a-GCST90038703	2021	Fracture	484598	9587836	NA
ebi-a-GCST90038705	2021	Wrist Fracture	484598	9587836	NA
ebi-a-GCST90038706	2021	Fracture of hip	484598	9587836	NA
finn-b-ST19_FRACT_LUMBAR_SPINE_PELVIS	2021	Fracture of spine and hip	215698	16380457	European

finn-b-ST19_INJURI_ABDOMEN_LOWER_BACK_LUMBAR_SPINE_PELVIS	2021	Fracture of spine and hip	218792	16380466	European

Table 5: Positive results between screened renal insufficiency and wrist fractures were demonstrated primarily by IVW methods.

id.exposure	id.outcome	method	nsnp	pval	or	or_lci95	or_uci95
ebi-a-GCST90010147	ebi-a-GCST90038705	MR Egger	10	0.11	1.0003	0.99997	1.00064
ebi-a-GCST90010147	ebi-a-GCST90038705	Weighted median	10	0.06	1.00029	0.99998	1.00059
ebi-a-GCST90010147	ebi-a-GCST90038705	IVW	10	0.02	1.00027	1.00004	1.0005
ebi-a-GCST90010147	ebi-a-GCST90038705	Simple mode	10	0.18	1.00031	0.99989	1.00073
ebi-a-GCST90010147	ebi-a-GCST90038705	Weighted mode	10	0.12	1.00028	0.99996	1.00059

10 exposure-related SNPs were screened (Supplementary Material 1). MR analysis (IVW primary) showed renal insufficiency causally associated with wrist fractures (IVW: OR=1.0003, CI=1.00004-1.00050, p=0.02; Table 5), not with the other two (Supplementary Material 2). Sensitivity analyses confirmed no horizontal pleiotropy/heterogeneity (p>0.05; Supplementary Material 1), with symmetrical funnel plot (Figure 3) and robust leave-one-out results (Figure 4). Findings were visualized via scatter (Figure 5) and forest plots (Figure 6). Reverse MR found no reverse causality (Supplementary Material 2).

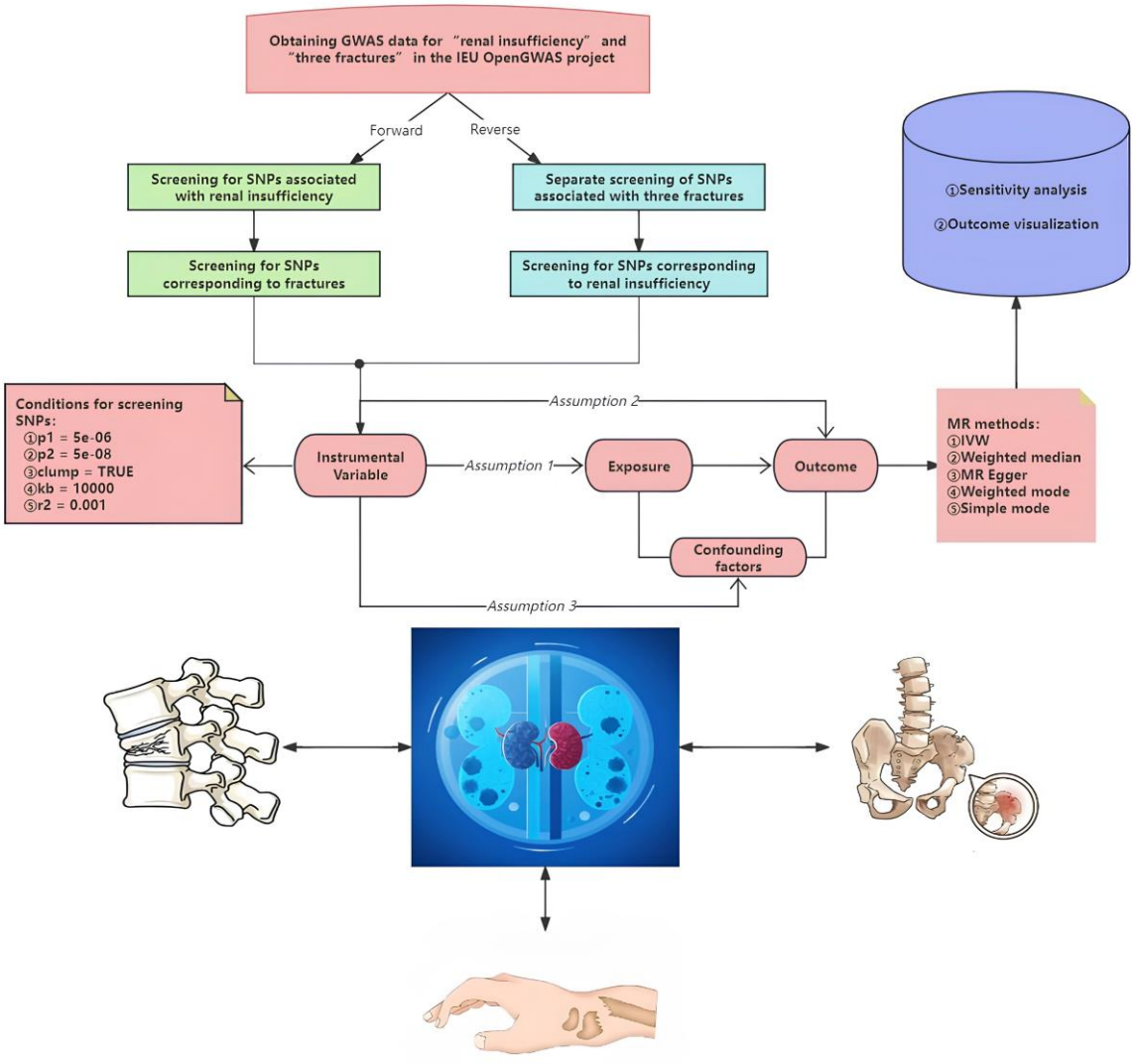

Figure 2: Flow chart of bidirectional analysis of fractures and renal insufficiency in MR studies.

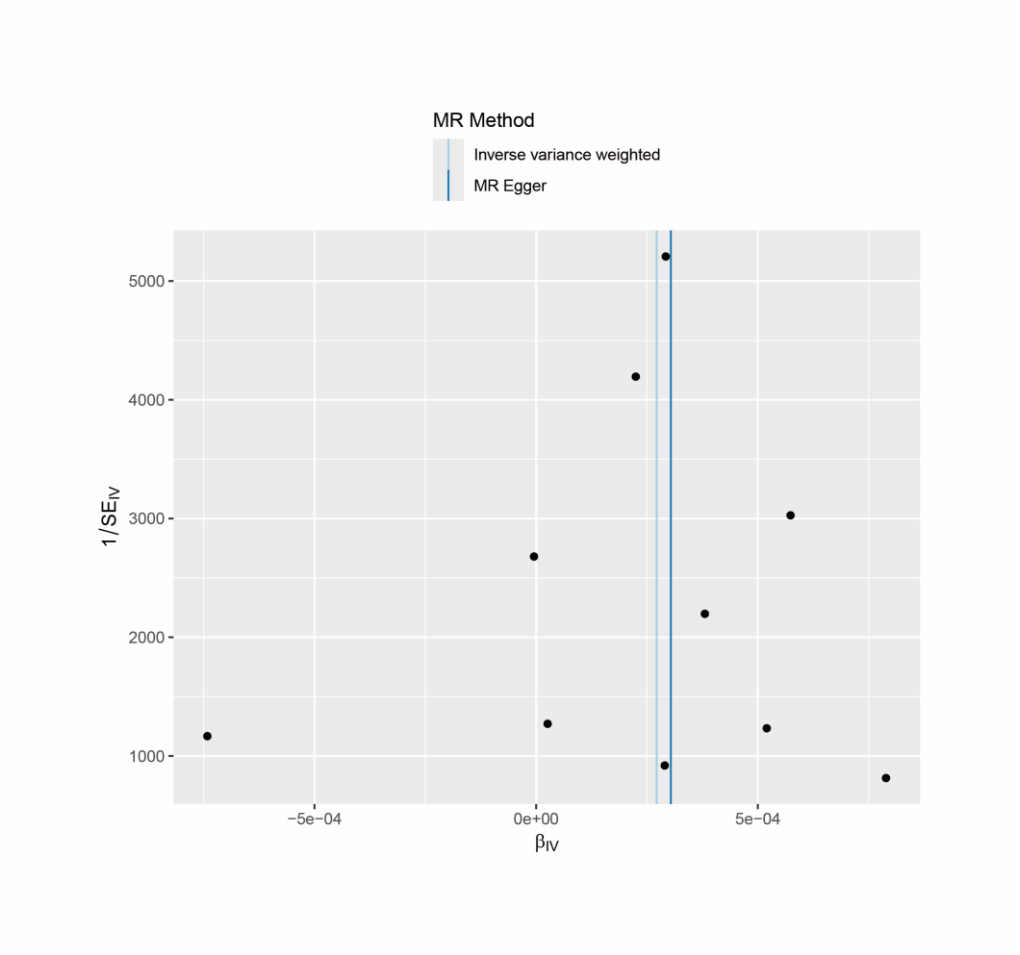

Figure 3: Funnel plot of renal insufficiency and wrist fracture.

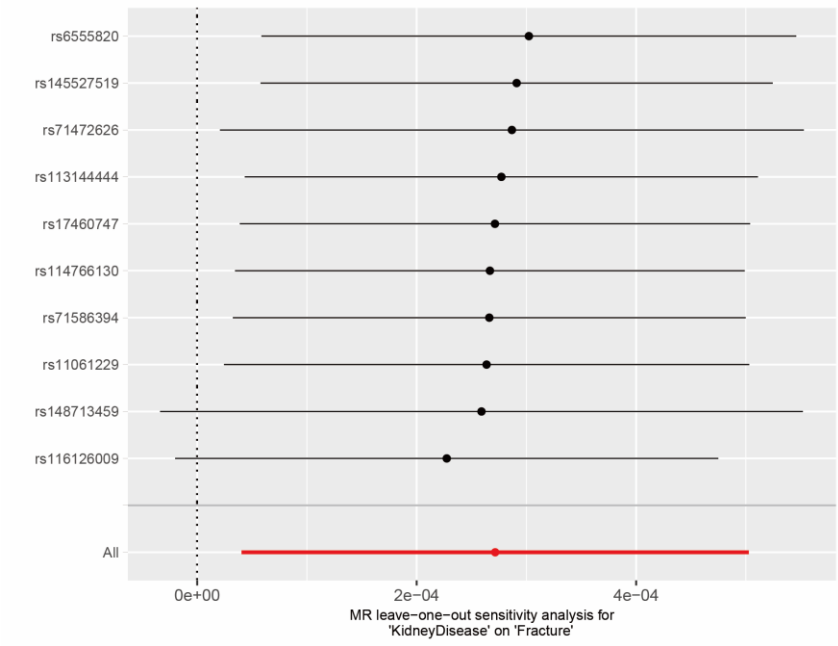

Figure 4: Leave-one-out sensitivity analysis of renal insufficiency and wrist fracture.

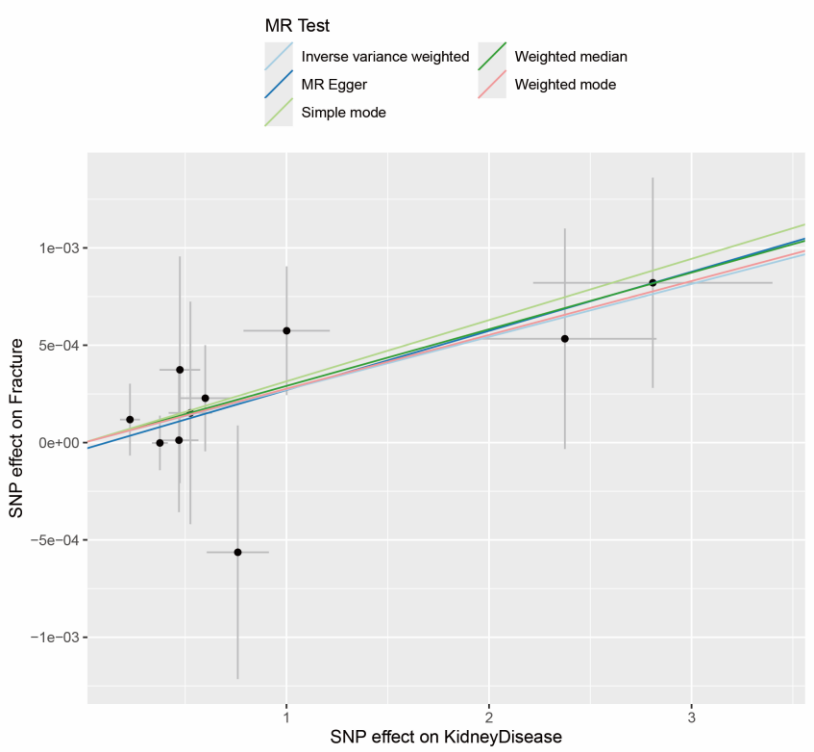

Figure 5: Scatter plot of renal insufficiency and wrist fracture.

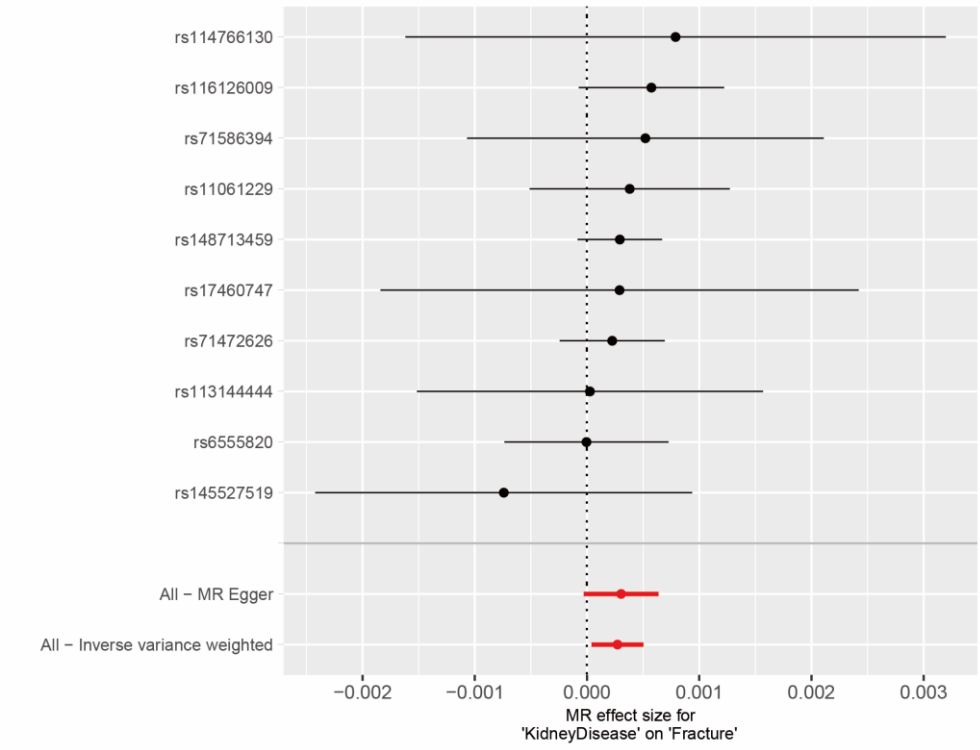

Figure 6: Forest plots of renal insufficiency and wrist fractures.

4. Discussion

The cross-sectional results of the present study align with previous findings that kidney disease

elevates fracture risk at multiple sites[16-17]. Renal osteodystrophy, primarily comprising high-turnover and low-turnover bone disease, arises from altered mineral and endocrine hormone metabolism (e.g., calcium, phosphorus, vitamin D, parathyroid hormone [PTH]) in renal insufficiency, which is a key driver of bone abnormalities[18]. In renal insufficiency, disturbances in the internal environment decrease intestinal calcium absorption and lower serum calcium levels. Concurrently, reduced renal phosphorus excretion elevates serum phosphorus, further depressing serum calcium. Hypocalcemia stimulates increased PTH secretion, mobilizing bone calcium release to maintain calcium homeostasis, ultimately leading to bone loss over time. Kidney damage also decreases expression of the "Klotho" protein, elevating fibroblast growth factor-23 (FGF-23)[19-21]. Increased FGF-23 promotes urinary phosphate excretion and reduces calcitriol synthesis. Reduced calcitriol further stimulates PTH secretion, exacerbating bone calcium loss and long-term osteoporosis and fracture risk[22-23]. Additionally, serum sclerostin rises with declining renal function. Sclerostin promotes osteoclast synthesis via RANK-L and binds LRP5/6 to inhibit Wnt signaling, contributing to bone loss[24-26].

Impaired kidney function also prevents the excretion of metabolic toxins, worsening mineral metabolism disruption and predisposing the body to acid-base imbalances, particularly acidosis. An acidic environment inhibits osteoblast activity and prolongs osteoclast survival, leading to abnormal bone remodeling and osteoporosis[27].

At the same moment, Mendel's results remind us that the mechanism of the relationship between abnormal renal function and fracture is not uniform and perfect, and the two will often occur together, but the causal relationship between them and the order of occurrence is unclear. This study identified the risk relationship between renal insufficiency and multiple fractures via cross-sectional analysis, subgroup analysis, and logistic regression (showing significant positive correlation), and used MR to reduce unmeasured confounders and verify potential bidirectional causality. Future research should involve large prospective cohort studies with precise confounding controls and standardized data collection to validate results, along with cell/animal experiments to explore mechanisms, aiming to enhance comprehensive management of renal insufficiency patients and fracture prevention.

5. Conclusions

In this study, we found renal insufficiency as a risk factor for all three fractures before and after adjusting for different models through the (NHANES) large cross sectional study in multiple populations, and further through a MR study based on genetic instrumental variables, we finally found that renal insufficiency was significantly causally associated with wrist fracture only among the three types of fracture, and the reverse study did not find any causal association between fracture and renal insufficiency. The above findings suggest that clinicians should pay attention to the risk of fracture in patients with renal insufficiency, especially as a risk factor for wrist fracture, and need to explore not only the extrinsic risk factors and common pathogenic mechanisms, but also the intrinsic genetic information.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability statement

Data used in this study are available from the public NHANES database (https://wwwn.cdc.gov/nchs/nhanes/default.aspx), representing the U.S. population with informed consent from all participants. The project was approved by the NCHS Research Ethics Review Board (https://www.cdc.gov/nchs/nhanes/about/erb.html). GWAS data were obtained from https://gwas.mrcieu.ac.uk/.

Competing interests

No competing interests.

Author contributions

All authors read and approved the final version of the manuscript.

Conceptualization and writing: Lintao Zhang. Data curation and investigation: Xue Yun.

Formal analysis: Shangyi Geng. .Software: Zhaopeng Fan Funding acquisition and supervision: Hua Guo.

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