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Associations of Mixed-Metal Exposure with Incident Chronic Kidney Disease in an Occupational Population: A Nested Case–Control Study

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Abstract

Long-term occupational exposure to multiple metals in mining environments may be associated with chronic kidney disease (CKD), but the associations between mixed metal exposure and CKD remain insufficiently characterized. A nested case–control study was conducted within the Jinchang Cohort, established in 2011 among workers with long-term multi-metal exposure at Jinchuan Group Co., Ltd. Among eligible cohort members, 1000 incident CKD cases identified at the third follow-up were compared with 1000 controls randomly selected from non-diseased cohort members. Bayesian Kernel Machine Regression (BKMR) was used to assess the joint association of mixed metal exposure with CKD, while multivariable logistic regression estimated odds ratios (ORs) and 95% confidence intervals (CIs) for individual metals. Restricted cubic splines (RCS) were used to evaluate potential nonlinear dose–response relationships. Mixed-metal exposure showed an exposure-dependent pattern, with the estimated association shifting from negative at lower mixture levels to positive at higher exposure levels. Li, Al, Cr, and Ni showed positive associations with CKD, whereas Zn and Se showed inverse associations.

Keywords: chronic kidney disease; occupational metal exposure; mixed metal exposure; nested case–control study; BKMR

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1. Introduction

Metals play essential roles in industrial production and daily life; however, the expansion of industrial activities has increased their release into the environment, raising concerns about potential adverse effects on human health. Metal smelting is an important source of environmental metal contamination, as inadequate waste management can result in substantial releases of metals into surrounding environments [1,2]. Early research identified smelters as key contributors to atmospheric As, Cu, Cd, and Zn pollution [3], and a recent study further supported these findings [4]. From 2000 to 2019, 80% of Chinese non-ferrous smelter sites showed severe Cd contamination in surrounding soil, with po-

tential implications for the health of local populations [1]. Workers in steel and non-ferrous metal smelting industries may be exposed to multiple metals through occupational contact with metal ores, molten metals, and metal-containing dust. Compared with nearby residents, smelting workers have been reported to have higher body levels of As, Pb, Cd, Sb, Tl, and Sn. Moreover, owing to incomplete elimination of metals from the body, internal metal burdens may accumulate with age [5–7].

Chronic kidney disease (CKD), characterized by abnormalities in renal structure or function, affects more than 10% of the global population and represents an increasing public health challenge [8–10]. In 2017, more than 850 million people worldwide were living with CKD, including an estimated 4.9–7.1 million who required renal replacement therapy for end-stage kidney disease [11,12]. Between 1990 and 2019, the global number of CKD cases approximately doubled, with a particularly substantial increase in disease burden in low- and middle-income countries [13,14]. In China, an estimated 150.5 million adults had CKD in 2019, with 196,726 deaths attributed to the disease [15]. More recent surveillance data from 2023, based on 176,874 participants, reported a CKD prevalence of 8.2%, representing an approximately 30% reduction compared with a decade earlier [16]. Although the prevalence of CKD in the general population has declined to some extent, the burden of CKD among highly exposed occupational populations remains insufficiently characterized [17]. This highlights the importance of identifying underlying risk factors to inform effective prevention and control strategies.

As major filtration organs, the kidneys can accumulate metals and are therefore particularly susceptible to metal-induced toxicity [18]. Metal exposure may impair renal function through multiple mechanisms, including induction of oxidative stress, disruption of immune and organelle function, and interference with renal transport processes and hormonal regulation [19,20]. Studies conducted in China have reported associations between exposure to Cr, Cd, Pb, and Mn and alterations in renal biomarkers [21]. In addition, several cross-sectional studies have linked blood levels of Pb, Cd, Hg, Mn, Cu, Zn, and Se to CKD [22–24]. However, existing evidence is predominantly based on cross-sectional studies, and longitudinal evidence regarding the associations between metal exposure and CKD incidence remains limited. In addition, previous studies have not sufficiently characterized the overall associations of mixed-metal exposure with CKD incidence or the relative contributions of individual metals within exposure mixtures. In occupational settings such as metal smelting and mining, workers may be simultaneously exposed to multiple metals through contact with ores, dust, and other metal-containing materials. Therefore, investigating mixed-metal exposure is important for better characterizing the potential renal health risks associated with complex occupational exposure profiles. This study utilized a nested case–control design within the Jinchang Cohort—a large-scale prospective cohort of metal-exposed workers established in collaboration with Jinchuan Group Co., Ltd. This cohort provides an important platform for investigating the long-term health effects of occupational multi-metal exposure [25,26]. To better characterize the association between mixed-metal exposure and CKD incidence, we applied BKMR to assess the overall mixture association and identify potentially important elements, while WQS regression was used as a complementary approach to examine the consistency of the mixture-level association and the contributions of individual elements. Herein, we aimed to evaluate the longitudinal associations of individual and mixed-metal exposures with the incidence of CKD.

2. Materials and Methods

2.1. Study Population

This nested case–control study was conducted within the Jinchang Cohort, which conducts biennial health examinations among employees of Jinchuan Group Co., Ltd., a large non-ferrous metal mining and smelting enterprise located in Jinchang, Gansu Province, China. A total of 48,001 participants were enrolled at baseline between June 2011 and December 2013. Data on human biological indicators at baseline and follow-up were obtained from routine health examination records. During the third follow-up examination, conducted between 2018 and 2019, participants who were newly identified as having CKD and had no physician-reported CKD diagnosis at baseline were selected as cases. Owing to financial constraints on metal measurements, our research group analyzed 1000 cases and 1000 controls. Controls (n = 1000) were randomly using R software selected from participants in the same cohort who had no documented CKD diagnosis at the third follow-up examination. Simple random sampling was performed without matching or adjustment for any covariates during control selection. Baseline demographic and lifestyle characteristics were adjusted for as covariates in subsequent multivariable models. The study protocol was approved by the Ethics Committee of the School of Public Health, Lanzhou University (IRB23042201).

2.2. Variable Definitions

CKD cases were identified based on physician-reported diagnoses, which were further assessed using eGFR calculated from serum creatinine (Scr) measurements obtained during routine health examinations [27–29]. CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 mL·min^{-1}·1.73 m^{-2}. The equation used to calculate eGFR is provided below:

Female: when Scr ≤ 0.7 mg/dL (62 μmol/L), eGFR = 144 × (Scr/0.7)$^{-0.329}$ × 0.993 ^{Age},
when Scr > 0.7 mg/dL (62 μmol/L), eGFR = 144 × (Scr/0.7)$^{-1.209}$ × 0.993 ^{Age};
Male: when Scr ≤ 0.9 mg/dL (80 μmol/L), eGFR = 141 × (Scr/0.9)$^{-0.411}$ × 0.993 ^{Age},
when Scr > 0.9 mg/dL (80 μmol/L), eGFR = 141 × (Scr/0.9)$^{-1.209}$ × 0.993 ^{Age}.

The questionnaire survey in this study collected data of participants' age (age was categorized for descriptive purposes as ≤ 25, 26–45, 46–65, and ≥ 66 years), sex, marital status (unmarried, married, divorced or widowed), occupational exposure level (low: cadres and logistics personnel; moderate: technical personnel; high: production workers; Cadres and logistics personnel were combined into the low-exposure group because of their relatively small numbers in the study population), monthly income (<2000 RMB, ≥2000 RMB), education level (secondary school or below, high school or technical secondary school, college or above), body mass index (<25.0, 25.0–29.9, or ≥30.0 kg/m^2), exercise frequency (never, occasionally, frequently), smoking status (never smoking, currently smoking, have quit smoking), drinking status (never drinking, currently drinking, have quit drinking). Physician-diagnosed cardiovascular disease, hypertension, and diabetes were also recorded (yes/no). Plasma metal concentrations were categorized into quartiles (Q1–Q4) according to their distributions, with the lowest quartile (Q1) serving as the reference category.

2.3. Measurement of Plasma Element Concentrations

At baseline, plasma concentrations of 13 elements, including 12 metals (Li, Al, Ti, Sr, Cu, Co, Cd, Pb, Cr, Ni, Zn, and Fe) and Se, were measured using inductively coupled plasma–mass spectrometry (ICP-MS) with a PQ-MS instrument equipped with a collision/reaction cell (Germany). For individual samples with measured concentrations be-

low the limit of detection (LOD), the values were imputed as LOD/2. Quality control results for plasma element measurements in the study population are presented in Table A1.

2.4. Statistical Analysis

Descriptive statistics were used to summarize plasma metal concentrations, and categorical variables were presented as proportions. Spearman's rank correlation analysis was used to assess correlations among metals, and the Wilcoxon rank-sum test was used to compare metal concentrations between groups.

BKMR was used to evaluate the joint association between metal mixtures and CKD, with adjustment for all covariates. Metal concentrations were log-transformed and standardized. The model was run for 10,000 Markov Chain Monte Carlo (MCMC) iterations. The overall mixture effect was estimated by comparing the joint exposure level at the 50th percentile of all metals with that at the 50th percentile as the reference. Posterior inclusion probabilities (PIPs) were calculated to assess the probability that each metal was included in the mixture model. Metals with PIPs ≥ 0.5 showed relatively high probabilities of inclusion in the mixture model. Model convergence was satisfactory, as shown in Figure A1.

To further characterize the mixture effects and evaluate the associations of individual metals with CKD incidence, multivariable logistic regression models were used to examine the associations between individual metal exposures and CKD incidence. Plasma metal concentrations were categorized into quartiles (Q1–Q4), with Q1 as the reference category, and odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for Q2–Q4. Metal concentrations were also modeled as continuous variables in multivariable logistic regression analyses to further evaluate the associations between individual metal exposures and CKD incidence. Restricted cubic spline (RCS) models were used to assess potential nonlinear dose–response relationships between metal exposure and CKD incidence.

The 13 metals were categorized into quartiles, and the dataset was divided into a training set (40%) and a validation set (60%). A positive-direction WQS model was fitted, with component weights estimated using 1000 bootstrap samples. The negative-direction WQS model did not converge; therefore, only the positive-direction model was retained for analysis. The corresponding component weights for each metal are presented in Figure A2. E-values were calculated based on the categorical multivariable logistic regression models to assess the potential influence of unmeasured confounding on the observed associations and thereby evaluate the robustness of the findings. Additionally, further sensitivity analyses were conducted to evaluate the impact of missing data handling. Multivariable logistic regression analyses based on multiple imputation datasets were performed, and RCS and BKMR models were re-evaluated using LOD/sqrt(2) substitution and multiple imputation, respectively, compared to the primary LOD/2 substitution.

Questionnaire data were double-entered using EpiData 3.1. Microsoft Excel for Office 365 (Version 16.0.4266.1001), IBM SPSS Statistics 27, R Project 4.3.3, and RStudio 2024.12.0+467 were used for data organization and cleaning. Statistical analyses and graphical presentations were performed using R Project 4.3.3 and RStudio 2024.12.0+467. All statistical tests were two-sided, and a significance level of $\alpha = 0.05$ was used.

3. Results

3.1. Description of the Study Population

As shown in Table 1, among the 2000 participants, 72.45% were male, 81.75% had a high level of occupational exposure, and 57.70% had a BMI < 25 kg/m^2. Overall, 45.40% were currently smoking, 22.60% were currently drinking, and 29.80%, 38.30%, and 13.90%

had physician-diagnosed cardiovascular disease, hypertension, and diabetes, respectively. Significant differences between the case and control groups were observed in age, sex, marital status, occupational exposure level, BMI, exercise frequency, smoking status, and drinking status ($p < 0.05$). No significant differences were observed in monthly income, education level, cardiovascular disease, hypertension, or diabetes ($p > 0.05$).

Table 1. Characteristics of participants.

Variables *n*(%)	Total (*N* = 2000)	Case Group (*n* = 1000)	Control Group (*n* = 1000)	*p* Value
Age				
≤25 years	69 (3.45)	51 (5.10)	18 (1.80)	<0.001
26–45 years	809 (40.45)	486 (48.60)	323 (32.30)	
46–65 years	778 (38.90)	307 (30.70)	471 (47.10)	
≥66 years	344 (17.20)	156 (15.60)	188 (18.80)	
Sex				
Male	1449 (72.45)	783 (78.30)	666 (66.60)	<0.001
Female	551 (27.55)	217 (21.70)	334 (33.40)	
Marriage status				
Unmarried	122 (6.10)	88 (8.80)	34 (3.40)	<0.001
Married	1723 (86.15)	836 (83.60)	887 (88.70)	
Divorce or widowhood	155 (7.75)	76 (7.60)	79 (7.90)	
Occupational exposure				
Low	300 (15.00)	119 (11.90)	181 (18.10)	<0.001
Moderate	65 (3.25)	33 (3.30)	32 (3.20)	
High	1635 (81.75)	848 (84.80)	787 (78.70)	
Monthly income				
<2000 RMB	1100 (55.00)	537 (53.70)	563 (56.30)	0.243
≥2000 RMB	900 (45.00)	463 (46.30)	437 (43.70)	
Education level				
Secondary school or below	975 (48.75)	469 (46.90)	506 (50.60)	0.231
High school or technical secondary school	582 (29.10)	298 (29.80)	284 (28.40)	
College degree or above	443 (22.15)	233 (23.30)	210 (21.00)	
BMI				
<25.0	1154 (57.70)	544 (54.40)	610 (61.00)	<0.001
25–29.9	738 (36.90)	378 (37.80)	360 (36.00)	
≥30.0	108 (5.40)	78 (7.80)	30 (3.00)	
Exercise frequency				
Never	202 (10.10)	110 (11.00)	92 (9.20)	<0.001
Occasionally	357 (17.85)	210 (21.00)	147 (14.70)	
Frequently	1441 (72.05)	680 (68.00)	761 (76.10)	
Smoking status				
Never smoking	868 (43.40)	405 (40.50)	463 (46.30)	0.030
Currently smoking	908 (45.40)	480 (48.00)	428 (42.80)	
Have quit smoking	224 (11.20)	115 (11.50)	109 (10.90)	
Drinking status				<0.001
Never drinking	1404 (70.20)	625 (62.50)	779 (77.90)	

Currently drinking	452 (22.60)	296 (29.60)	156 (15.60)	
Have quit drinking	144 (7.20)	79 (7.90)	65 (6.50)	
Cardiovascular disease				0.557
Yes	596 (29.80)	292 (29.20)	304 (30.40)	
No	1404 (70.20)	708 (70.80)	696 (69.60)	
Hypertension				
Yes	766 (38.30)	385 (38.50)	381 (38.10)	0.854
No	1234 (61.70)	615 (61.50)	619 (61.90)	
Diabetes				
Yes	278 (13.90)	151 (15.10)	127 (12.70)	0.121
No	1722 (86.10)	849 (84.90)	873 (87.30)	

Note: Data are presented as n (%). *p* values were calculated using Pearson's chi-square test. Occupational exposure level was categorized based on job duties into low (cadres and logistics personnel), moderate (technical personnel), and high (production workers).

3.2. Environmental Metal Exposure

3.2.1. Differences in Plasma Metal Concentrations Between the CKD Case and Control Groups

As shown in Table 2, significant differences were observed in plasma concentrations of all 13 elements between the CKD case group and the control group. Specifically, the case group exhibited markedly higher plasma concentrations of Li, Al, Cu, Cd, Cr, and Ni compared with the control group. Conversely, plasma concentrations of Ti, Sr, Co, Pb, Zn, Fe, and Se were significantly lower in the case group than in the control group.

Table 1. Plasma Metal Concentrations in the CKD Case and Control Groups (μg/L).

Metal	Total (*N* = 2000)	Case Group (*n* = 1000)	Control Group (*n* = 1000)	*p* Value
Li	13.66 (8.26, 20.85)	14.82 (8.98, 21.70)	12.74 (7.65, 19.75)	<0.001
Al	206.18 (129.33, 359.77)	246.85 (127.80, 476.36)	182.25 (131.21, 290.31)	<0.001
Ti	227.17 (208.24, 248.49)	227.12 (209.12, 242.14)	227.24 (208.01, 316.05)	<0.001
Sr	83.73 (69.85, 105.00)	80.70 (68.85, 98.03)	88.11 (70.90, 112.00)	<0.001
Cu	908.39 (813.42, 1025.91)	925.24 (813.32, 1060.26)	896.74 (814.73, 999.55)	<0.001
Co	0.10 (0.10, 0.33)	0.10 (0.10, 0.31)	0.21 (0.10, 0.37)	<0.001
Cd	0.10 (0.10, 0.34)	0.10 (0.10, 0.78)	0.10 (0.10, 0.10)	<0.001
Pb	2.00 (2.00, 7.60)	2.00 (2.00, 4.75)	2.00 (2.00, 15.54)	<0.001
Cr	18.42 (15.18, 25.03)	22.41 (16.78, 31.61)	16.11 (14.80, 20.34)	<0.001
Ni	2.54 (1.00, 8.15)	5.01 (1.00, 15.00)	1.00 (1.00, 3.74)	<0.001
Zn	1074.68 (920.02, 1279.83)	1034.63 (899.90, 1197.42)	1139.47 (946.80, 1348.87)	<0.001
Fe	2356.56 (1948.80, 3005.40)	2246.31 (1866.95, 2694.85)	2511.22 (2009.27, 3377.79)	<0.001
Se	109.81 (96.59, 124.97)	106.06 (93.41, 119.89)	114.46 (100.92, 130.65)	<0.001

Note: Data are presented as median (25th percentile, 75th percentile). SI conversion factors: To convert metal concentrations to micromoles per liter (μmol/L), multiply values by: Li, 0.1441; Al, 0.0371; Ti, 0.0209; Sr, 0.0114; Cu, 0.0157; Co, 0.0170; Cd, 0.0089; Pb, 0.0048; Cr, 0.0192; Ni, 0.0170; Zn, 0.0153; Fe, 0.0179; and Se, 0.0127. *p* values were calculated using the Wilcoxon rank-sum test to compare plasma metal concentrations between the CKD case and control groups.

3.2.2. Correlations Among Plasma Metal Concentrations

Spearman's rank correlation coefficients among plasma metals ranged from −0.15 to 0.57. The strongest positive correlation was observed between Ni and Cr (r = 0.57), while Cd showed positive correlations with Ni (r = 0.49) and Cr (r = 0.46). The strongest negative correlation was observed between Li and Cr (r = −0.15). Detailed correlation results are presented in Figure A3.

3.3. Association Between Environmental Metal Exposure and CKD Incidence

3.3.1. Overall Association Between Mixed Metal Exposure and CKD Incidence Assessed by BKMR

As shown in Figure 1, the BKMR model indicated that the overall effect estimates of the metal mixture shifted from negative to positive with increasing exposure quantiles. The estimated effects were generally below zero at lower exposure quantiles and became positive at higher quantiles, indicating a positive association between higher levels of the metal mixture and CKD. Li, Al, Ti, Cu, Cd, Cr, Ni, and Se each had a PIP of 1.00, indicating a high probability of inclusion in the mixture model (Table A2).

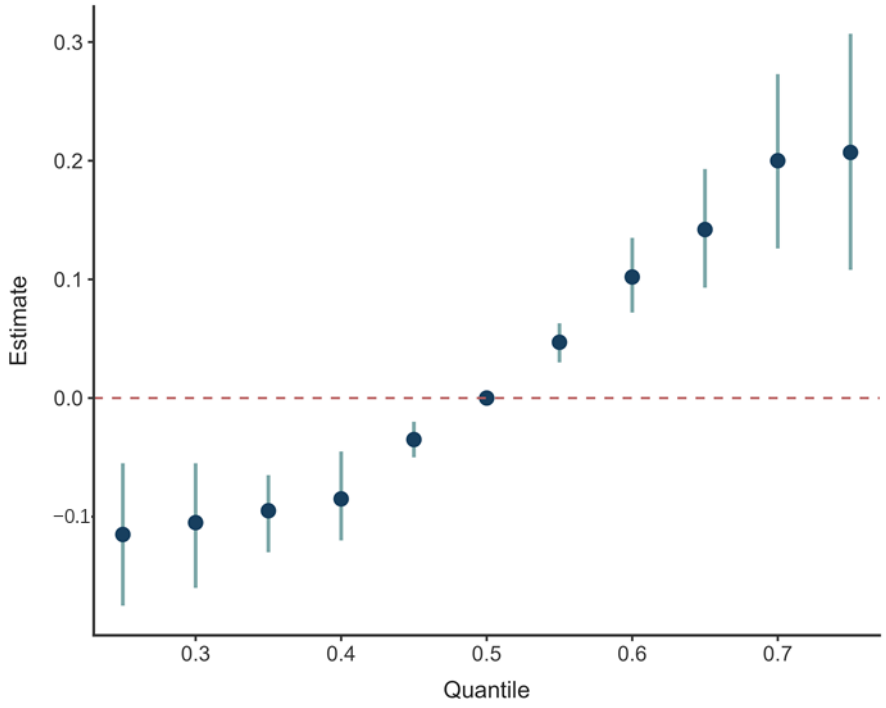


Figure 1. The total effect of combined plasma metal exposure levels on the risk of developing CKD. Note: The BKMR model was adjusted for all covariates.

3.3.2. Single-Metal Associations with CKD Incidence

Associations Between Metal Exposure and CKD Incidence Assessed by Multivariable Logistic Regression

As shown in Table 3, after adjustment for all covariates, the associations between plasma metal concentrations and CKD incidence varied across exposure quartiles. Compared with Q1, Li exposure was associated with higher odds of CKD at Q2, Q3, and Q4, with ORs of 1.62, 2.61, and 3.25, respectively. For Al, exposure was associated with lower odds of CKD at Q2 (OR, 0.51; 95% CI, 0.34–0.74) but higher odds at Q4 (OR, 2.54; 95% CI, 1.62–3.97). Sr exposure was associated with higher odds of CKD at Q2 (OR, 1.55; 95% CI, 1.05–2.29) but lower odds at Q4 (OR, 0.59; 95% CI, 0.39–0.91). Cu exposure at Q2 was associated with higher odds of CKD (OR, 1.36; 95% CI, 1.06–1.77), whereas Cd exposure at

Q2 was associated with lower odds (OR, 0.54; 95% CI, 0.38–0.78). Pb exposure at Q3 was also associated with lower odds of CKD (OR, 0.40; 95% CI, 0.27–0.60).

Cr exposure was associated with higher odds of CKD at Q3 (OR, 1.99; 95% CI, 1.37–2.90) and Q4 (OR, 8.27; 95% CI, 5.07–13.50). Similarly, Ni exposure at Q4 was associated with higher odds of CKD (OR, 3.35; 95% CI, 2.31–4.85). In contrast, Zn, Fe, and Se exposures at Q4 were associated with lower odds of CKD, with ORs of 0.51 (95% CI, 0.33–0.78), 0.48 (95% CI, 0.31–0.74), and 0.27 (95% CI, 0.18–0.41), respectively. No statistically significant associations were observed across exposure quartiles for Co, while Ti showed no statistically significant association in any quartile.

Table 3. Multivariable logistic regression analysis of plasma metal concentrations and the odds of developing CKD.

Variables	Model 1 [a]		Model 2 [b]		Model 3 [c]	
	p Value	OR (95%CI)	*p* Value	OR (95%CI)	*p* Value	OR (95%CI)
			Li			
Q1		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)
Q2	0.095	1.43 (0.94, 2.17)	0.072	1.46 (0.97, 2.20)	0.014	1.62 (1.10, 2.38)
Q3	<0.001	2.47 (1.58, 3.87)	<0.001	2.46 (1.58, 3.81)	<0.001	2.61 (1.74, 3.92)
Q4	<0.001	2.98 (1.87, 4.73)	<0.001	3.00 (1.90, 4.74)	<0.001	3.25 (2.13, 4.97)
			Al			
Q1		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)
Q2	<0.001	0.45 (0.30, 0.68)	<0.001	0.44 (0.30, 0.66)	<0.001	0.51 (0.34, 0.74)
Q3	0.205	1.32 (0.86, 2.03)	0.244	1.28 (0.84, 1.96)	0.160	1.33 (0.89, 1.98)
Q4	<0.001	2.52 (1.57, 4.06)	<0.001	2.54 (1.58, 4.07)	<0.001	2.54 (1.62, 3.97)
			Ti			
Q1		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)
Q2	0.862	0.96 (0.64, 1.45)	0.743	0.93 (0.63, 1.40)	0.809	0.95 (0.65, 1.39)
Q3	0.213	1.31 (0.86, 2.01)	0.312	1.24 (0.82, 1.89)	0.204	1.30 (0.87, 1.94)
Q4	0.111	0.68 (0.42, 1.09)	0.077	0.65 (0.40, 1.05)	0.051	0.64 (0.41, 1.00)
			Sr			
Q1		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)
Q2	0.007	1.78 (1.17, 2.70)	0.004	1.82 (1.21, 2.74)	0.027	1.55 (1.05, 2.29)
Q3	0.253	1.28 (0.84, 1.97)	0.165	1.35 (0.88, 2.06)	0.396	1.19 (0.80, 1.77)
Q4	0.047	0.62 (0.39, 0.99)	0.066	0.65 (0.41, 1.03)	0.017	0.59 (0.39, 0.91)
			Cu			
Q1		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)
Q2	0.013	1.40 (1.07, 1.82)	0.019	1.35 (1.05, 1.73)	0.016	1.36 (1.06, 1.77)
Q3	0.058	1.29 (0.99, 1.69)	0.527	1.08 (0.85, 1.39)	0.393	1.27 (0.98, 1.65)
Q4	0.683	0.94 (0.72, 1.24)	0.006	0.71 (0.55, 0.91)	0.591	0.73 (0.23, 2.30)
			Co			
Q1		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)
Q2	0.227	1.21 (0.89, 1.64)	0.331	1.16 (0.86, 1.56)	0.291	1.17 (0.87, 1.57)
Q3	0.382	0.86 (0.62, 1.20)	0.408	0.87 (0.64, 1.20)	0.343	0.86 (0.62, 1.18)
Q4	0.383	1.23 (0.78, 1.94)	0.447	1.19 (0.76, 1.84)	0.674	1.10 (0.71, 1.69)
			Cd			
Q1		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)
Q2	0.002	0.55 (0.38, 0.80)	0.001	0.55 (0.39, 0.79)	<0.001	0.54 (0.38, 0.78)
Q3	0.731	0.86 (0.35, 2.08)	0.557	0.77 (0.32, 1.84)	0.612	0.80 (0.34, 1.89)
Q4	0.205	4.06(0.47,35.38)	0.194	4.16(0.48, 35.76)	0.185	4.25(0.50, 36.00)
			Pb			
Q1		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)
Q2	0.008	0.41 (0.21, 0.79)	0.017	0.45 (0.24, 0.87)	0.013	0.44 (0.23, 0.84)

Q3	<0.001	0.40 (0.26, 0.61)	<0.001	0.41 (0.27, 0.62)	<0.001	0.40 (0.27, 0.60)
Q4	0.247	0.74 (0.45, 1.23)	0.350	0.79 (0.49, 1.29)	0.331	0.79 (0.49, 1.27)
			Cr			
Q1		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)
Q2	0.798	0.95 (0.65, 1.40)	0.773	0.95 (0.65, 1.38)	0.424	0.86 (0.60, 1.24)
Q3	<0.001	2.40 (1.59, 3.64)	<0.001	2.41 (1.60, 3.64)	<0.001	1.99 (1.37, 2.90)
Q4	<0.001	8.63 (5.08, 14.66)	<0.001	8.76 (5.18, 14.80)	<0.001	8.27 (5.07, 13.50)
			Ni			
Q1		1.0 (Reference)		1.0 (Reference)		1.0 (Reference)
Q2	<0.001	2.33 (1.49, 3.65)	<0.001	2.28 (1.47, 3.53)	<0.001	2.25 (1.46, 3.48)
Q3	0.031	1.42 (1.03, 1.97)	0.034	1.40 (1.03, 1.90)	0.057	1.35 (0.99, 1.83)
Q4	<0.001	3.53 (2.40, 5.21)	<0.001	3.40 (2.34, 4.94)	<0.001	3.35 (2.31, 4.85)
			Zn			
Q1		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)
Q2	0.950	1.01 (0.67, 1.53)	0.930	1.02 (0.68, 1.53)	0.903	1.02 (0.70, 1.51)
Q3	0.261	0.79 (0.52, 1.19)	0.249	0.79 (0.52, 1.18)	0.265	0.80 (0.54, 1.18)
Q4	0.001	0.47 (0.30, 0.75)	0.001	0.48 (0.31, 0.75)	0.002	0.51 (0.33, 0.78)
			Fe			
Q1		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)
Q2	0.418	0.84 (0.56, 1.27)	0.523	0.88 (0.58, 1.32)	0.309	0.82 (0.56, 1.20)
Q3	0.615	0.90 (0.58, 1.37)	0.626	0.90 (0.59, 1.37)	0.467	0.87 (0.59, 1.28)
Q4	<0.001	0.46 (0.29, 0.72)	<0.001	0.46 (0.29, 0.72)	<0.001	0.48 (0.31, 0.74)
			Se			
Q1		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)
Q2	<0.001	0.46 (0.30, 0.70)	<0.001	0.46 (0.31, 0.70)	<0.001	0.50 (0.34, 0.75)
Q3	<0.001	0.30 (0.19, 0.45)	<0.001	0.31 (0.20, 0.47)	<0.001	0.37 (0.25, 0.54)
Q4	<0.001	0.24 (0.16, 0.38)	<0.001	0.24 (0.16, 0.37)	<0.001	0.27 (0.18, 0.41)

Note: Plasma concentrations of the 13 metals were categorized into four groups (Q1–Q4) with Q1 as the reference. For low-detection metals (Cd, Pb, Co, Ni), Q1 represents values below the LOD, and concentrations above the LOD were divided into three equal groups (Q2–Q4); remaining metals used standard quartiles. The specific cutoff values and the number of participants in each group are provided in Table A3. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multivariable logistic regression models. All 13 metals were included simultaneously in each model. [a]: Model 1: Unadjusted for covariates.; [b]: Model 2: Adjusted for age, sex, marital status, occupational exposure level, monthly income, education level, BMI, exercise frequency, smoking status, and drinking status; [c]: Model 3: Additionally adjusted for cardiovascular disease, hypertension, and diabetes beyond the covariates included in Model 2. *p* values represent tests of association between each metal quartile and the odds of CKD, with Q1 as the reference group. Statistical significance was defined as $p < 0.05$.

Dose–Response Relationships Between Single-Metal Exposure and CKD Incidence

As shown in Figure 2, plasma concentrations of Li, Sr, Cr, and Ni were significantly associated with CKD in positive non-linear patterns ($P_{non\text{-}linear} < 0.05$). In contrast, Ti, Zn, Fe, and Se showed significant negative overall associations with CKD incidence ($P_{overall} < 0.05$). Cu exhibited a significant inverted U-shaped association with CKD incidence ($P_{non\text{-}linear} < 0.05$).

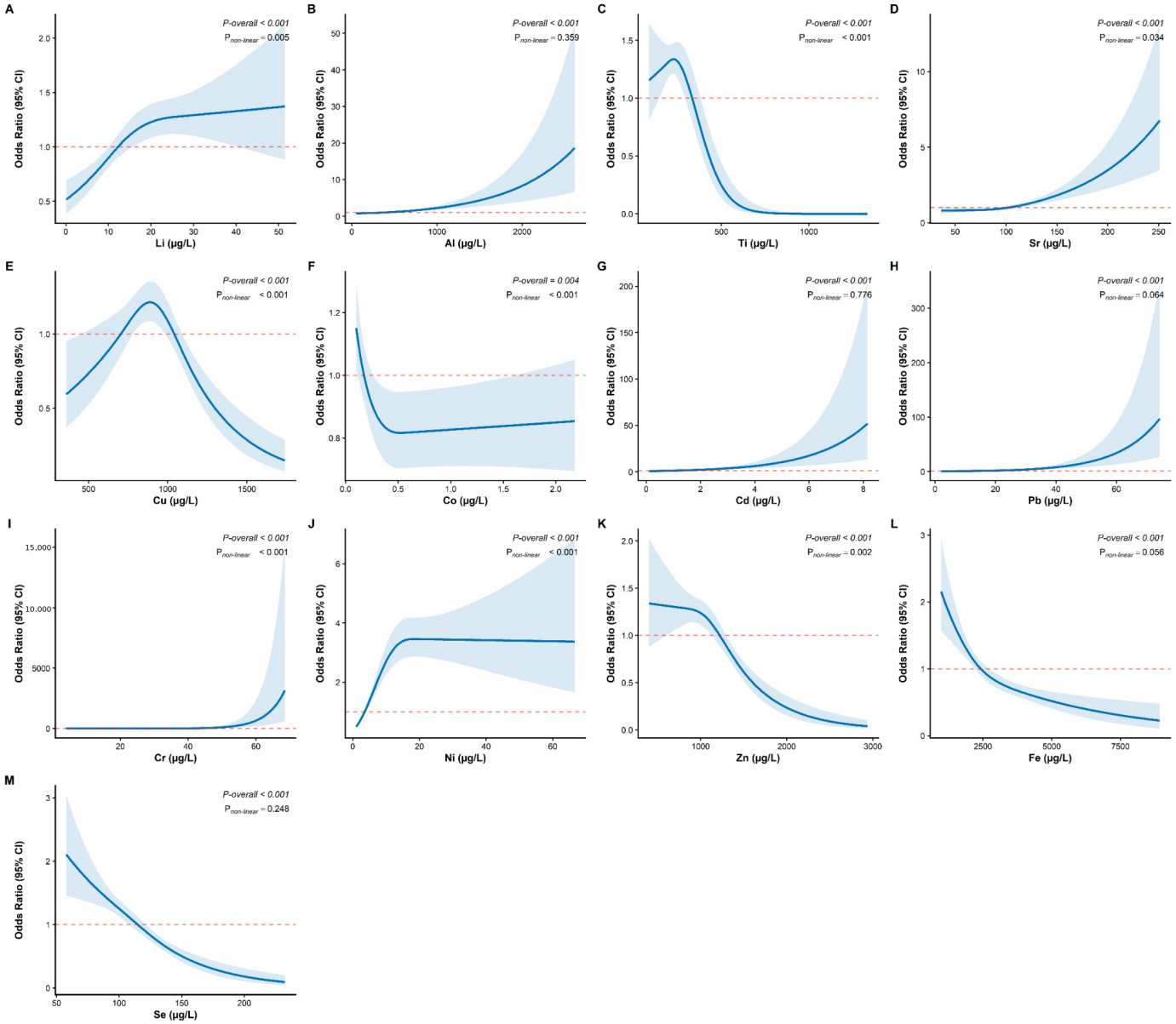


Figure 2. Cubic splines for the associations of metal concentration and CKD. Note: Dose–response relationships between individual plasma metal concentrations and incident CKD evaluated using RCS models. (**A**) Li; (**B**) Al; (**C**) Ti; (**D**) Sr; (**E**) Cu; (**F**) Co; (**G**) Cd; (**H**) Pb; (**I**) Cr; (**J**) Ni; (**K**) Zn; (**L**) Fe; (**M**) Se. Solid blue lines represent estimated ORs, and light blue shaded areas represent 95% CIs. The horizontal red dashed line indicates the reference line (OR = 1.0). The number and locations of knots were determined according to the metal concentration distributions. Models were adjusted for all covariates.

3.4. Sensitivity Analysis

Three sensitivity analyses were performed to assess the robustness of the findings. First, WQS regression showed significant associations between the metal mixture and CKD incidence in both directions, with an OR of 4.44 (95% CI, 3.52–5.62) for the positive-direction model and 0.29 (95% CI, 0.23–0.37) for the negative-direction model (Table A4). Second, in multivariable logistic regression models treating metal concentrations as continuous variables, Li, Al, Ti, Cu, Cr, Ni, Zn, and Se remained significantly associated with CKD after full adjustment for covariates (Table A5). Third, E-value analysis was conducted to assess the potential influence of unmeasured confounding on the observed associations (Table A6). The associations for Cr, Se, and Li showed greater robustness to

potential unmeasured confounding, whereas those for Al, Ni, Zn, and Fe showed moderate robustness.

Table A7 Logistic regression analysis after multiple imputation, Figures A4–A7 showed that using alternative missing data handling methods did not alter the overall trends of our primary findings.

4. Discussion

This study showed that mixed-metal exposure was significantly associated with CKD incidence. Across complementary analyses, Li, Al, Cr, and Ni showed positive associations with CKD, whereas Zn and Se showed relatively robust inverse associations. These findings indicate that the associations between individual metals and CKD may differ substantially within a metal mixture, highlighting the importance of considering both the overall mixture-level association and the contributions of individual metals. WQS regression showed significant associations in both the positive and negative directions, highlighting the directional dependence of mixture-level estimates.

In the present study, all 13 metals differed significantly between cases and controls. Compared with a Swiss population-based study, our occupational population had higher concentrations of Al, Cr, Ni, Pb, and Cd, while several metal concentrations were also higher than those reported in healthy Australians [30,31]. Plasma metal levels may partly reflect occupational exposure, but they can also be influenced by environmental and dietary sources and other factors affecting metal levels.

Metal exposure has been associated with adverse effects on multiple human systems, including the nervous, digestive, and reproductive systems. Increasing evidence has also linked metal exposure to urinary system health and kidney function [32]. A cross-sectional study based on the U.S. National Health and Nutrition Examination Survey (NHANES) reported a positive association between mixed-metal exposure and CKD [33]. Similarly, case–control studies conducted in China suggested that combined metal exposure may be associated with CKD development and impaired kidney function [34,35]. Although the types of metals examined varied across these studies, their findings were generally consistent with our results. However, metal concentrations were measured only at baseline and may not fully reflect changes in exposure during follow-up.

Previous studies have explored potential mechanisms underlying these associations, suggesting that metal exposure may be involved in biological processes such as oxidative stress and inflammatory responses [36]. These mechanisms may contribute to metal-related kidney injury and the subsequent development of CKD. Notably, the associations between metal exposure and kidney outcomes are not uniformly adverse. The inverse estimates observed at lower mixture exposure levels may be partly consistent with the inverse associations observed for Zn, Fe, and Se in the single-metal analyses. Experimental studies have provided supporting evidence, showing that Zn and Se can attenuate Cd-induced oxidative stress in rat kidneys [37]. In addition, supplementation with Zn and Fe has been reported to mitigate the adverse effects of toxic metals by improving the activity of oxidative stress-related enzymes [38]. Occupational kidney disease, such as Mesoamerican nephropathy, highlights the potential relevance of heat exposure, dehydration, and strenuous physical work to kidney injury. However, these factors were not assessed in our study [39]. Residual confounding from unmeasured or incompletely controlled factors, including other occupational exposures, heat exposure, dehydration, physical workload, nephrotoxic medication use, and dietary habits, may also have influenced the observed associations.

Li has been widely used as a medication for the treatment of psychiatric disorders since the 1950s and is also utilized in various industrial applications. Inappropriate use of Li-containing medications or exposure to environments with high Li concentrations may

result in Li toxicity and have adverse effects on multiple organ systems [40,41]. Previous studies have reported that long-term Li exposure may adversely affect the urinary system and may be associated with an increased risk of CKD and end-stage renal disease [42,43]. Although these findings provide evidence of the potential nephrotoxicity of Li, they cannot be directly extrapolated to the exposure levels observed in our occupational population. Experimental studies further suggest that oxidative stress, mitochondrial dysfunction, cellular energy dysregulation, and inflammation may be involved in Li-induced kidney injury [44,45]. These findings are consistent with the positive association between Li exposure and CKD observed in our study. However, further research is needed to clarify whether renal effects associated with occupational Li exposure differ from those reported with long-term therapeutic use.

Humans can be exposed to Al through inhalation, ingestion, and dermal contact [46]. A longitudinal study conducted among Chinese adults reported a significant positive association between plasma Al levels and declining kidney function [47]. Experimental evidence suggests that Al exposure can induce oxidative stress and interact with cellular membranes, cytoskeletal structures, and nucleic acids, resulting in cellular injury [48]. In addition, Al exposure may impair renal function and promote apoptosis and renal fibrosis through activation of the TGF-β1/Smads pathway, potentially being involved in the development of CKD [49]. This evidence is also consistent with the positive association between higher Al exposure levels and CKD observed in our study.

Excessive environmental exposure to Cr may result in its accumulation in human and animal tissues, potentially leading to toxic effects and adverse health outcomes [50]. Exposure to Cr(VI)-containing compounds has also been associated with an increased susceptibility to kidney injury and other adverse health outcomes [51]. A repeated-measures study using urinary Cr as an exposure biomarker reported that kidney injury in older adults became more pronounced with prolonged Cr exposure [52]. Similarly, a study conducted in India found significant positive associations between Cr concentrations measured in whole blood and urine and CKD [53]. Mechanistically, the adverse effects of Cr have been largely attributed to its ability to promote the generation of reactive oxygen species, thereby inducing oxidative stress [54]. In particular, Cr(VI) may induce oxidative DNA damage and alter protein expression, which may subsequently impair renal structure and function and contribute to the development of CKD [55]. These mechanisms may provide a possible explanation for the positive association between Cr exposure and CKD observed in our study. However, our study measured total plasma Cr without distinguishing its chemical species. Therefore, the Cr(VI)-specific mechanisms should be interpreted cautiously.

Humans are primarily exposed to Ni through the consumption of contaminated water and food, whereas inhalation is an important route of occupational Ni exposure and may contribute to respiratory and immune toxicity [56]. Ni is predominantly accumulated and excreted through the kidneys [57]. Data from the 2017–2018 NHANES indicated an association between urinary Ni exposure and reduced kidney function in the general population [58]. Similarly, a 2021 study reported poorer kidney function among residents living near petrochemical industries, which was suggested to be related to higher urinary Ni levels [59]. Ni exposure has also been associated with renal dysfunction and oxidative stress in humans [60]. However, experimental evidence suggests that the mechanisms underlying Ni-related toxicity may be more complex. Animal studies have shown that co-exposure to Ni can exacerbate genotoxicity in the liver and kidneys of rats, with these effects not necessarily being mediated primarily by oxidative stress or inflammation [61]. These findings provide a potential biological basis for the positive association between Ni exposure and CKD observed in our study.

Zn is essential for mitochondrial function, energy production, and intracellular homeostasis, and Zn deficiency may adversely affect these processes [62]. Low dietary Zn intake has been associated with CKD [63]. In patients with CKD, disturbances in Zn homeostasis are common, and plasma Zn levels have been reported to decline with decreasing eGFR [64]. Consistent with these observations, an NHANES-based study found that higher dietary Zn intake was associated with better kidney function and a lower prevalence of CKD [65]. Reduced Zn levels may also contribute to vascular calcification [66]. Mechanistically, Zn deficiency may increase oxidative stress and promote cellular injury and inflammation, thereby contributing to the onset and progression of CKD [67,68]. Conversely, higher plasma Zn levels have been associated with a lower risk of CKD among older adults [69]. However, dietary intake, nutritional status, and changes in Zn metabolism and excretion due to early renal impairment may have influenced this association; therefore, reverse causality cannot be excluded. Taken together, these findings provide biological and epidemiological support for the inverse association between Zn exposure and CKD observed in our study.

Higher plasma Se levels have been associated with a lower risk of CKD and higher eGFR [70]. Consistent with these findings, data from both NHANES and the CHNS have indicated that higher dietary Se intake is inversely associated with CKD incidence [71,72]. Experimental studies have further suggested that Se supplementation may reduce oxidative stress and improve renal and immune function in patients with kidney disease, thereby providing potential renal protection [73]. Following Se supplementation, serum glutathione peroxidase 3 levels may increase and accumulate in the basement membrane surrounding the renal proximal tubules, facilitating the detoxification of intracellular peroxides and protecting cells from ROS-induced injury [74]. These findings suggest that adequate Se exposure may be beneficial for kidney health [72]. However, the potential benefits of Se may depend on the exposure level, as some studies have reported that excessively high Se levels may adversely affect renal function [75]. Therefore, the relationship between Se exposure and kidney health may be characterized by an optimal exposure range rather than a uniformly inverse association. Se levels may also be affected by dietary intake and nutritional status, while early renal impairment may alter Se metabolism and excretion. These factors may partly explain the observed association, and reverse causality cannot be ruled out.

In addition to the metals discussed above, Cd was inversely associated with CKD in Q2, but no statistically significant associations were observed in Q3 or Q4. Pb showed significant inverse associations in Q2 and Q3, but not in Q4. Previous studies have shown that Cd can accumulate in the kidneys and damage proximal tubular epithelial cells [76–78]. Similarly, Pb can exert nephrotoxic effects through multiple pathways [77,79,80], and co-exposure to Cd and Pb may cause tubular or glomerular injury [81]. Therefore, the inverse associations observed in this study should not be interpreted as evidence of renal protective effects of Cd or Pb, particularly given the lack of statistically significant associations at higher exposure levels. These findings may reflect uncertainty in exposure estimates due to LOD/2 substitution, residual confounding, or correlations among co-occurring metals. Similar uncertainty may also affect the estimates for Ni and Co, which had relatively low detection rates. Further studies with more precise exposure assessment and appropriate sensitivity analyses are needed to verify these associations.

This study has several strengths. First, it was based on a longitudinal cohort, which supports the temporal ordering between metal exposure and CKD onset and strengthens the interpretation of the observed associations. Second, by applying complementary analytical approaches, including BKMR, WQS, multivariable logistic regression, and RCS, we

evaluated both the joint and individual associations of metal exposure with CKD incidence, providing a more comprehensive assessment of the associations between metal exposure and CKD.

Several limitations should also be considered. First, although we adjusted for a broad range of potential confounding factors, residual confounding from unmeasured or unknown factors cannot be completely excluded. Potential residual confounding may also arise from factors that were not measured or fully accounted for, such as chronic medication use, exposure to other occupational contaminants, and dietary habits. Second, the analysis included only 13 elements and therefore could not fully capture the potential effects of other metals or more complex exposure mixtures. Third, metal concentrations were measured only at baseline, and changes in exposure levels during follow-up were not assessed. In addition, plasma metal concentrations may not fully reflect occupational exposure levels or cumulative exposure over time. Thus, the analyses could not fully account for temporal variations in metal exposure or cumulative exposure over time. Furthermore, because metal concentrations were measured in plasma rather than whole blood, whole-blood metal concentrations were unavailable, and our findings should be interpreted in the context of plasma metal concentrations. Fourth, CKD diagnosis data from the first and second follow-up examinations were unavailable, limiting the precision of disease onset determination. Although eGFR measurements were available, repeated measurements at least 3 months apart were unavailable to confirm persistent reductions in eGFR. Data on albuminuria and other markers of kidney damage were also unavailable, limiting the assessment of CKD severity and the potential influence of renal function on circulating element concentrations. Pre-existing renal impairment may influence circulating element concentrations. Finally, although the longitudinal design supports the temporal ordering of metal exposure and CKD onset, the observational nature of the study precludes definitive causal inference. Furthermore, eGFR was not analyzed as a continuous outcome, and stage-specific analyses were not performed, limiting the assessment of renal function and the characterization of CKD severity. In addition, the eGFR-based definition may have missed individuals with kidney damage but preserved eGFR. In addition, the generalizability of our findings is limited, and they may not be directly applicable to the general population, workers in other industries, or populations in other countries.

5. Conclusions

In this nested case–control study, mixed-metal exposure was associated with a higher likelihood of incident CKD among workers with occupational metal exposure. Li, Al, Cr, and Ni showed positive associations with CKD, whereas Zn and Se showed inverse associations. Given the observational nature of this study, these findings do not establish causal relationships. Further studies with repeated exposure measurements and more diverse populations are needed to validate these findings.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the School of Public Health, Lanzhou University (protocol code IRB23042201, 22 April 2023).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy and ethical restrictions.

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Abbreviations

The following abbreviations are used in this manuscript:

BKMR	Bayesian Kernel Machine Regression
BMI	Body Mass Index
CHNS	China Health and Nutrition Survey
CI	Confidence Interval
CKD	Chronic Kidney Disease
eGFR	Estimated Glomerular Filtration Rate
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
LOD	Limit of Detection
MCMC	Markov Chain Monte Carlo
NHANES	National Health and Nutrition Examination Survey
OR	Odds Ratio
PIP	Posterior Inclusion Probability
RCS	Restricted Cubic Spline
ROS	Reactive Oxygen Species
Scr	Serum creatinine
WQS	Weighted Quantile Sum

Appendix A

Table A1. Quality Control Data for Plasma Metal Concentration Assays in Study Populations.

Metal	LOD (μg/L)	Detection Rate (%)	Detection Rate in Cases (%)	Detection Rate in Controls (%)
Li	0.20	99.45	99.90	99.00
Al	100.00	86.65	84.40	88.90
Ti	0.20	100.00	100.00	100.00
Sr	0.20	99.90	99.90	99.90
Cu	100.00	99.90	99.80	100.00
Co	0.20	49.45	46.50	52.40
Cd	0.20	29.85	35.50	24.20
Pb	4.00	35.70	42.30	29.10

Cr	0.20	99.95	99.90	100.00
Ni	2.00	57.15	70.70	43.60
Zn	100.00	99.95	100.00	99.90
Fe	100.00	99.85	99.80	99.90
Se	2.00	99.95	100.00	99.90

Table A2. PIPs of metals in the BKMR model.

Metal	PIPs
Li	1.00
Al	1.00
Ti	1.00
Sr	0.50
Cu	1.00
Co	0.98
Cd	1.00
Pb	0.86
Cr	1.00
Ni	1.00
Zn	0.97
Fe	0.50
Se	1.00

Table A3. Metal Exposure Cutoff Values and Number of Participants in Each Group.

Variables	Cutoff	*N*
Li		
Q1	8.2585	500
Q2	13.657	500
Q3	20.848	500
Q4	—	500
Al		
Q1	129.326	501
Q2	206.182	499
Q3	359.773	500
Q4	—	500
Ti		
Q1	208.2405	500
Q2	227.173	500
Q3	248.494	500
Q4	—	500
Sr		
Q1	69.8475	500
Q2	83.733	500
Q3	104.998	500
Q4	—	500
Cu		
Q1	813.4235	500
Q2	908.392	500
Q3	1025.9055	500
Q4	—	500
Co		
Q1	0.1	1011
Q2	0.28	331

	Q3	0.4513	328
	Q4	—	330
Cd			
	Q1	0.1	1403
	Q2	0.608	201
	Q3	1.5207	197
	Q4	—	199
Pb			
	Q1	2	1286
	Q2	8.256	238
	Q3	19.822	238
	Q4	—	238
Cr			
	Q1	15.1835	500
	Q2	18.416	500
	Q3	25.0265	500
	Q4	—	500
Ni			
	Q1	1	857
	Q2	4.0373	381
	Q3	11.456	381
	Q4	—	381
Zn			
	Q1	920.0225	500
	Q2	1074.679	500
	Q3	1279.832	500
	Q4	—	500
Fe			
	Q1	1948.796	500
	Q2	2356.555	500
	Q3	3005.3995	500
	Q4	—	500
Se			
	Q1	96.5935	500
	Q2	109.808	500
	Q3	124.972	500
	Q4	—	500

Table A4. WQS Index of Metal Mixture Exposure and CKD Incidence.

Outcome	OR (95%CI)	
	Positive	Negative
CKD	4.44 (3.52, 5.62)	0.29 (0.23, 0.37)

Table A5. Multivariable logistic regression analysis of the associations between continuous metal concentrations and CKD.

Variables	Univariate Regression		Multivariate Regression	
	p Value	OR (95%CI)	*p* Value	OR (95%CI)
Li	<0.001	1.03 (1.02, 1.04)	<0.001	1.07 (1.05, 1.08)
Al	<0.001	1.01 (1.01, 1.01)	<0.001	1.01 (1.01, 1.01)
Ti	<0.001	0.99 (0.99, 0.99)	<0.001	0.99 (0.99, 0.99)
Sr	<0.001	1.01 (1.01, 1.01)	0.560	1.00 (1.00, 1.00)

Cu	0.143	1.00 (1.00, 1.00)	0.038	1.01 (1.01, 1.01)
Co	0.760	1.01 (0.93, 1.11)	0.436	1.06 (0.91, 1.23)
Cd	<0.001	1.63 (1.44, 1.85)	0.285	0.89 (0.71, 1.11)
Pb	<0.001	1.05 (1.04, 1.06)	0.137	1.02 (1.00, 1.04)
Cr	<0.001	1.11 (1.09, 1.12)	<0.001	1.09 (1.07, 1.11)
Ni	<0.001	1.07 (1.06, 1.09)	0.017	1.02 (1.01, 1.03)
Zn	<0.001	0.99 (0.99, 0.99)	0.011	0.99 (0.99, 0.99)
Fe	<0.001	0.99 (0.99, 0.99)	0.987	1.00 (1.00, 1.00)
Se	<0.001	0.98 (0.98, 0.98)	<0.001	0.98 (0.98, 0.99)

Table A6. E-values for Significant Associations between Metal Exposure and CKD.

Metal	Q	OR (95% CI)	*p* Value	E-Value for Estimate	E-Value for CI Limit
Li	Q4	3.25 (2.13, 4.97)	<0.001	3.01	2.28
Al	Q4	2.54 (1.62, 3.97)	<0.001	2.57	1.86
Sr	Q4	0.59 (0.39, 0.91)	0.017	1.93	1.27
Cu	Q2	1.36 (1.06, 1.77)	0.016	1.61	1.20
Cd	Q2	0.54 (0.38, 0.78)	<0.001	1.55	1.21
Pb	Q3	0.40 (0.27, 0.60)	<0.001	1.34	1.15
Cr	Q4	8.27 (5.07, 13.50)	<0.001	5.2	3.93
Ni	Q4	3.35 (2.31, 4.85)	<0.001	2.26	1.80
Zn	Q4	0.51 (0.33, 0.78)	0.002	2.15	1.52
Fe	Q4	0.48 (0.31, 0.74)	<0.001	2.24	1.60
Se	Q4	0.27 (0.18, 0.41)	<0.001	3.26	2.50

Table A7. Logistic regression analysis after multiple imputation.

Variables	Univariate Regression		Multivariate Regression	
	p	OR (95%CI)	*p*	OR (95%CI)
Li				
Q1		1.00 (Reference)		1.00 (Reference)
Q2	0.310	1.14 (0.89, 1.46)	0.006	1.56 (1.14 ~ 2.14)
Q3	0.002	1.47 (1.15, 1.89)	<0.001	2.29 (1.66 ~ 3.16)
Q4	<0.001	1.62 (1.26, 2.08)	<0.001	3.50 (2.51 ~ 4.89)
Al				
Q1		1.00 (Reference)		1.00 (Reference)
Q2	0.243	0.86 (0.67, 1.11)	0.039	0.73 (0.54 ~ 0.98)
Q3	<0.001	1.56 (1.21, 2.00)	0.008	1.51 (1.11 ~ 2.05)
Q4	<0.001	3.42 (2.63, 4.44)	<0.001	4.09 (2.94 ~ 5.67)
Ti				
Q1		1.00 (Reference)		1.00 (Reference)
Q2	0.487	1.09 (0.85, 1.40)	0.873	1.03 (0.76 ~ 1.39)
Q3	<0.001	1.82 (1.41, 2.34)	0.020	1.46 (1.06 ~ 2.02)
Q4	<0.001	0.59 (0.46, 0.76)	<0.001	0.54 (0.37 ~ 0.78)
S				
Q1		1.00 (Reference)		1.00 (Reference)
Q2	0.098	0.81 (0.63, 1.04)	0.070	0.76 (0.57 ~ 1.02)
Q3	0.486	1.09 (0.85, 1.40)	0.144	0.79 (0.58 ~ 1.08)
Q4	<0.001	1.90 (1.48, 2.45)	0.643	0.92 (0.65 ~ 1.30)
Cu				
Q1		1.00 (Reference)		1.00 (Reference)
Q2	0.019	1.35 (1.05, 1.73)	<0.001	1.79 (1.31 ~ 2.45)

	Q3	0.527	1.08 (0.85, 1.39)	0.050	1.36 (1.00 ~ 1.86)
	Q4	0.006	0.71 (0.55, 0.91)	0.900	1.02 (0.74 ~ 1.41)
Co					
	Q1		1.00 (Reference)		1.00 (Reference)
	Q2	0.251	1.16 (0.90, 1.49)	0.054	1.36 (1.00 ~ 1.85)
	Q3	0.029	0.76 (0.59, 0.97)	0.214	0.82 (0.60 ~ 1.12)
	Q4	0.919	0.99 (0.77, 1.27)	0.601	1.09 (0.80 ~ 1.49)
Cd					
	Q1		1.00 (Reference)		1.00 (Reference)
	Q2	0.991	1.00 (0.78, 1.28)	0.836	1.03 (0.77 ~ 1.39)
	Q3	0.254	1.16 (0.90, 1.48)	0.077	0.75 (0.54 ~ 1.03)
	Q4	<0.001	1.70 (1.32, 2.19)	0.002	0.53 (0.36 ~ 0.79)
Pb					
	Q1		1.00 (Reference)		1.00 (Reference)
	Q2	0.543	0.92 (0.72, 1.19)	0.399	0.88 (0.65 ~ 1.19)
	Q3	0.015	1.37 (1.06, 1.76)	0.150	1.26 (0.92 ~ 1.71)
	Q4	<0.001	3.49 (2.68, 4.53)	<0.001	2.19 (1.46 ~ 3.29)
Cr					
	Q1		1.00 (Reference)		1.00 (Reference)
	Q2	0.639	0.94 (0.72, 1.22)	0.440	0.89 (0.66 ~ 1.20)
	Q3	<0.001	2.04 (1.58, 2.63)	<0.001	1.68 (1.25 ~ 2.26)
	Q4	<0.001	8.96 (6.68, 12.03)	<0.001	6.80 (4.66 ~ 9.93)
Ni					
	Q1		1.00 (Reference)		1.00 (Reference)
	Q2	0.008	0.71 (0.55, 0.92)	<0.001	0.60 (0.44 ~ 0.80)
	Q3	0.004	1.44 (1.12, 1.85)	0.490	0.90 (0.66 ~ 1.22)
	Q4	<0.001	3.46 (2.66, 4.50)	0.289	1.22 (0.85 ~ 1.74)
Zn					
	Q1		1.00 (Reference)		1.00 (Reference)
	Q2	0.798	1.03 (0.80, 1.33)	0.985	1.00 (0.74 ~ 1.37)
	Q3	0.014	0.73 (0.57, 0.94)	0.218	0.82 (0.60 ~ 1.12)
	Q4	<0.001	0.42 (0.33, 0.55)	0.003	0.59 (0.42 ~ 0.84)
Fe					
	Q1		1.00 (Reference)		1.00 (Reference)
	Q2	0.443	0.91 (0.71, 1.16)	0.072	0.76 (0.56 ~ 1.03)
	Q3	0.049	0.78 (0.61, 0.99)	0.079	0.75 (0.55 ~ 1.03)
	Q4	<0.001	0.37 (0.29, 0.48)	<0.001	0.43 (0.30 ~ 0.62)
Se					
	Q1		1.00 (Reference)		1.00 (Reference)
	Q2	0.018	0.74 (0.57, 0.95)	<0.001	0.55 (0.40 ~ 0.75)
	Q3	<0.001	0.58 (0.45, 0.75)	<0.001	0.46 (0.34 ~ 0.63)
	Q4	<0.001	0.32 (0.24, 0.41)	<0.001	0.29 (0.21 ~ 0.40)

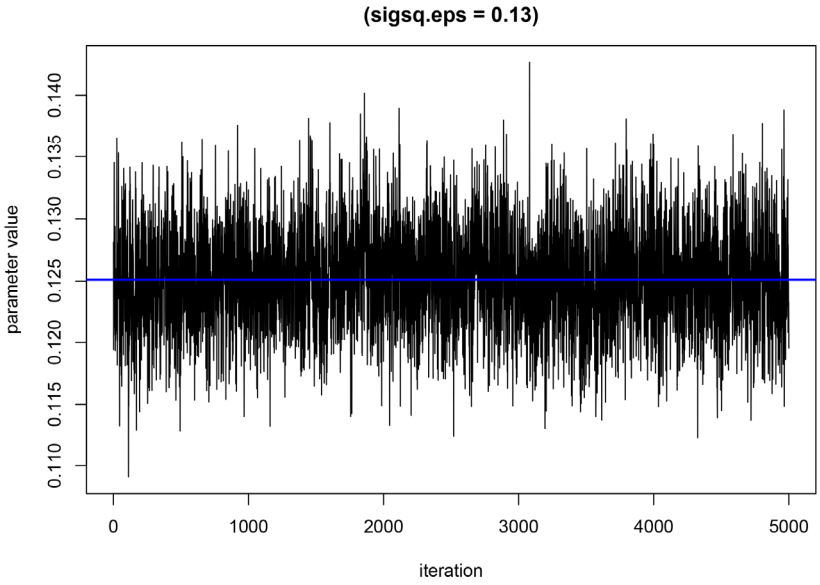


Figure A1. Trace plots of the BKMR model. Note: The blue horizontal lines indicate the corresponding mean values of the sampled parameters.

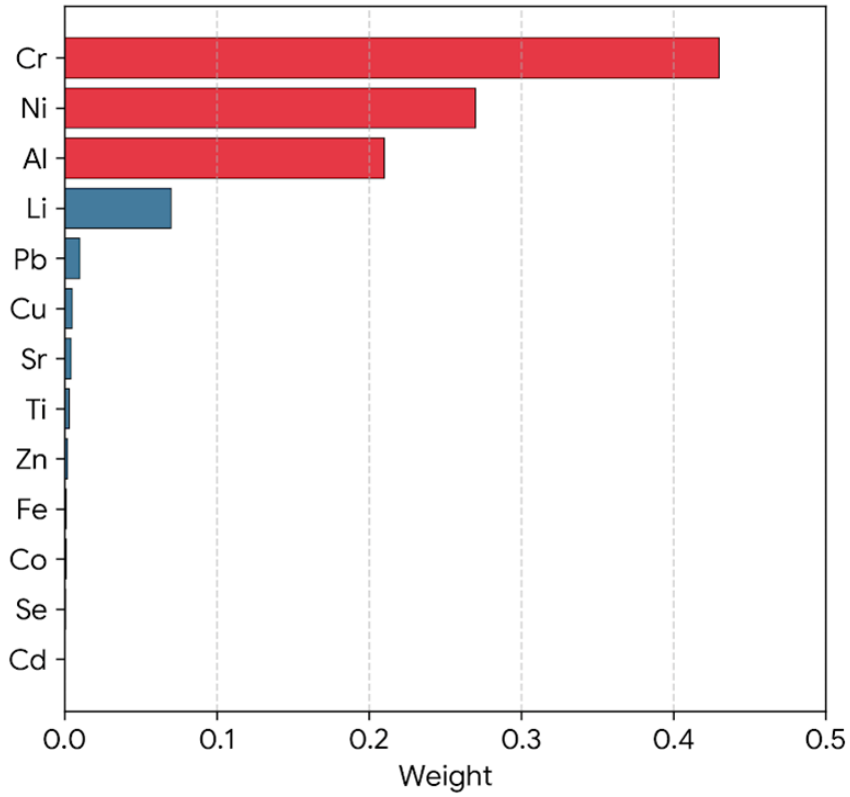


Figure A2. Component weights of metals in WQS regression. Note: Red indicates the metals identified as important contributors in the BKMR model (Cr, Ni, and Al), whereas blue indicates the other metals.

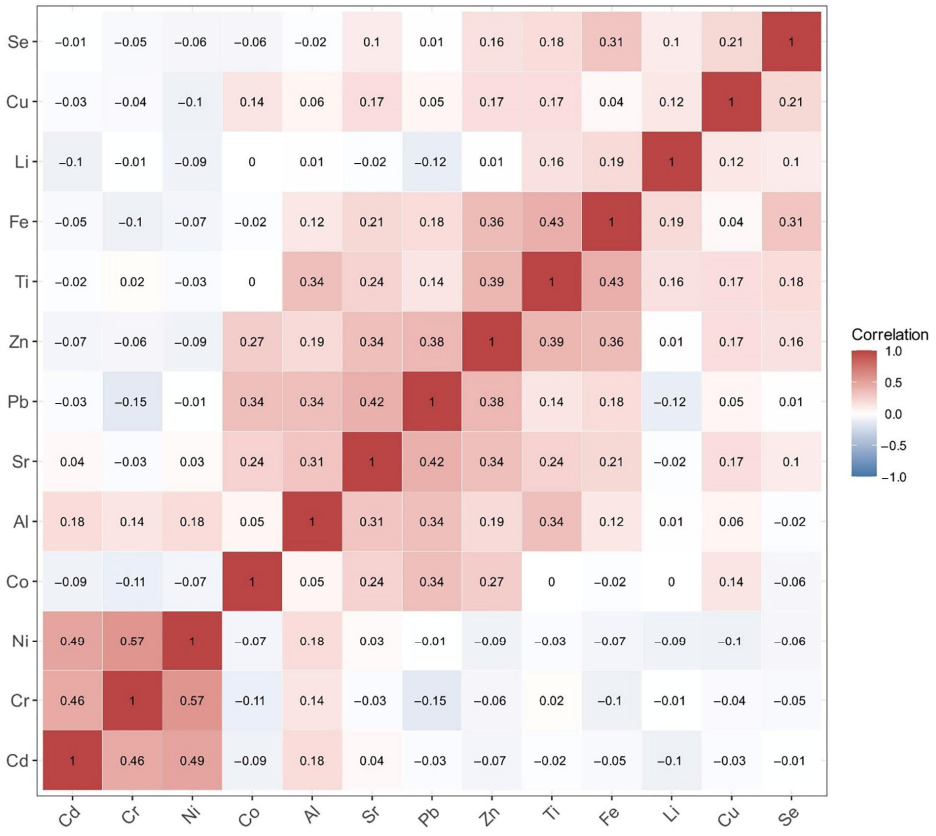


Figure A3. Heatmap of plasma metal-related coefficients.

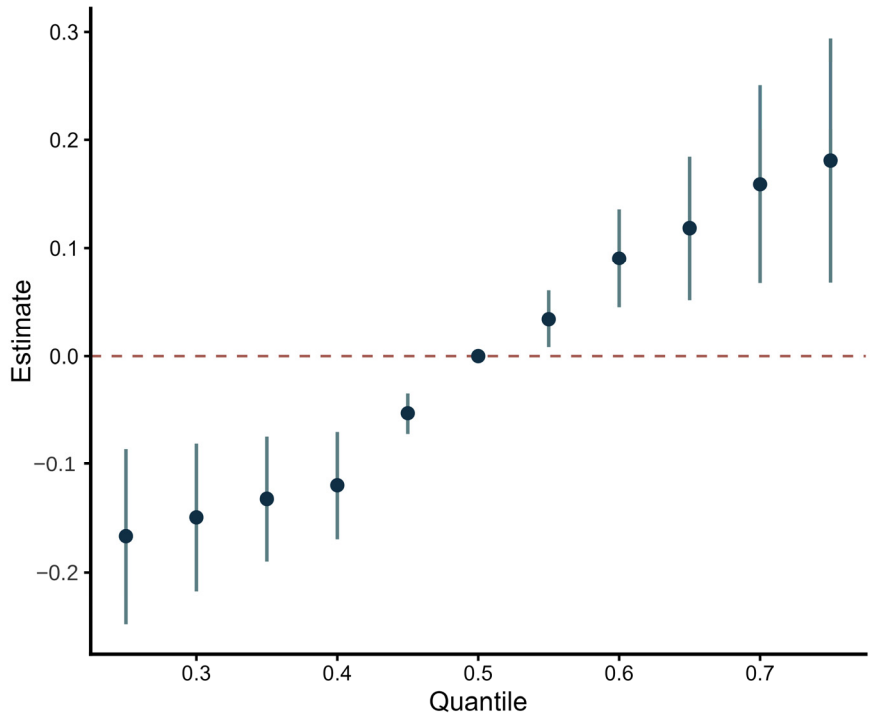


Figure A4. BKMR analysis using LOD/sqrt(2) substitution for metal concentrations below the limit of detection.

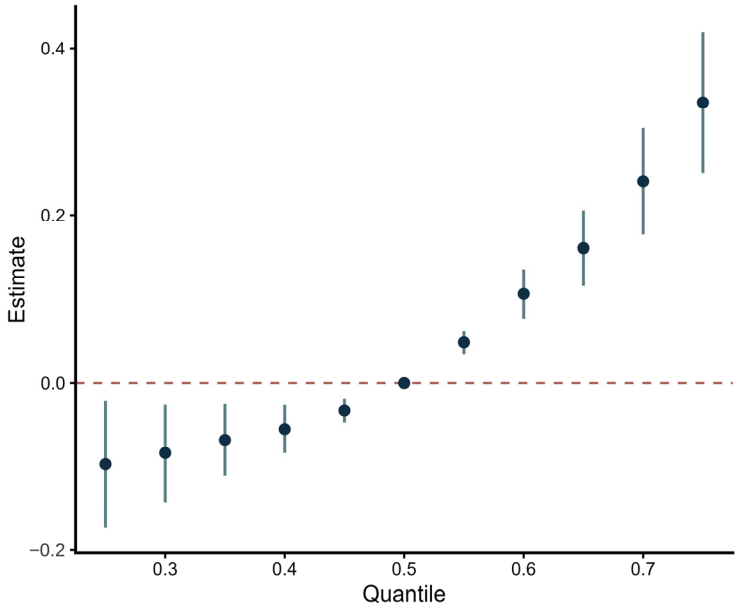


Figure A5. BKMR analysis after multiple imputation of metal concentrations below the limit of detection.

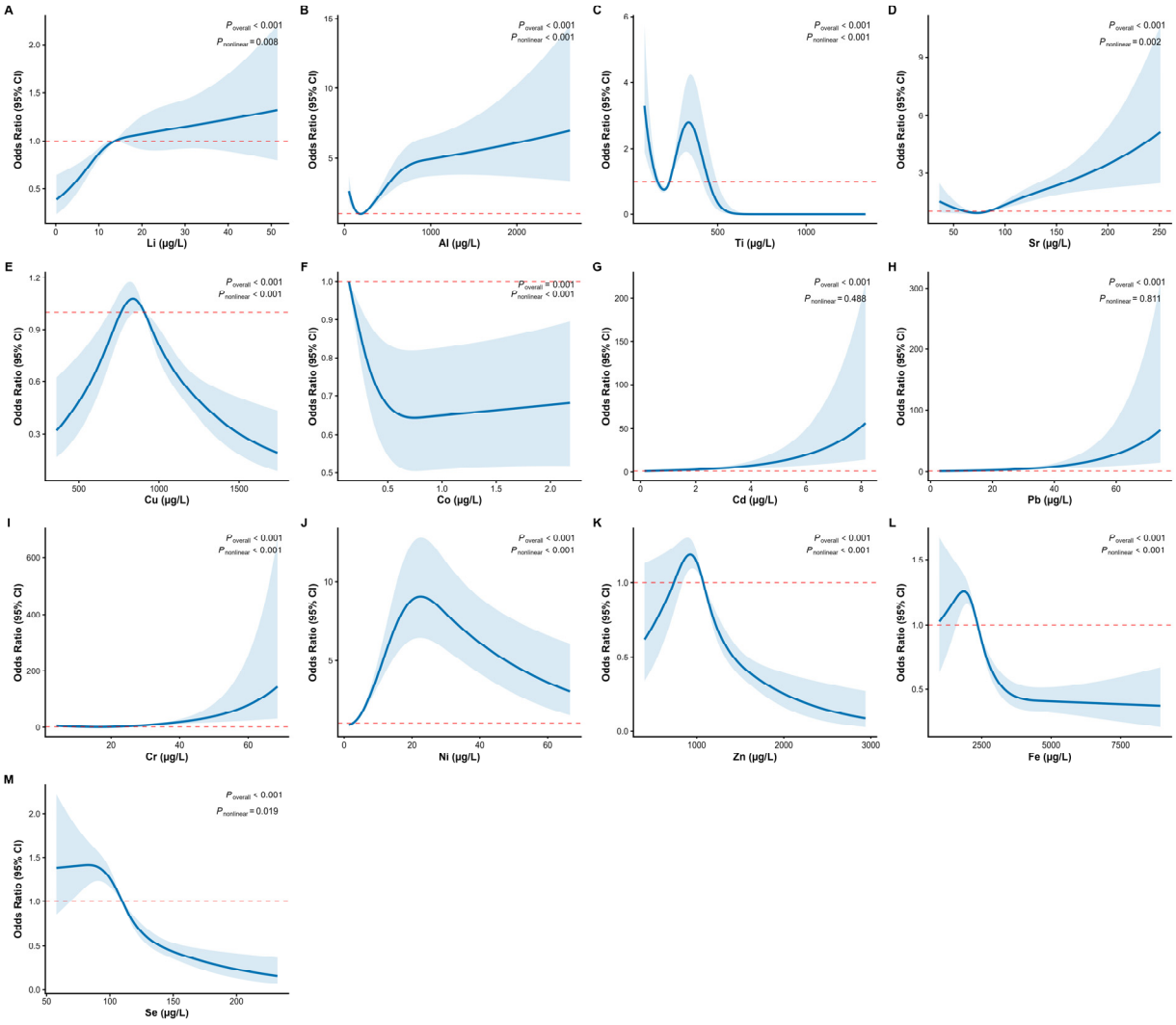


Figure A6. RCS analysis using LOD/sqrt(2) substitution for metal concentrations below the limit of detection. Note: RCS of the associations between individual metal concentrations and CKD in the sensitivity analyses. (**A**) Li; (**B**) Al; (**C**) Ti; (**D**) Sr; (**E**) Cu; (**F**) Co; (**G**) Cd; (**H**) Pb; (**I**) Cr; (**J**) Ni; (**K**) Zn;

(**L**) Fe; (**M**) Se. Solid blue lines represent estimated ORs, and light blue shaded areas represent 95% CIs. The horizontal red dashed line indicates the reference line (OR = 1.0). The number and locations of knots were determined according to the metal concentration distributions. Models were adjusted for all covariates.

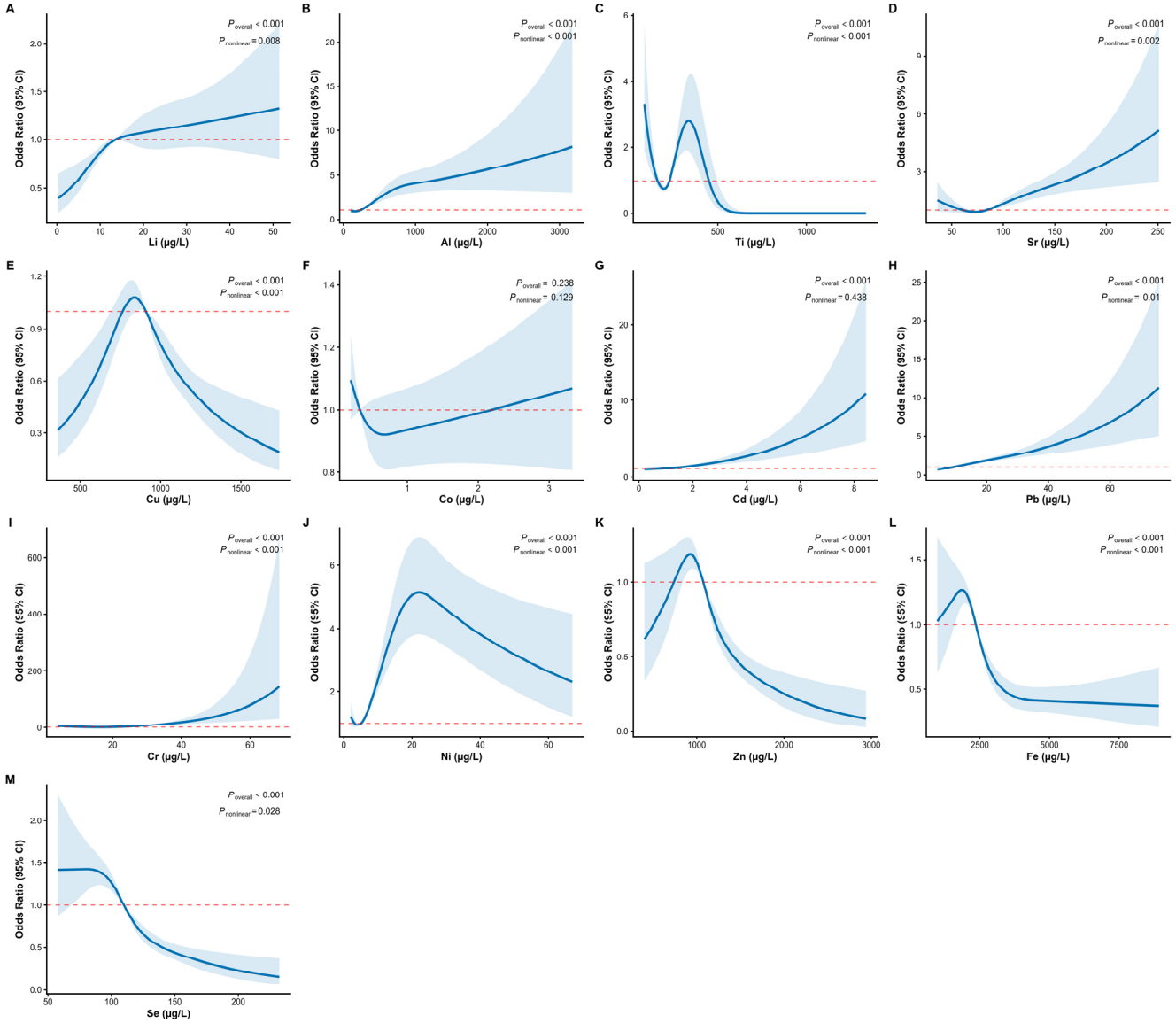


Figure A7. RCS analysis after multiple imputation of metal concentrations below the limit of detection. Note: RCS of the associations between individual metal concentrations and CKD in the sensitivity analyses. (**A**) Li; (**B**) Al; (**C**) Ti; (**D**) Sr; (**E**) Cu; (**F**) Co; (**G**) Cd; (**H**) Pb; (**I**) Cr; (**J**) Ni; (**K**) Zn; (**L**) Fe; (**M**) Se. Solid blue lines represent estimated ORs, and light blue shaded areas represent 95% CIs. The horizontal red dashed line indicates the reference line (OR = 1.0). The number and locations of knots were determined according to the metal concentration distributions. Models were adjusted for all covariates.

References

1. Jiang, Z.; Guo, Z.; Peng, C.; Liu, X.; Zhou, Z.; Xiao, X. Heavy metals in soils around non-ferrous smelteries in China: Status, health risks and control measures. *Environ. Pollut.* **2021**, *282*, 117038. https://doi.org/10.1016/j.envpol.2021.117038.
2. Li, H.; Yao, J.; Sunahara, G.; Min, N.; Li, C.; Duran, R. Quantifying ecological and human health risks of metal (loid) s pollution from non-ferrous metal mining and smelting activities in Southwest China. *Sci. Total Environ.* **2023**, *873*, 162364. https://doi.org/10.1016/j.scitotenv.2023.162364.

3. Dudka, S.; Adriano, D.C. Environmental Impacts of Metal Ore Mining and Processing: A Review. *J. Environ. Qual.* **1997**, *26*, 590–602. https://doi.org/10.2134/jeq1997.00472425002600030003x.
4. He, Y.; Wang, W.; Chen, Y.; Hua, J.; Deng, C.; Li, H. Source-sink response analysis of heavy metals and soil pollution assessment in non-ferrous metal industrial agglomeration areas based on decision unit. *Sci. Total Environ.* **2024**, *906*, 167437. https://doi.org/10.1016/j.scitotenv.2023.167437.
5. Ceballos, D.M.; Dong, Z.; Peters, J.L.; Herrick, R.F.; Gupta, P.; Spengler, J.D. Metals dust in workers' homes and potential for take home in the Greater Boston area: Pilot study. *Environ. Res.* **2022**, *209*, 112893. https://doi.org/10.1016/j.envres.2022.112893.
6. Du, B.; Zhou, J.; Lu, B.; Zhang, C.; Li, D.; Zhou, J.; Jiao, S.; Zhao, K.; Zhang, H. Environmental and human health risks from cadmium exposure near an active lead-zinc mine and a copper smelter, China. *Sci. Total Environ.* **2020**, *720*, 137585. https://doi.org/10.1016/j.scitotenv.2020.137585.
7. Wu, Y.; Qi, M.; Yu, H.; Li, G.; An, T. Assessment of internal exposure risk from metals pollution of occupational and non-occupational populations around a non-ferrous metal smelting plant. *J. Environ. Sci.* **2025**, *147*, 62–73.
8. Hill, N.R.; Fatoba, S.T.; Oke, J.L.; Hirst, J.A.; O'Callaghan, C.A.; Lasserson, D.S.; Hobbs, F.R. Global prevalence of chronic kidney disease–a systematic review and meta-analysis. *PLoS ONE* **2016**, *11*, e0158765. https://doi.org/10.1371/journal.pone.0158765.
9. Kovesdy, C.P. Epidemiology of chronic kidney disease: An update 2022. *Kidney Int. Suppl.* **2022**, *12*, 7–11. https://doi.org/10.1016/j.kisu.2021.11.003.
10. Zoccali, C.; Vanholder, R.; Massy, Z.A.; Ortiz, A.; Sarafidis, P.; Dekker, F.W.; Fliser, D.; Fouque, D.; Heine, G.H.; Jager, K.J. The systemic nature of CKD. *Nat. Rev. Nephrol.* **2017**, *13*, 344–358. https://doi.org/10.1038/nrneph.2017.52.
11. Jager, K.J.; Kovesdy, C.; Langham, R.; Rosenberg, M.; Jha, V.; Zoccali, C. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. *Nephrol. Dial. Transpl.* **2019**, *34*, 1803–1805. https://doi.org/10.1093/ndt/gfz174.
12. Lv, J.-C.; Zhang, L.-X. Prevalence and Disease Burden of Chronic Kidney Disease. *Adv. Exp. Med. Biol.* **2019**, *1165*, 3–15. https://doi.org/10.1007/978-981-13-8871-2_1.
13. Ke, C.; Liang, J.; Liu, M.; Liu, S.; Wang, C. Burden of chronic kidney disease and its risk-attributable burden in 137 low-and middle-income countries, 1990–2019: Results from the global burden of disease study 2019. *BMC Nephrol.* **2022**, *23*, 17. https://doi.org/10.1186/s12882-021-02597-3.
14. Ying, M.; Shao, X.; Qin, H.; Yin, P.; Lin, Y.; Wu, J.; Ren, J.; Zheng, Y. Disease Burden and Epidemiological Trends of Chronic Kidney Disease at the Global, Regional, National Levels from 1990 to 2019. *Nephron* **2023**, *148*, 113–123. https://doi.org/10.1159/000534071.
15. Li, Y.; Ning, Y.; Shen, B.; Shi, Y.; Song, N.; Fang, Y.; Ding, X. Temporal trends in prevalence and mortality for chronic kidney disease in China from 1990 to 2019: An analysis of the Global Burden of Disease Study 2019. *Clin. Kidney J.* **2022**, *16*, 312–321. https://doi.org/10.1093/ckj/sfac218.
16. Wang, L.; Xu, X.; Zhang, M.; Hu, C.; Zhang, X.; Li, C.; Nie, S.; Huang, Z.; Zhao, Z.; Hou, F.F.; et al. Prevalence of Chronic Kidney Disease in China: Results From the Sixth China Chronic Disease and Risk Factor Surveillance. *JAMA Intern. Med.* **2023**, *183*, 298–310. https://doi.org/10.1001/jamainternmed.2022.6817.
17. Rubinstein, S.; Wang, C.; Qu, W. Occupational risk and chronic kidney disease: A population-based study in the United States adult population. *Int. J. Nephrol. Renov. Dis.* **2013**, *6*, 53–59. https://doi.org/10.2147/IJNRD.S39522.
18. Lentini, P.; Zanoli, L.; Granata, A.; Signorelli, S.S.; Castellino, P.; Dell'Aquila, R. Kidney and heavy metals-The role of environmental exposure. *Mol. Med. Rep.* **2017**, *15*, 3413–3419. https://doi.org/10.3892/mmr.2017.6389.
19. Mishra, M.; Nichols, L.; Dave, A.A.; Pittman, E.H.; Cheek, J.P.; Caroland, A.J.; Lotwala, P.; Drummond, J.; Bridges, C.C. Molecular mechanisms of cellular injury and role of toxic heavy metals in chronic kidney disease. *Int. J. Mol. Sci.* **2022**, *23*, 11105. https://doi.org/10.3390/ijms231911105.
20. Paithankar, J.G.; Saini, S.; Dwivedi, S.; Sharma, A.; Chowdhuri, D.K. Heavy metal associated health hazards: An interplay of oxidative stress and signal transduction. *Chemosphere* **2021**, *262*, 128350. https://doi.org/10.1016/j.chemosphere.2020.128350.
21. Yin, G.; Zhao, S.; Zhao, M.; Xu, J.; Ge, X.; Wu, J.; Zhou, Y.; Liu, X.; Wei, L.; Xu, Q. Complex interplay of heavy metals and renal injury: New perspectives from longitudinal epidemiological evidence. *Ecotoxicol. Environ. Saf.* **2024**, *278*, 116424. https://doi.org/10.1016/j.ecoenv.2024.116424.
22. Wang, Y.; Qiao, M.; Yang, H.; Chen, Y.; Jiao, B.; Liu, S.; Duan, A.; Wu, S.; Wang, H.; Yu, C. Investigating the relationship of co-exposure to multiple metals with chronic kidney disease: An integrated perspective from epidemiology and adverse outcome pathways. *J. Hazard. Mater.* **2024**, *480*, 135844. https://doi.org/10.1016/j.jhazmat.2024.135844.

23. Yu, Y.; Meng, W.; Kuang, H.; Chen, X.; Zhu, X.; Wang, L.; Tan, H.; Xu, Y.; Ding, P.; Xiang, M.; et al. Association of urinary exposure to multiple metal(loid)s with kidney function from a national cross-sectional study. *Sci. Total Environ.* **2023**, *882*, 163100. https://doi.org/10.1016/j.scitotenv.2023.163100.
24. Zhou, T.-T.; Hu, B.; Meng, X.-L.; Sun, L.; Li, H.-B.; Xu, P.-R.; Cheng, B.-J.; Sheng, J.; Tao, F.-B.; Yang, L.-S. The associations between urinary metals and metal mixtures and kidney function in Chinese community-dwelling older adults with diabetes mellitus. *Ecotoxicol. Environ. Saf.* **2021**, *226*, 112829. https://doi.org/10.1016/j.ecoenv.2021.112829.
25. Bai, Y.; Yang, A.; Pu, H.; Dai, M.; Cheng, N.; Ding, J.; Li, J.; Li, H.; Hu, X.; Ren, X.; et al. Cohort Profile: The China Metal-Exposed Workers Cohort Study (Jinchang Cohort). *Int. J. Epidemiol.* **2017**, *46*, 1095–1096e. https://doi.org/10.1093/ije/dyw223.
26. Bai, Y.; Yang, J.; Cheng, Z.; Zhang, D.; Wang, R.; Zhang, R.; Bai, Z.; Zheng, S.; Wang, M.; Yin, C.; et al. Cohort Profile Update: The China Metal-Exposed workers Cohort Study (Jinchang Cohort). *Eur. J. Epidemiol.* **2022**, *37*, 641–649. https://doi.org/10.1007/s10654-022-00875-4.
27. Levey, A.S.; Stevens, L.A.; Schmid, C.H.; Zhang, Y.L.; Castro, A.F., 3rd; Feldman, H.I.; Kusek, J.W.; Eggers, P.; Van Lente, F.; Greene, T.; et al. A new equation to estimate glomerular filtration rate. *Ann. Intern Med.* **2009**, *150*, 604–612. https://doi.org/10.7326/0003-4819-150-9-200905050-00006.
28. Stevens, L.A.; Claybon, M.A.; Schmid, C.H.; Chen, J.; Horio, M.; Imai, E.; Nelson, R.G.; Van Deventer, M.; Wang, H.-Y.; Zuo, L.; et al. Evaluation of the Chronic Kidney Disease Epidemiology Collaboration equation for estimating the glomerular filtration rate in multiple ethnicities. *Kidney Int.* **2011**, *79*, 555–562. https://doi.org/10.1038/ki.2010.462.
29. Stevens, P.E.; Levin, A. Evaluation and management of chronic kidney disease: Synopsis of the kidney disease: Improving global outcomes 2012 clinical practice guideline. *Ann. Intern Med.* **2013**, *158*, 825–830. https://doi.org/10.7326/0003-4819-158-11-201306040-00007.
30. Komarova, T.; McKeating, D.; Perkins, A.V.; Tinggi, U. Trace Element Analysis in Whole Blood and Plasma for Reference Levels in a Selected Queensland Population, Australia. *Int. J. Environ. Res. Public Health* **2021**, *18*, 2652.
31. Xie, S.; Thomas, A.; Ponte, B.; Ackermann, D.; Pruijm, M.; Marques-Vidal, P.; Bochud, M. Associations of plasma concentrations of heavy metals and trace elements with estimated glomerular filtration rate and chronic kidney disease: A population-based study. *Clin. Kidney J.* **2026**, *19*, sfaf383. https://doi.org/10.1093/ckj/sfaf383.
32. Hermenean, A.; Damache, G.; Albu, P.; Ardelean, A.; Ardelean, G.; Puiu Ardelean, D.; Horge, M.; Nagy, T.; Braun, M.; Zsuga, M.; et al. Histopatological alterations and oxidative stress in liver and kidney of Leuciscus cephalus following exposure to heavy metals in the Tur River, North Western Romania. *Ecotoxicol. Environ. Saf.* **2015**, *119*, 198–205. https://doi.org/10.1016/j.ecoenv.2015.05.029.
33. Shi, X.; Wang, X.; Zhang, J.; Dang, Y.; Ouyang, C.; Pan, J.; Yang, A.; Hu, X. Associations of mixed metal exposure with chronic kidney disease from NHANES 2011–2018. *Sci. Rep.* **2024**, *14*, 13062. https://doi.org/10.1038/s41598-024-63858-3.
34. Hu, W.; Li, G.; He, J.; Zhao, H.; Zhang, H.; Lu, H.; Liu, J.; Huang, F. Association of exposure to multiple serum metals with the risk of chronic kidney disease in the elderly: A population-based case–control study. *Environ. Sci. Pollut. Res.* **2023**, *30*, 17245–17256. https://doi.org/10.1007/s11356-022-23303-2.
35. Wang, T.; Zhang, L.; Liu, Y.; Li, J.; Chen, G.; Zhou, H.; Yu, L.; Wan, Z.; Dong, C.; Qin, L.; et al. Combined Exposure to Multiple Metals and Kidney Function in a Midlife and Elderly Population in China: A Prospective Cohort Study. *Toxics* **2023**, *11*, 274. https://doi.org/10.3390/toxics11030274.
36. Liu, L.; Urch, B.; Szyszkowicz, M.; Evans, G.; Speck, M.; Van Huang, A.; Leingartner, K.; Shutt, R.H.; Pelletier, G.; Gold, D.R.; et al. Metals and oxidative potential in urban particulate matter influence systemic inflammatory and neural biomarkers: A controlled exposure study. *Environ. Int.* **2018**, *121*, 1331–1340. https://doi.org/10.1016/j.envint.2018.10.055.
37. Messaoudi, I.; El Heni, J.; Hammouda, F.; Saïd, K.; Kerkeni, A. Protective effects of selenium, zinc, or their combination on cadmium-induced oxidative stress in rat kidney. *Biol. Trace Elem. Res.* **2009**, *130*, 152–161. https://doi.org/10.1007/s12011-009-8324-y.
38. Jamakala, O.; Rani, U.A. Amelioration effect of zinc and iron supplementation on selected oxidative stress enzymes in liver and kidney of cadmium-treated male albino rat. *Toxicol. Int.* **2015**, *22*, 1. https://doi.org/10.4103/0971-6580.172289.
39. Valdivia Mazeyra, M.F.; Muñoz Ramos, P.; Serrano, R.; Alonso Riaño, M.; Gil Giraldo, Y.; Quiroga, B. Mesoamerican nephropathy: A not so unknown chronic kidney disease. *Nefrología (Engl. Ed.)* **2021**, *41*, 612–619. https://doi.org/https://doi.org/10.1016/j.nefroe.2021.12.009.
40. Baird-Gunning, J.; Lea-Henry, T.; Hoegberg, L.C.G.; Gosselin, S.; Roberts, D.M. Lithium Poisoning. *J. Intensive Care Med.* **2017,** 32, 249–263. https://doi.org/10.1177/0885066616651582.

41. Chevalier, N.; Guillou, P.; Viguié, C.; Fini, J.B.; Sachs, L.M.; Michel-Caillet, C.; Mhaouty-Kodja, S. Lithium and endocrine disruption: A concern for human health? *Environ. Int.* **2024**, *190*, 108861. https://doi.org/10.1016/j.envint.2024.108861.
42. Gitlin, M.; Bauer, M. Key questions on the long term renal effects of lithium: A review of pertinent data. *Int. J. Bipolar Disord.* **2023**, *11*, 35. https://doi.org/10.1186/s40345-023-00316-5.
43. Schoretsanitis, G.; de Filippis, R.; Brady, B.M.; Homan, P.; Suppes, T.; Kane, J.M. Prevalence of impaired kidney function in patients with long-term lithium treatment: A systematic review and meta-analysis. *Bipolar Disord.* **2022**, *24*, 264–274. https://doi.org/10.1111/bdi.13154.
44. Jing, H.; Wang, F.; Gao, X.-J. Lithium intoxication induced pyroptosis via ROS/NF-κB/NLRP3 inflammasome regulatory networks in kidney of mice. *Environ. Toxicol.* **2022**, *37*, 825–835. https://doi.org/https://doi.org/10.1002/tox.23446.
45. Ommati, M.M.; Niknahad, H.; Farshad, O.; Azarpira, N.; Heidari, R. In Vitro and In Vivo Evidence on the Role of Mitochondrial Impairment as a Mechanism of Lithium-Induced Nephrotoxicity. *Biol. Trace Elem. Res.* **2021**, *199*, 1908–1918. https://doi.org/10.1007/s12011-020-02302-9.
46. Niu, Q. Overview of the Relationship Between Aluminum Exposure and Health of Human Being. *Adv. Exp. Med. Biol.* **2018**, *1091*, 1–31. https://doi.org/10.1007/978-981-13-1370-7_1.
47. Liu, Y.; Yuan, Y.; Xiao, Y.; Li, Y.; Yu, Y.; Mo, T.; Jiang, H.; Li, X.; Yang, H.; Xu, C. Associations of plasma metal concentrations with the decline in kidney function: A longitudinal study of Chinese adults. *Ecotoxicol. Environ. Saf.* **2020**, *189*, 110006. https://doi.org/10.1016/j.ecoenv.2019.110006.
48. Skalny, A.V.; Aschner, M.; Jiang, Y.; Gluhcheva, Y.G.; Tizabi, Y.; Lobinski, R.; Tinkov, A.A. Molecular mechanisms of aluminum neurotoxicity: Update on adverse effects and therapeutic strategies. *Adv. Neurotoxicol* **2021**, *5*, 1–34. https://doi.org/10.1016/bs.ant.2020.12.001.
49. Wei, H.; Li, D.; Luo, Y.; Wang, Y.; Lin, E.; Wei, X. Aluminum exposure induces nephrotoxicity via fibrosis and apoptosis through the TGF-β1/Smads pathway in vivo and in vitro. *Ecotoxicol. Environ. Saf.* **2023**, *249*, 114422. https://doi.org/10.1016/j.ecoenv.2022.114422.
50. Prasad, S.; Yadav, K.K.; Kumar, S.; Gupta, N.; Cabral-Pinto, M.M.S.; Rezania, S.; Radwan, N.; Alam, J. Chromium contamination and effect on environmental health and its remediation: A sustainable approaches. *J. Environ. Manag.* **2021**, *285*, 112174. https://doi.org/10.1016/j.jenvman.2021.112174.
51. Sharma, P.; Singh, S.P.; Parakh, S.K.; Tong, Y.W. Health hazards of hexavalent chromium (Cr (VI)) and its microbial reduction. *Bioengineered* **2022**, *13*, 4923–4938. https://doi.org/10.1080/21655979.2022.2037273.
52. Wu, J.; Xu, J.; Zhao, M.; Li, K.; Yin, G.; Ge, X.; Zhao, S.; Liu, X.; Wei, L.; Xu, Q. Threshold effect of urinary chromium on kidney function biomarkers: Evidence from a repeated-measures study. *Ecotoxicol. Environ. Saf.* **2023**, *262*, 115139. https://doi.org/10.1016/j.ecoenv.2023.115139.
53. Atlani, M.; Kumar, A.; Ahirwar, R.; Meenu, M.N.; Goel, S.K.; Kumari, R.; Anirudhan, A.; Vallamshetla, S.; Reddy, G.S.T. Heavy metal association with chronic kidney disease of unknown cause in central India-results from a case-control study. *BMC Nephrol.* **2024**, *25*, 120. https://doi.org/10.1186/s12882-024-03564-4.
54. Mohamed, A.A.-R.; El-Houseiny, W.; Abd Elhakeem, E.-M.; Ebraheim, L.L.; Ahmed, A.I.; Abd El-Hakim, Y.M. Effect of hexavalent chromium exposure on the liver and kidney tissues related to the expression of CYP450 and GST genes of Oreochromis niloticus fish: Role of curcumin supplemented diet. *Ecotoxicol. Environ. Saf.* **2020**, *188*, 109890. https://doi.org/10.1016/j.ecoenv.2019.109890.
55. Singh, V.; Singh, N.; Verma, M.; Kamal, R.; Tiwari, R.; Sanjay Chivate, M.; Rai, S.N.; Kumar, A.; Singh, A.; Singh, M.P.; et al. Hexavalent-Chromium-Induced Oxidative Stress and the Protective Role of Antioxidants against Cellular Toxicity. *Antioxidants* **2022**, *11*, 2375. https://doi.org/10.3390/antiox11122375.
56. Genchi, G.; Carocci, A.; Lauria, G.; Sinicropi, M.S.; Catalano, A. Nickel: Human Health and Environmental Toxicology. *Int. J. Environ. Res. Public Health* **2020**, *17*, 679. https://doi.org/10.3390/ijerph17030679.
57. Buxton, S.; Garman, E.; Heim, K.E.; Lyons-Darden, T.; Schlekat, C.E.; Taylor, M.D.; Oller, A.R. Concise review of nickel human health toxicology and ecotoxicology. *Inorganics* **2019**, *7*, 89. https://doi.org/10.3390/inorganics7070089.
58. Nan, Y.; Yang, J.; Ma, L.; Jin, L.; Bai, Y. Associations of nickel exposure and kidney function in US adults, NHANES 2017–2018. *J. Trace Elem. Med. Biol.* **2022**, *74*, 127065. https://doi.org/10.1016/j.jtemb.2022.127065.
59. Yuan, T.H.; Jhuang, M.J.; Yeh, Y.P.; Chen, Y.H.; Lu, S.; Chan, C.C. Relationship between renal function and metal exposure of residents living near the No. 6 Naphtha Cracking Complex: A cross-sectional study. *J. Formos. Med. Assoc.* **2021**, *120*, 1845–1854. https://doi.org/10.1016/j.jfma.2021.04.009.

60. Xu, L.; Guan, H.; Zhang, X.; Qiao, S.; Ma, W.; Liu, P.; Liu, Q.; Sun, Y.; Liu, Y.; Cai, J.; et al. Role of Txnrd3 in NiCl(2)-induced kidney cell apoptosis in mice: Potential therapeutic effect of melatonin. *Ecotoxicol. Environ. Saf.* **2023**, *265*, 115521. https://doi.org/10.1016/j.ecoenv.2023.115521.
61. Owumi, S.E.; Olayiwola, Y.O.; Alao, G.E.; Gbadegesin, M.A.; Odunola, O.A. Cadmium and nickel co-exposure exacerbates genotoxicity and not oxido-inflammatory stress in liver and kidney of rats: Protective role of omega-3 fatty acid. *Environ. Toxicol.* **2020**, *35*, 231–241. https://doi.org/10.1002/tox.22860.
62. Lee, S.R. Critical role of zinc as either an antioxidant or a prooxidant in cellular systems. *Oxidative Med. Cell. Longev.* **2018**, *2018*, 9156285. https://doi.org/10.1155/2018/9156285.
63. Joo, Y.S.; Kim, H.W.; Lee, S.; Nam, K.H.; Yun, H.-R.; Jhee, J.H.; Han, S.H.; Yoo, T.-H.; Kang, S.-W.; Park, J.T. Dietary zinc intake and incident chronic kidney disease. *Clin. Nutr.* **2021**, *40*, 1039–1045. https://doi.org/10.1016/j.clnu.2020.07.005.
64. Damianaki, K.; Lourenco, J.M.; Braconnier, P.; Ghobril, J.-P.; Devuyst, O.; Burnier, M.; Lenglet, S.; Augsburger, M.; Thomas, A.; Pruijm, M. Renal handling of zinc in chronic kidney disease patients and the role of circulating zinc levels in renal function decline. *Nephrol. Dial. Transplant.* **2020**, *35*, 1163–1170. https://doi.org/10.1093/ndt/gfz065.
65. Liu, C.; Zhang, H.; Yang, Y.; Cao, Y.; Liang, D. Association between dietary zinc intake and increased renal function in US adults. *Biol. Trace Elem. Res.* **2024**, *202*, 3871–3885. https://doi.org/10.1007/s12011-023-03969-6.
66. Zhang, D.; Zhu, Y.; Li, H.; Wang, Y.; Niu, Z.; Zhou, W.; Wang, D. Associations of whole blood zinc levels with coronary artery calcification and future cardiovascular events in CKD patients. *Biol. Trace Elem. Res.* **2024**, *202*, 46–55. https://doi.org/10.1007/s12011-023-03655-7.
67. Chen, W.; Lu, H.; Ying, Y.; Li, H.; Shen, H.; Cai, J. Zinc and Chronic Kidney Disease: A Review. *J. Nutr. Sci. Vitaminol.* **2024**, *70*, 98–105. https://doi.org/10.3177/jnsv.70.98.
68. Xu, Y.; Li, A.; Li, X.; Deng, X.; Gao, X.-J. Zinc deficiency induces inflammation and apoptosis via oxidative stress in the kidneys of mice. *Biol. Trace Elem. Res.* **2023**, *201*, 739–750. https://doi.org/10.1007/s12011-022-03166-x.
69. Shen, Y.; Yin, Z.; Lv, Y.; Luo, J.; Shi, W.; Fang, J.; Shi, X. Plasma element levels and risk of chronic kidney disease in elderly populations (≥90 Years old). *Chemosphere* **2020**, *254*, 126809. https://doi.org/10.1016/j.chemosphere.2020.126809.
70. Wu, C.-Y.; Wong, C.-S.; Chung, C.-J.; Wu, M.-Y.; Huang, Y.-L.; Ao, P.-L.; Lin, Y.-F.; Lin, Y.-C.; Shiue, H.-S.; Su, C.-T. The association between plasma selenium and chronic kidney disease related to lead, cadmium and arsenic exposure in a Taiwanese population. *J. Hazard. Mater.* **2019**, *375*, 224–232. https://doi.org/10.1016/j.jhazmat.2019.04.082.
71. Pi, Y.; Liao, X.; Song, X.; Cao, Y.; Tang, X.; Lin, G.; Zhong, Y. Association between dietary intake of selenium and chronic kidney disease in US adults: A cross-sectional study of NHANES 2015–2018. *Front. Nutr.* **2024**, *11*, 1396470. https://doi.org/10.3389/fnut.2024.1396470.
72. Xie, C.; Zeng, M.; Shi, Z.; Li, S.; Jiang, K.; Zhao, Y. Association between Selenium Status and Chronic Kidney Disease in Middle-Aged and Older Chinese Based on CHNS Data. *Nutrients* **2022**, *14*, 2695. https://doi.org/10.3390/nu14132695.
73. Bogacka, A.; Olszewska, M.; Ciechanowski, K. Effects of Diet and Supplements on Parameters of Oxidative Stress, Inflammation, and Antioxidant Mechanisms in Patients with Chronic Renal Failure Undergoing Hemodialysis. *Int. J. Mol. Sci.* **2024**, *25*, 11036. https://doi.org/10.3390/ijms252011036.
74. He, J.; Wu, X.; Qiao, J.; Xie, X.; Wang, Y.; Zhang, H.; Zhang, W. Tubular specific glutathione peroxidase 3 deletion exacerbates kidney damage in IRI-AKI mice. *Biochim. Et Biophys. Acta (BBA) Mol. Basis Dis.* **2025**, *1871*, 167895. https://doi.org/10.1016/j.bbadis.2025.167895.
75. Fu, S.; Zhang, L.; Ma, F.; Xue, S.; Sun, T.; Xu, Z. Effects of selenium on chronic kidney disease: A mendelian randomization study. *Nutrients* **2022**, *14*, 4458. https://doi.org/10.3390/nu14214458.
76. Doccioli, C.; Sera, F.; Francavilla, A.; Cupisti, A.; Biggeri, A. Association of cadmium environmental exposure with chronic kidney disease: A systematic review and meta-analysis. *Sci. Total Environ.* **2024**, *906*, 167165. https://doi.org/10.1016/j.scitotenv.2023.167165.
77. Prozialeck, W.C.; Edwards, J.R. Mechanisms of cadmium-induced proximal tubule injury: New insights with implications for biomonitoring and therapeutic interventions. *J. Pharmacol. Exp. Ther.* **2012**, *343*, 2–12. https://doi.org/10.1124/jpet.110.166769.
78. Zając-Nędza, M.; Langauer-Lewowicka, H. Kadm Mark Kazimierz (Pod Red.). In *Choroby Zawodowe*; Wydawnictwo Lekarskie PZWL: Warsaw, Poland, 2001; pp. 195–199.
79. Balachandar, R.; Bagepally, B.S.; Kalahasthi, R.; Haridoss, M. Blood lead levels and male reproductive hormones: A systematic review and meta-analysis. *Toxicology* **2020**, *443*, 152574. https://doi.org/10.1016/j.tox.2020.152574.

80. Rădulescu, A.; Lundgren, S. A pharmacokinetic model of lead absorption and calcium competitive dynamics. *Sci. Rep.* **2019**, *9*, 14225. https://doi.org/10.1038/s41598-019-50654-7.
81. Yuan, G.; Dai, S.; Yin, Z.; Lu, H.; Jia, R.; Xu, J.; Song, X.; Li, L.; Shu, Y.; Zhao, X. Sub-chronic lead and cadmium co-induce apoptosis protein expression in liver and kidney of rats. *Int. J. Clin. Exp. Pathol.* **2014**, *7*, 2905.

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