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Association of urinary exposure to multiple metal(loid)s with kidney function from a national cross-sectional study

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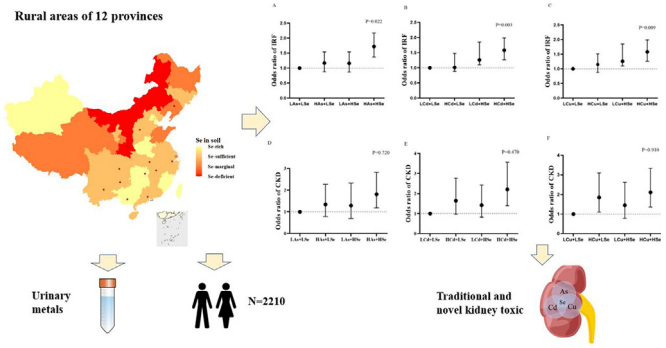
HIGHLIGHTS

- We found urinary arsenic, cadmium, copper and selenium levels were associated with higher odds of impaired renal function.
- We explored Se exposure may strength the association of arsenic, cadmium and copper with impaired renal function.
- Selenium and copper contributed the most in BKMR models on impaired renal function.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Arsenic (As), cadmium (Cd) and copper (Cu) are hazardous for kidney function, while the effects of selenium (Se) and zinc (Zn) were unexplored for the narrow safe range of intake. Interactions exists between these multiple metal/metalloid exposures, but few studies have investigated the effects.

Methods: A cross-sectional survey was performed among 2210 adults across twelve provinces in China between 2020 and 2021. Urinary As, Cd, Cu, Se and Zn were measured using inductively coupled plasma–mass spectrometry (ICP–MS). Serum creatinine (Scr) and *N*-acetyl-beta-D glucosaminidases (urine NAG) were quantified in serum and urine, respectively. Kidney function was evaluated by the estimated glomerular filtration rate (eGFR). We employed logistic regression and Bayesian kernel machine regression (BKMR) models to explore the individual and joint effects of urinary metals/metalloids on the risk of impaired renal function (IRF) or chronic kidney disease (CKD), respectively.

Results: Association was found between As (OR = 1.24, 95 % CI: 1.03, 1.48), Cd (OR = 1.65, 95 % CI: 1.35, 2.02), Cu (OR = 1.90, 95 % CI: 1.59, 2.29), Se (OR = 1.51, 95 % CI: 1.24, 1.85) and Zn (OR = 1.33, 95 % CI: 1.09, 1.64) and the risk of CKD. Moreover, we observed association between As (OR = 1.18, 95 % CI: 1.07, 1.29), Cu (OR = 1.14, 95 % CI: 1.04, 1.25), Se (OR = 1.15, 95 % CI: 1.06, 1.26) and Zn (OR = 1.12, 95 % CI: 1.02, 1.22) and the risk of IRF. Additionally, it was found that Se exposure may strength the association of urinary As, Cd and Cu with IRF. Furthermore, it is worth noting that Se and Cu contributed greatest to the inverse association in IRF and CKD, respectively.

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Conclusion: Our findings suggested that metal/metalloid mixtures were associated with kidney dysfunction, Se and Cu were inverse factors. Additionally, interactions between them may affect the association. Further studies are needed to assess the potential risks for metal/metalloid exposures.

1. Introduction

Chronic kidney disease (CKD) is an important public health issue that severely influences human health, with approximately 697.5 million cases worldwide and 132.3 million cases in China in 2017 (Collaboration, 2020). Additionally, CKD remains one of the leading causes of death and disease both in China and globally (Lv and Zhang, 2019). Environmental pollution that caused by metals and metalloids has been regarded as important risk factor for the development of kidney disease (Shlipak et al., 2021).

Many previous studies reported that exposure to heavy metals, including arsenic (As), cadmium (Cd), and copper (Cu), were associated with kidney damage (Ferraro et al., 2010; Sanders et al., 2019; Tsai et al., 2018; Yang et al., 2019). In addition, some trace elements such as selenium (Se) and zinc (Zn) are essential for biological processes (Livingstone, 2015; Rayman, 2012, 2020), while their very narrow safe range of intake is a public concern (Efsa Panel on Nutrition NF et al., 2023). For example, Se has been proven to alter the tertiary structure of proteins and induce oxidative stress (Fukumoto et al., 2020; Misra et al., 2015). Clinical research has also suggested that excessi ve intake of Se is associated with renal dysfunction, and renal failure anemia (Kamble et al., 2009; Matoba et al., 1986; Nantel et al., 1985). Although epidemiologic studies have reported that exposure to Se might contribute to the incidence of CKD (Chen et al., 2021; Karmaus et al., 2008), these studies have been restricted to highly polluted areas or patients. There is a need to provide large-scale evidence to explore the association between Se exposure and CKD in the general population. Such evidence could lead to environmental regulation.

Importantly, people are exposed to various metals/metalloids simultaneously in the real world, which can be conducive to interactions between Se and hazardous metals/metalloids, in the form of As and Cd. Previous studies have reported that excess Se exposure can enhance the toxicity of As by modifying the structure and activity of arsenite methyltransferase (Chitta et al., 2013; Fukumoto et al., 2020). However, inconsistent results have shown that Se could interact with As and Cd to attenuate the harmful effects of metals/metalloids (Binte Hossain et al., 2018; Liu et al., 2015). Additionally, the impact of different mixtures of metals/metalloids can vary with a particular mixture of exposures compounding effects in either an additive or a synergistic way. Thus far, the effect of the interactions of Se and As/Cd on CKD is worthy of further investigation.

Impaired renal function (IRF, 60 ≤ estimated glomerular filtration rate < 90 mL/min/1.73 m^2) has been proven to be the early stage of the CKD process (Chan et al., 2007; Smart et al., 2014), but it is not currently classified as a disease in mainland China. Previous studies have suggested an association of As and lead (Pb) with an increased risk of IRF in Sweden, the US and Taiwan (Chen et al., 2011; Cheng et al., 2017; Harari et al., 2018; Navas-Acien et al., 2009), while such studies conducted in Se-enriched regions (Jones et al., 2017) could introduce confounding bias from Se and miss potential synergy from their joint effects on kidney diseases. More evidence is needed to determine and explore interactions between the effects of Se and other metals/metalloids across a wider range of Se distributions. To address these knowledge gaps, we conducted a large, stratified, and representative population-based study to estimate the associations of As, Cd, Cu, Se and Zn with kidney dysfunction among 2210 adults across twelve provinces.

2. Methods

2.1. Study population

We launched the Chinese Exposure and Response Mapping Project (CERMP) to investigate the associations between environmental pollutant exposure and human health effects. This study was approved by the Research Ethics Committee of Sun Yat-sen University. We recruited a national population in rural areas across 12 provinces (Chongqing, Guangdong, Guangxi, Guizhou, Jiangxi, Liaoning, Hubei, Hunan, Shaanxi, Shanxi, Yunnan and Zhejiang) in China. One village was selected by the simple random sampling (SRS) method in each province. Approximately 250 adults aged 18 to 75 years who lived in rural areas for at least 5 years were recruited. A total of 2883 participants were recruited for the study. In this study, we focused on the examination of relationships between urinary metals/metalloids and kidney function. We excluded participants with missing data on urinary metals/metalloids (17.1 %) and outlying data regarding urinary metals/metalloids (6.3 %) [1.5 times the interquartile range (IQR)], leaving 2210 (76.7 %) adults in the current analyses (Fig. S1). We obtained written informed consent from all participants before biospecimen collection.

2.2. Measurement of urine metals/metalloids

Urine samples from participants were collected by trained nurses in the morning after an overnight fast (>12 h). The concentrations of 5 metals/metalloids, including As, Cd, Cu, Se, and Zn, were determined using inductively coupled plasma–mass spectrometry (ICP–MS, Agilent 7700 × series; Agilent Technologies; USA) (Text S1). The limits of detection (LODs) of all metals/metalloids ranged from 0.004 to 0.163 ng/mL (Table S1). Values lower than the LODs were replaced by LOD/√2 (Hornung and Reed, 1990). The detection rates of all metals/metalloids were >80 %. All quality control samples, blanks, and urine samples were diluted 10-fold in a diluent consisting of a 2 % nitric acid (HNO_3) solution containing the internal standards and gold. Standards were prepared in 1 % trace metal–grade HNO_3 and diluted 10-fold with a diluent consisting of 2 % HNO_3 solution containing the internal standards to minimize any matrix effect. The rinse solution for the instrument was 1 % trace metal–grade HNO_3. The percentages of the coefficients of variation were between 0.8 % and 7.0 % for all elements. Five field blanks were sent out for testing, and 96 % of the measures were less than the LODs.

2.3. Detection of kidney function biomarkers

Serum creatinine (Scr) and urinary *N*-acetyl-beta-D glucosaminidases (urine NAG) were measured as biomarkers of kidney function. The colorimetric assay by a standardized method was employed to detect the levels of urine NAG and Scr using an automatic biochemistry analyzer (Roche Cobas c702 type; Roche Ltd.; Mannheim, Germany). Estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration 2021 (CKD-EPI-2021) equation. We identified participants having CKD with an eGFR of <60 mL/min per 1.73 m^2, having IRF with an eGFR of <90 mL/min per 1.73 m^2.

2.4. Covariates

Potential confounders were selected a priori based on previous studies. We selected age (years), sex (male/female), body mass index (BMI; kg/m^2), hypertension (yes if systolic blood pressure was ≥140 mmHg or diastolic blood pressure was ≥90 mmHg, otherwise no), smoking (never/current), drinking (yes/no), ethnicity (Han/minority), education (< high school/≥ high school), exercises (yes/no), area (12 provinces), self-reported cardiovascular disease such as heart diseases and arrhythmia (normal/abnormal), and self-reported kidney diseases including nephritis, nephrolithiasis, hydronephrosis, and chronic kidney disease (normal/abnormal).

2.5. Statistical analysis

The distribution of characteristic variables was expressed as the mean (standard deviation, SD), number (percentage), or median (interquartile range, IQR). All metal/metalloid concentrations were log-transformed to facilitate distribution among each element in the regression models.

We applied restricted cubic splines (RCS) and logistic regression models to explore relationships between single metal/metalloid exposures and kidney function with adjustment for the above covariates. RCSs were used to explore the nonlinear association between urine NAG and eGFR in single metal/metalloid exposures. Interactive associations among elements in the logistics models of IRF or CKD were also evaluated. Elements that were associated with CKD in the logistic regression models were included in the interaction analyses.

To estimate the joint effect of metals/metalloids and potential nonlinear effects, we implemented the BKMR model to evaluate the joint effect of a mixture using a kernel function. The BKMR model is specified as follows:

$$Y_i = h\left(\mathrm{As_i}, \mathrm{Cd_i}, \mathrm{Cu_i}, \mathrm{Se_i}, \mathrm{Zn_i}\right) + \beta^{\mathrm{T}}\mathrm{Z_i} + e_i$$

where Y represents the outcome (odds ratio of IRF/CKD) for individual I, and h represents a kernel function of the mixture exposure (As, Cd, Cu, Se, Zn). Z_i is a vector of covariates of interest, and β denotes the corresponding effects of the covariates. BKMR models were fit using a Markov chain Monte Carlo algorithm with 5000 iterations using the Gaussian kernel. BKMR results are displayed as estimates of the: a) overall effect of the metal/metalloid mixture; and b) single-metal associations. The single effect of metals/metalloids was analyzed by estimating univariate summaries of the change in the IRF or CKD associated with a change in a single metal from its 25th percentile to the 75th percentile, with all of the other metals fixed at the median.

2.6. Sensitivity analysis

We evaluated the robustness of the main results by conducting several sensitivity analyses. First, we excluded smokers ($n = 511$) because smoking is considered an unhealthy lifestyle habit linked to kidney dysfunction. Second, we excluded participants with self-reported CKD ($n = 55$). Third, considering that bias stemmed from using the same value (LOD/√2) to substitute urine metal/metalloid concentrations lower than the LOD, we further applied a left-censored missing value imputation approach based on the Gibbs sampler (GSimp) to obtain singly imputed values for participants with urine metal and metalloid levels less than the LOD (Wei et al., 2018). Fourth, we stratified the analysis by sex due to the sex differences in filtration rate for some metals/metalloids. All analyses were performed using R software (version 4.0.1).

3. Results

3.1. General characteristics

Table 1 presents the demographic characteristics and clinical kidney function indicators of the 2210 participants in this study. The population was composed of adult residents with an average age of 59.2 ± 13.0 years old who were predominantly female (63.3 %). Most of our participants were nonsmokers (76.9 %), nonalcohol drinkers (78.4 %), lower educational attainment (89.6 % < high school) and had nonself-reported kidney diseases (97.5 %). Few participants were defined as having CKD (6.9 %); however, nearly half of the participants were met the criteria for IRF (45.5 %).

The highest median concentration of metals/metalloids in urine was for Zn (481.06 μg/g creatinine), followed by As (38.66 μg/g creatinine), Se (20.55 μg/g creatinine), Cu (18.06 μg/g creatinine), and Cd (2.68 μg/g creatinine). The concentrations of urinary metals/metalloids varied greatly across the 12 provinces of China (Table S2). The correlation of metals/metalloids is shown in Fig. S2.

Table 1
General characteristics of the participants in the study.

Characteristics	Participants (N = 2210)
Age	59.2 ± 13.0
BMI [a]	24.7 ± 7.3
Females	1398 (63.3 %)
Annual household income	
≤ 30,000	1801 (81.5 %)
30,000 − 50,000	255 (11.5 %)
> 50,000	152 (6.9 %)
Education	
< High school	1981 (89.6 %)
≥ High school	229 (10.4 %)
Exercises	763 (34.5 %)
Smoking	511 (23.1 %)
Drinking	477 (21.6 %)
Kidney function biomarkers	
eGFR (mL/min/1.73 m^2)	92.8 (77.1, 112.4)
Urine NAG (U/g creatinine)	8.6 (5.4, 13.6)
Self-reported renal diseases [b]	55 (2.5 %)
eGFR <90 (IRF) [c]	1005 (45.5 %)
eGFR <60 (CKD) [d]	152 (6.9 %)
Metal/metalloid concentrations (μg/g creatinine) [e]	
As	38.66 (21.46, 73.50)
Cd	2.68 (1.30, 5.92)
Cu	18.06 (12.56, 26.66)
Se	20.55 (12.57, 33.53)
Zn (10^2)	4.81 (2.98, 7.56)

[a] BMI means body mass index.
[b] Self-reported renal diseases include nephritis, nephrolithiasis, hydronephrosis, and chronic kidney disease which are collected by questionnaire.
[c] eGFR means estimate glomerular filtration rate; IRF means impaired renal function.
[d] CKD means chronic kidney disease.
[e] Metal/metalloid concentrations were adjusted by urine creatinine, represented with quantiles.

3.2. Association between single metal/metalloid exposures and kidney function

We observed that As and Zn had inverse linear associations with eGFR after adjusting for confounders. While the associations between Cd, Cu, and Se with eGFR were found to be nonlinear (Fig. 1), the dose-response curve was smooth before the turning point and rapidly declined after the turning point (1.79 μg/g creatinine for Cd, 17.81 μg/g creatinine for Cu, and 16.17 μg/g creatinine for Se). In terms of urine NAG levels, elevated Cu, Cd, and Zn levels were found to have nonlinear associations with increased urine NAG levels. Specifically, negative associations were observed for As and Se (Fig. S3).

The results of the associations between metals/metalloids and IRF or CKD using logistic regression models are shown in Table 2. Elevated odd of CKD were associated with increasing metals/metalloids concentrations as As (OR: 1.24, 95 % CI = 1.03,1.48), Cd (OR:1.65, 95 % CI = 1.35,2.02), Cu (OR: 1.90, 95 % CI = 1.59,2.29), Se (OR: 1.51, 95 % CI = 1.24,1.85), and Zn (OR: 1.33, 95 % CI = 1.09,1.22) in the adjusted single-metal models. Similarly, all the metals/metalloids analyzed in the logistic model were associated with IRF risk, though for Cd the risk of IRF was only slightly increased.

We stratified urine Se into two groups according to the median values (20.55 μg/g creatinine) to further assess whether Se could be a modifier and to what extent (Tables S3–5). When stratified regression models were used for urine Se, the levels of urine NAG were positively correlated with As and Cu in the high Se group. We found association of increased As, Cd and Cu levels with the increased risk of IRF in the high Se group (Fig. 2). However, no association was observed for other metals/metalloids with CKD in the high Se group.

3.3. Joint regression analyses between metal/metalloid exposure and kidney function

We further analyzed the joint effect of these metals/metalloids in the BKMR model. We found an association of increased log-transformed

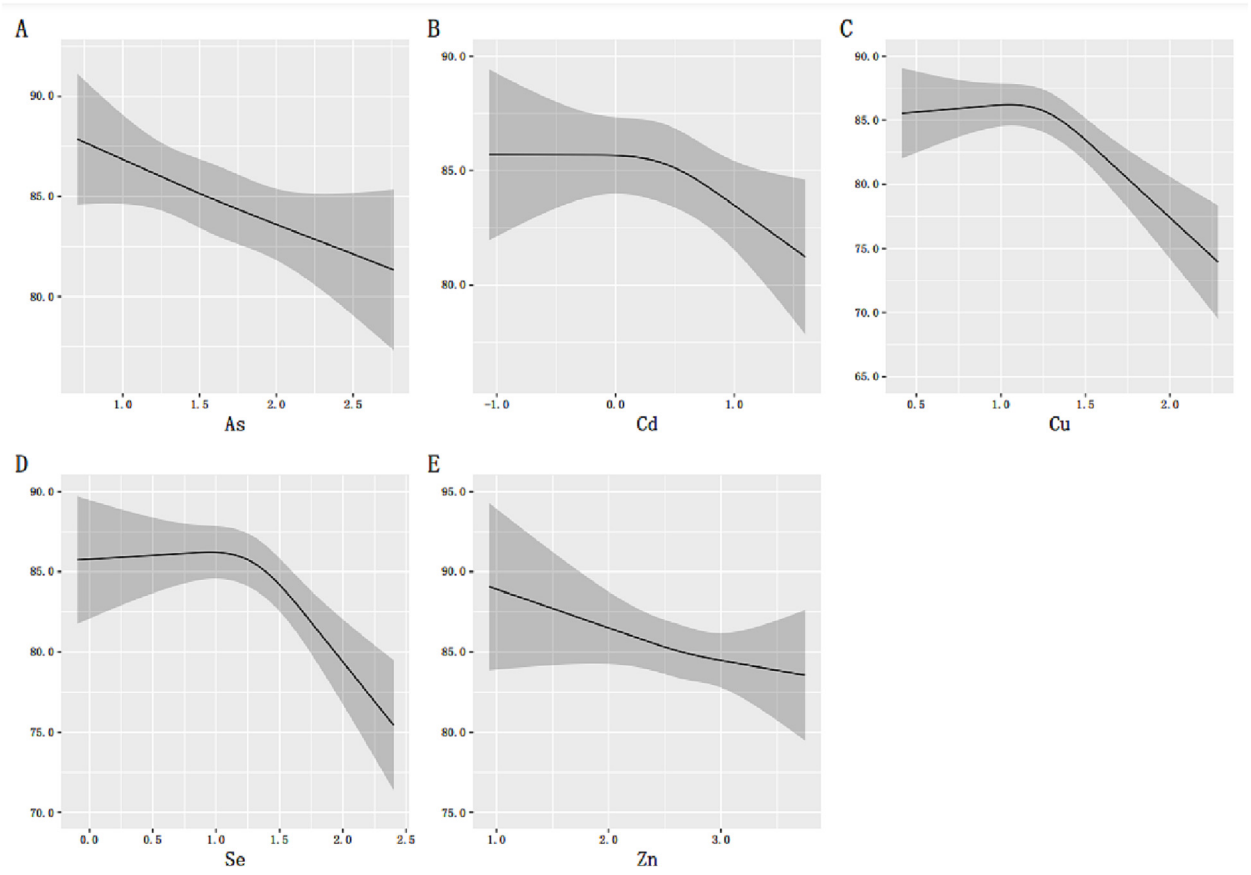

Fig. 1. The association between urinary metal/metalloid concentrations and eGFR.
Note: Metal/metalloid concentrations were log-transformed; eGFR was calculated by the CKD-EPI formulas; all models were adjusted for sex, age, ethnicity, smoking, drinking, BMI, hypertension, cardiovascular disease, area and self-reported kidney diseases. Nonlinear effects are shown with 95 % CIs. Knots are at the 5th, 50th, and 90th percentiles (the junction between two intervals is called a 'knot'). The nonlinear associations of As, Cd, Cu, Se and Zn with eGFR are shown in panels A to E.

metal/metalloid exposure with an increased risk of IRF from their 25th to 75th percentiles (Fig. 3A). The risk of CKD increased along with elevated log-transformed exposure (Fig. 3C). For example, coexposure to metal/metalloid mixtures was associated with an increased risk of IRF (OR = 1.14, 95 % CI: 1.04, 1.18) and an increased risk of CKD (OR = 1.16, 95 % CI: 1.09, 1.24) with concentrations of metal/metalloid mixtures fixed at the 75th percentile compared to the median. A change in Se concentration from the 25th to the 75th percentile was associated with increase of 1.10 (95 % CI: 1.01, 1.21) and 1.12 (1.01, 1.23) in the odds of IRF with other metals fixed at the median, respectively (Fig. 3B). A change in Cu concentration from the 25th to the 75th percentile was associated with an increase of 1.26 (1.14, 1.39) and 1.25 (1.13, 1.37) in the odds of CKD with other metals fixed at the median, respectively (Fig. 3D). Furthermore, we found that Se and Cu had the highest posterior inclusion probabilities (PIPs) (Table S6) and jointly made the greatest contributions to the associations of metals/metalloids with IRF and CKD.

3.4. Subgroup analyses

The subgroup analysis of single-metal models indicated that no difference between smokers and nonsmokers was found in the subgroup (Table S7). No difference was found in the results excluding self-reported kidney diseases (Table S8). We applied the GSimp method to provide the undetectable urine metal/metalloid concentrations rather than replacing them with the same value of LOD/√2, and the result was similar to that of the main analyses (Table S9). Moreover, negative association of metals/metalloids with the risk of CKD among men and women was shown (Table S10), with As, Cd and Cu showing difference.

Table 2
The association between metal/metalloid exposures and the risk of IRF and CKD in the logistic model.

Metals/metalloids[a]	IRF (OR, 95 % CI)		CKD (OR, 95 % CI)	
	Crude	Adjusted[b]	Crude	Adjusted[b]
As	1.55 (1.24, 1.95)	1.18 (1.07, 1.29)	1.61 (1.03, 2.50)	1.24 (1.03, 1.48)
Cd	0.98 (0.83, 1.17)	1.05 (0.97, 1.16)	1.68 (1.18, 2.40)	1.65 (1.35, 2.02)
Cu	1.59 (1.18, 2.15)	1.14 (1.04, 1.25)	3.92 (2.38, 6.48)	1.90 (1.59, 2.29)
Se	1.11 (0.89, 1.37)	1.15 (1.06, 1.26)	1.45 (0.94, 2.26)	1.51 (1.24, 1.85)
Zn	1.46 (1.15, 1.86)	1.12 (1.02, 1.22)	1.66 (1.02, 2.75)	1.33 (1.09, 1.64)

Note: 95 % CI: 95 % confidence interval; IRF: impaired renal function; CKD: chronic kidney disease.
[a] Metal/metalloid concentrations were log transformed.
[b] All models were adjusted for sex, age, ethnicity, smoking, drinking, BMI, hypertension, cardiovascular diseases, area and self-reported kidney diseases.

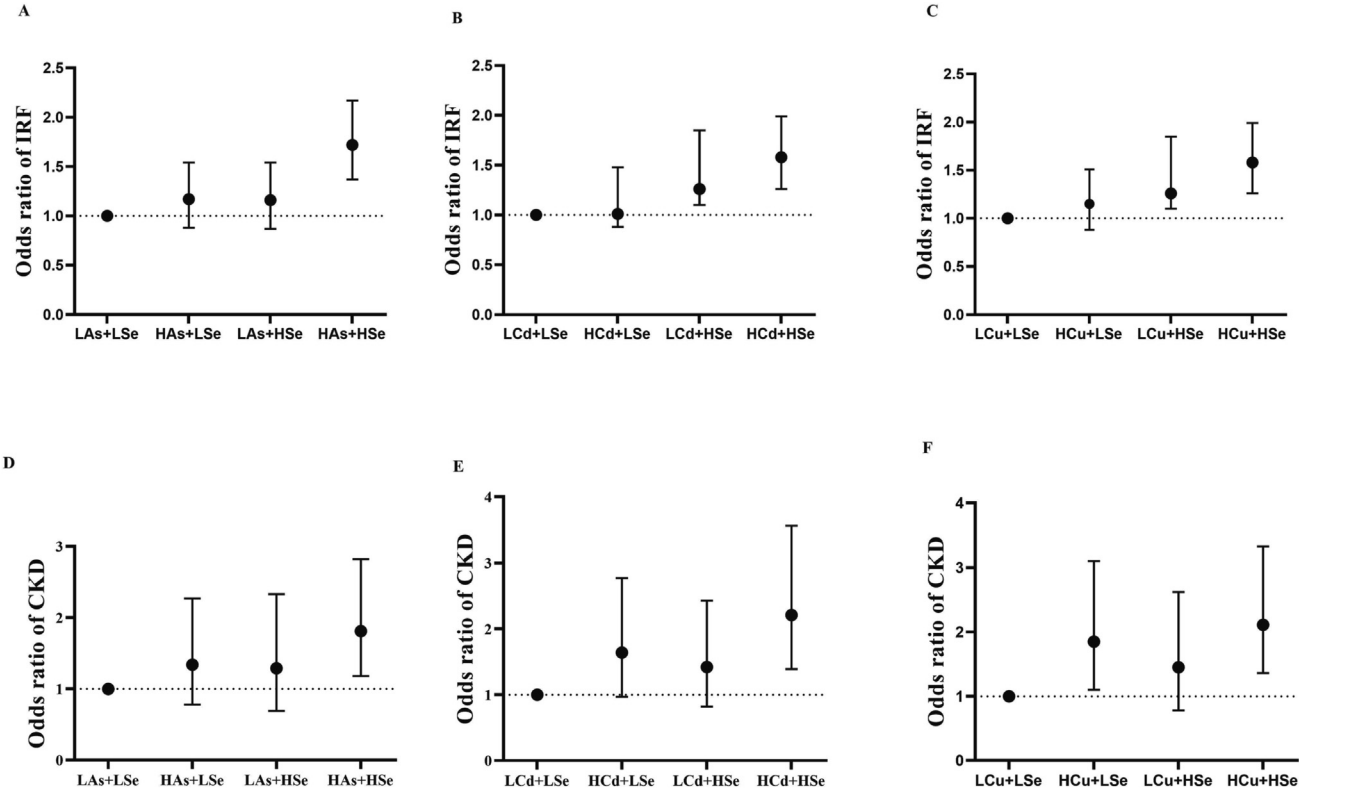

Fig. 2. Interactions between Se and other metal/metalloids on IRF(A-C) or CKD(D—F).
Note: Metals/metalloids exhibiting a confidence interval did not encompass 1 in IRF/CKD models were included in the combined effect analysis: As, Cd, Cu, Se, IRF: impaired renal function; CKD: chronic kidney disease.
The interactions of As, Cd and Cu based on Se on IRF/CKD are shown in Fig. 3A to 3F, respectively. The combined categories of elements levels (Low As <38.66 μg/g creatinine, High As ≥38.66 μg/g creatinine; Low Cd < 2.68 μg/g creatinine, High Cd ≥ 2.68 μg/g creatinine; Low Cu < 18.07 μg/g creatinine, High Cu ≥ 18.07 μg/g creatinine, Low Se < 20.56 μg/g creatinine, High Se ≥ 20.56 μg/g creatinine; Low Zn < 481.06 μg/g creatinine, High Zn ≥ 481.06 μg/g creatinine) and adjusted for sex, age, ethnicity, smoking, drinking, BMI, hypertension, cardiovascular diseases, area and self-reported kidney diseases.

4. Discussion

To our knowledge, this study is the first to report a positive association between urine Se levels and the risk of IRF or CKD across rural areas in China. We also found an association between other higher metal/metalloid (As, Cd, Cu and Zn) exposures and an increased risk of IRF or CKD in the Chinese population, with the relationships primarily driven by Se and Cu, respectively.

Although direct comparisons have been limited, our finding of the the associations between Se exposure and the risk of CKD is supported by a study of CKD among 461 participants older than 90 years in China (Shen et al., 2020). The study reported that plasma Se was lower in participants without CKD (108.76 μg/L) than in those with CKD (120.51 μg/L). Even though the mechanism of Se toxicity remains unclear, some researchers have reported that Se exposure could enhance the toxicity of other hazardous elements, including As and Cd. Huang and colleagues found that lower serum urine Se levels (< 50 μg/L) were correlated with As-associated skin lesions in 63 As-exposed populations. It is worth noting that these cutoffs for urine Se fall within our highest quartile of exposure (> 31.52 μg/L), and we also observed interaction association between urine As and Se in kidney function impairment (Table S3). Similarly, Chen et al. recruited 160 participants in areas with high Cd and Se levels and 153 in areas with low levels and estimated the associations of urine, blood and hair Se with kidney biomarkers (Chen et al., 2020). They reported that *N*-acetyl-β-D-glucosaminidase, an important biomarker for kidney function (Xu et al., 2018), was negatively associated with the interaction between Cd and Se, consistent with our interaction results. However, the amount of Se present in humans is very diverse depending on the geographic region and diet (Kieliszek, 2019). The lack of these data has limited the explanation of our results.

Several studies reporting worldwide associations between traditional heavy metal exposures (As, Cd or Zn) and kidney function. Our results were consistent with some previous studies. Wiedemann and colleagues reported an association between urinary As and decreased eGFR levels using the 2009–2012 National Health and Nutrition Examination Survey (NHANES) of the US population (Weidemann et al., 2015), while the urinary As concentration (median = 30.89 μg/L) in our findings was almost 5 times higher than that in the NHANES data (median = 6.3 μg/L). The As exposure in our study was even higher than that in an occupational study conducted in Guatemala (median = 8.05 μg/L), which suggests that exposures to As in China should be a focus (Butler-Dawson et al., 2022). Our results were partially consistent (median = 2.68 μg/g creatinine) with a cross-sectional study conducted in Bahia, Brazil that also found an association between Cd exposure (median = 0.20 μg/g creatinine) and impaired renal function (Martinez et al., 2022). A cohort study conducted in Zaragoza, Spain involving 1493 participants (median = 295 μg/g creatinine) revealed an association between Zn and a decrease in eGFR annual change (Grau-Perez et al., 2023). These results support a more comprehensive understanding of the kidney function deficits caused by As, Cd or Zn on a global scale. It should be noted that metal/metalloid exposures in our study were higher than those. This may be due to a greater focus on metal pollutants in China, which could have important implications for public health efforts in the region.

The mechanism by which Se affects kidney function could be related to direct and indirect aspects. Se is known to induce oxidative stress, which plays a key role in the pathogenesis of CKD (Daenen et al., 2019; Duni

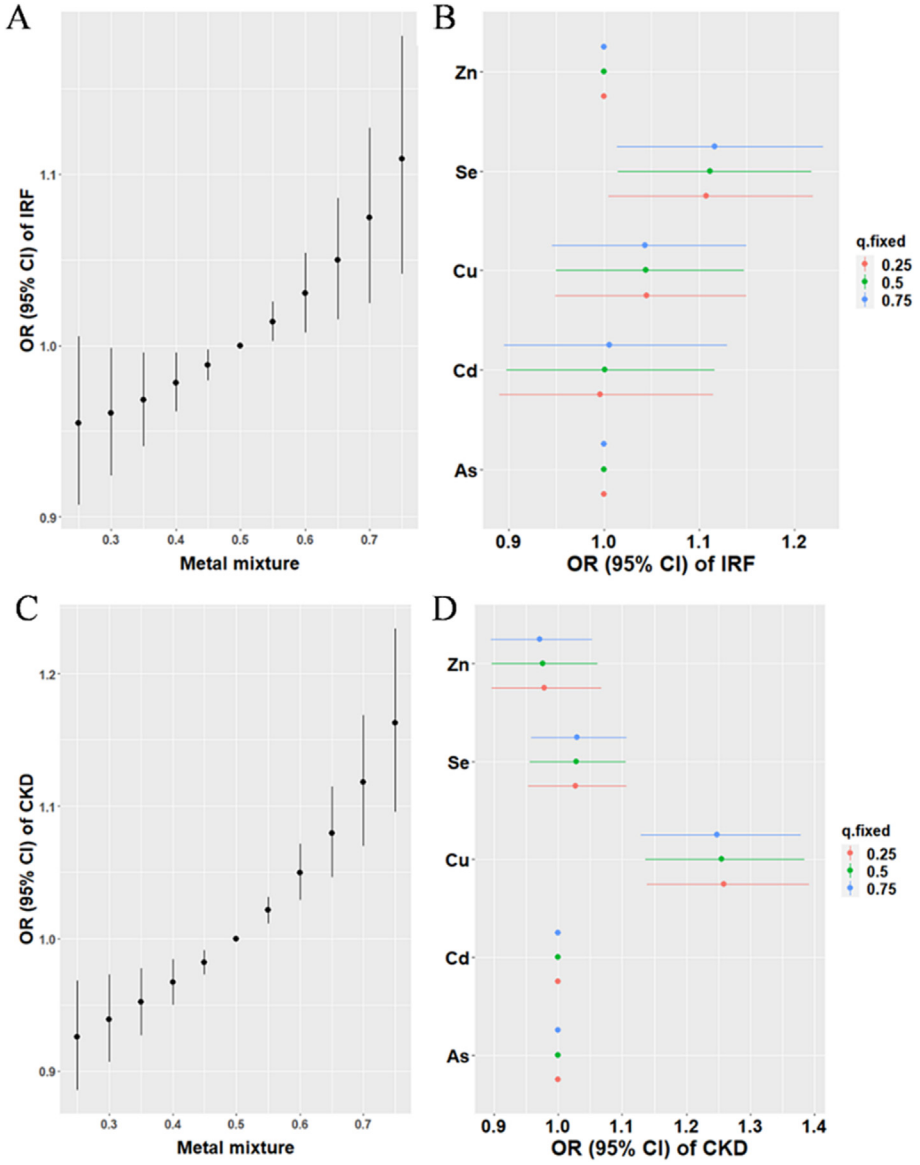

Fig. 3. Associations between urinary metal/metalloid concentrations and IRF/CKD by BKMR model.
Note: Metal/metalloid concentrations were log-transformed; IRF: impaired renal function; CKD: chronic kidney disease.
Overall associations of exposure to metal/metalloid mixtures on IRF (A) or CKD (C) when all the metals/metalloids were set at particular percentiles compared to the 50th percentile. Associations of interquartile range increase of single elements with IRF (B) and CKD (D) while all the other pollutants were fixed at either the 25th, 50th or 75th percentile. The associations of metal/metalloid mixtures with IRF/CKD were expressed as ORs and 95 % CI. The joint associations were assessed by the BKMR model, adjusted for sex, age, ethnicity, smoking, drinking, BMI, hypertension, cardiovascular diseases, area and self-reported kidney diseases.

et al., 2019). However, Se has no biological activity of its own, and the direct mechanisms might exist through the active site of several biological selenoproteins such as selenomethionine (SeMet) (Kim et al., 2021; Liu et al., 2022). Se exposure increases the level of SeMet (Rayman, 2004), which can induce apoptosis through the direct oxidation of vicinal sulfhydryl groups within the catalytic domains of cellular enzymes (e.g., protein kinase C) (Rahmanto and Davies, 2012; Rayman et al., 2018). However, urinary excretion of Se may be increased for patients with CKD (Zachara et al., 2006), as is true with all cross-sectional studies, there is some risk of reverse causation.

The indirect mechanisms might include inhibiting the excretion and interaction effects with hazardous metals/metalloids (As, Cd and Cu). A previous in vivo study reported that Se-deficient mice appeared to eliminate As more slowly than Se-sufficient mice (Kenyon et al., 1997), suggesting that low Se status might exacerbate the nephrotoxicity of hazardous metals/metalloids, such as As, Cd and Zn, by inhibiting the excretion of metals/metalloids (Chmielnicka et al., 1988; Matović et al., 2011; Zeng et al., 2005). Previous vivo studies indicated that As decreases the kidney function possibly by triggering TNF-α mediated apoptosis with associated with ROS-mediated inflammation (Ramanathan et al., 2005; Rizwan et al., 2014). Free Cd initiates the damage to kidneys through perturbing Ca2+ homeostasis, electrochemical gradient (Nordberg, 2009), inducing oxidative stress, inflammatory cell infiltration and downregulating mitochondrial coenzymes Q (Amamou et al., 2015; Renugadevi and Prabu, 2009, 2010; Zhai et al., 2014). Zn can disturb the energy metabolism and cause mitochondria and cell membrane impairment in rat kidney, which may contribute to Zn -induced nephrotoxicity (Xiao et al., 2016; Yan et al., 2012). In addition, Sun et al. suggested that Se addition interfered with the normal metabolism of As via several pathways, including decreasing the contents of glutathione and s-adenosylmethionine for As methylation and inhibiting the activity of As (+3 oxidation state) methyltransferase for As methylation (Sun et al., 2014), which might increase the risk for As nephrotoxicity. Cu metabolism was also found to produce ceruloplasmin, which is an acute phase reactant that binds with heavy metals

(Raudenska et al., 2017). Additionally, a previous study reporting the cumulative damage of ceruloplasmin-Se bond colocalization in the kidney (Weekley et al., 2014) can be affected by Cu—Se interactions.

Our study identified Cu as the most important element in the joint effects of mixtures on the risk of CKD. Our finding was in line with that of a cross-sectional study among 3553 participants in Hunan, China (Yang et al., 2019), in which increased urine Cu levels were found to be associated with an increased risk of CKD. However, other studies did not suggest an association between Cu and kidney function in US and Taiwanese populations (Smpokou et al., 2019; Tsai et al., 2018). Notably, we observed nonlinear association for urine Cu exposure, in which the eGFR decreased and plateaued with increasing exposure before 12.59 μg/g of creatinine and decreased monotonically afterward. Since such studies did not examine the nonlinearity of the association, it could have led to inaccuracy in the association between Cu and kidney function.

Interestingly, we found associations between metal/metalloid exposure and the risk of IRF in the Chinese population. IRF is known to pose an elevated risk of CKD and associated mortality (Chan et al., 2007). A previous study suggested that the prevalence of IRF (3.4 %, 95 % CI: 3.1–3.7) was 2 times as high as the prevalence of CKD (1.7 %) in mainland China and could affect 45.6 million adults (Zhang et al., 2012). However, to our knowledge, no previous study has reported an association between metal/metalloid exposure and IRF in mainland China, while only two studies have reported an association between As and renal dysfunction (eGFR <90 mL/min/1.73 m^2) in Taiwan. Thus, our results suggest that public health initiatives should focus more on the prevention of IRF.

The present study has several strengths. First, our analyses were based on a large sample of adults from 12 provinces of China, which could better represent the metal/metalloid exposure levels in China. Second, we used multiple methods to examine the effects of metal/metalloid exposures on kidney dysfunction, which allowed us to adjust the sensitivity and ensure the robustness of our analyses. Third, the comparisons between IRF and CKD strengthen the cumulative evidence that Se levels are associated with decreased kidney function and underscore the need to raise awareness of the prevention of and interventions for Se exposure among people with IRF.

Our study also has several limitations. The present cross-sectional study design could not examine the causal relationships between urine metal/metalloid exposures and kidney dysfunction. Considering that progressing kidney dysfunction as IRF and CKD contributes to Se excretion, our results may be produced by 'reverse causality'. Additionally, eGFR of participants were based on only one spot measurement, the false positives were increased and the test potency was reduced. However, we performed sensitivity analysis by defining CKD participants in the questionnaire and showed consistent results. In addition, the lack of information on the diet of participants, which can affect the form of Se excreted in urine, may potentially reduce the generalizability of our findings. Moreover, we did not analyze the speciation of urinary Se, which potentially hinders the explanation of our findings.

In summary, our study suggested that metal/metalloid mixtures were associated with kidney dysfunction, while Se and Cu were inverse factors, additionally, interactions between them may partially affect the association. These findings add to the understanding of the adverse effects of Se and Cu exposure on the risk of IRF or CKD. Future epidemiologic and mechanistic studies are warranted to confirm and generalize our results.

CRediT authorship contribution statement

Study concept and design: G.H.D., Y·Y; Acquisition of data: Y.Z., G.H.D., W.J.M., L.B.W., Y.J.X., P.D.; Analysis and interpretation of data: Y.Y., Y.Z., L.B.W., W.J.M., X.C.C., Y.J.X., H.X.K., G.H.D. Drafting of the manuscript: Y.Z., W.J.M., Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Y.Y., Y.Z., W.J.M., W.L.B., H.P.T., M.D.X., G.C.H., G.H.D. Obtained funding: Y.Y., G.H.D.

Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.163100.

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