Association of urinary exposure to multiple metals with ...

[a,*], Wenjie Meng [a], Hongxuan Kuang [a], Xichao Chen [a], Xiaohui Zhu [a], Lebing Wang [b], Haiping Tan [a], Yujie Xu [b], Ping Ding [a], Mingdeng Xiang [a], Guocheng Hu [a], Yang Zhou [a,b,*], Guang-Hui Dong [b,**]

[a] State Key Laboratory of Environmental Health (Incubating), State Key Laboratory of Environmental Science, Minist... of Environmental Protection, Guangzhou 510655, PR China

[b] Guangdong Provincial Engineering Technology Research Center of Environmental Health and Occupational Medicine, Department of Occupational and Environmental Health, School of Public Health, Sun Yat-sen University, Guangzhou 510080, PR China

C c i : 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. I d c

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

2.5. S a i ica a a i

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. Se i i a a i

We evaluated the robustness of the main results by conducting several sensitivity analyses. First, we excluded smokers (= 511) because smoking is considered an unhealthy lifestyle habit linked to kidney dysfunction. Second, we excluded participants with self-reported CKD (= 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. Re

3.1. Ge e a cha ac e i ic

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.

Tab e 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. A cia i be ee i ge ea / ea id e e a d kid e f ci

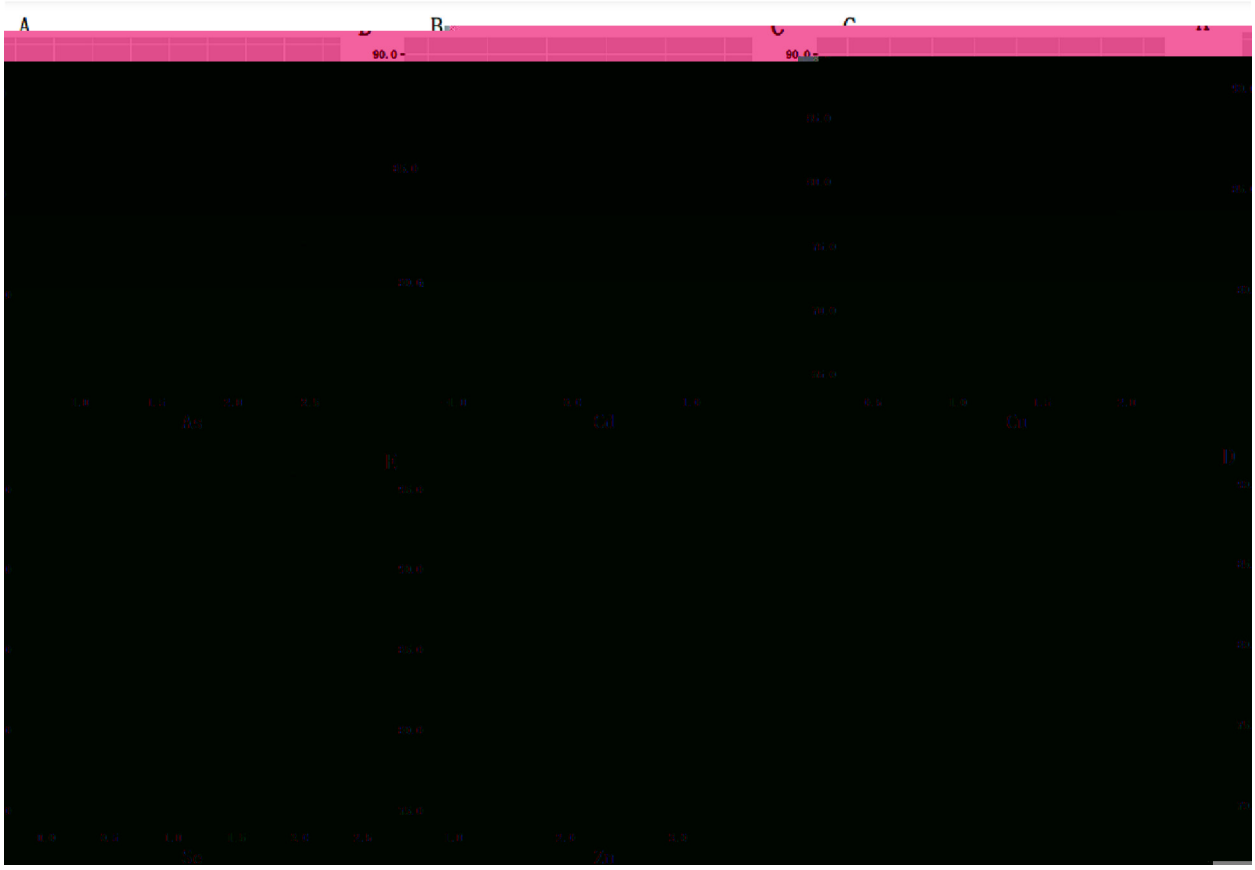
We observed that As and Zn had inverse linear associations with eGFR after adjusting for confounders. While the associations between Cd, Cu, and Se with eGFR were found to be nonlinear (Fig. 1), the dose-response curve was smooth before the turning point and rapidly declined after the turning point (1.79 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. J i eg e i a e be ee e a / ea id e e a d kid e f ci

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



F . 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.

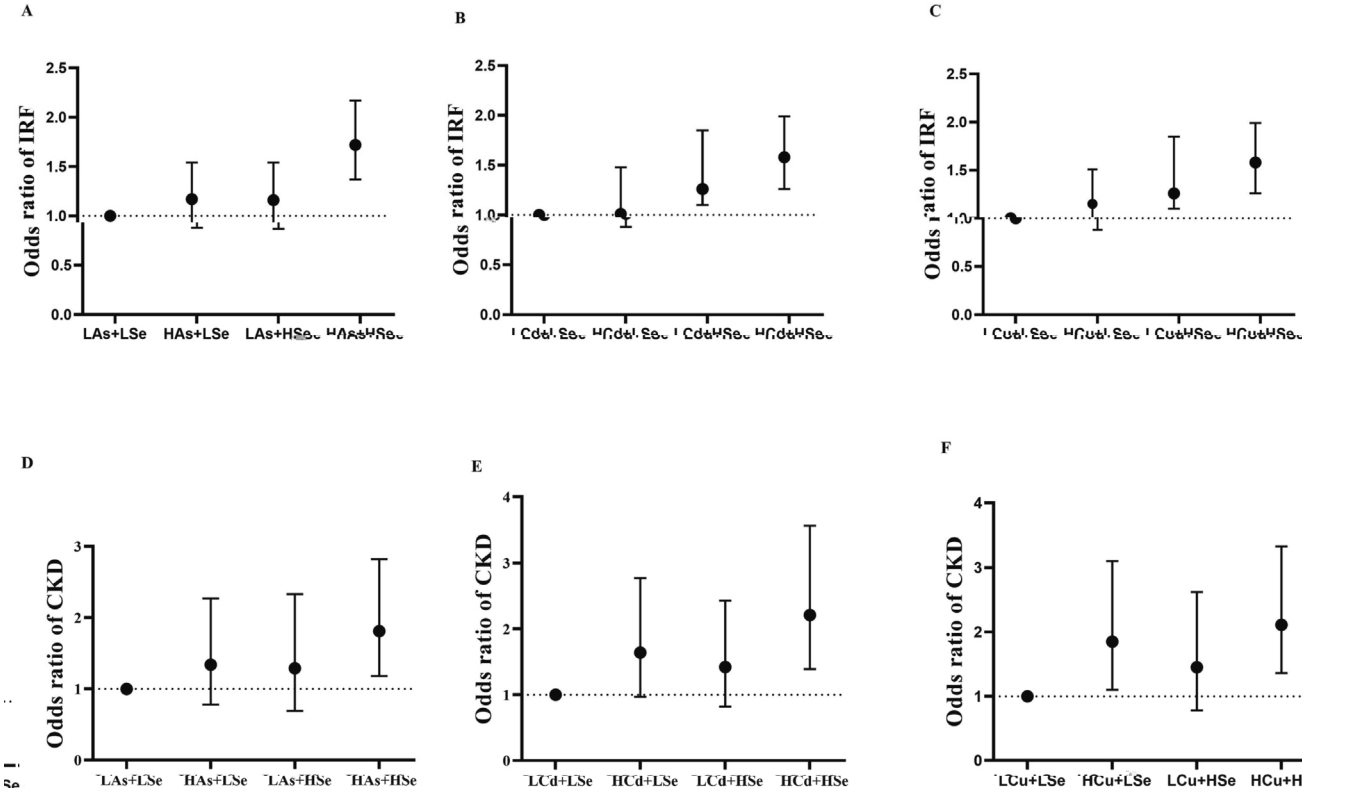
3.4. S bg a ɟa e

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.

Tab e 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.



F . 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.

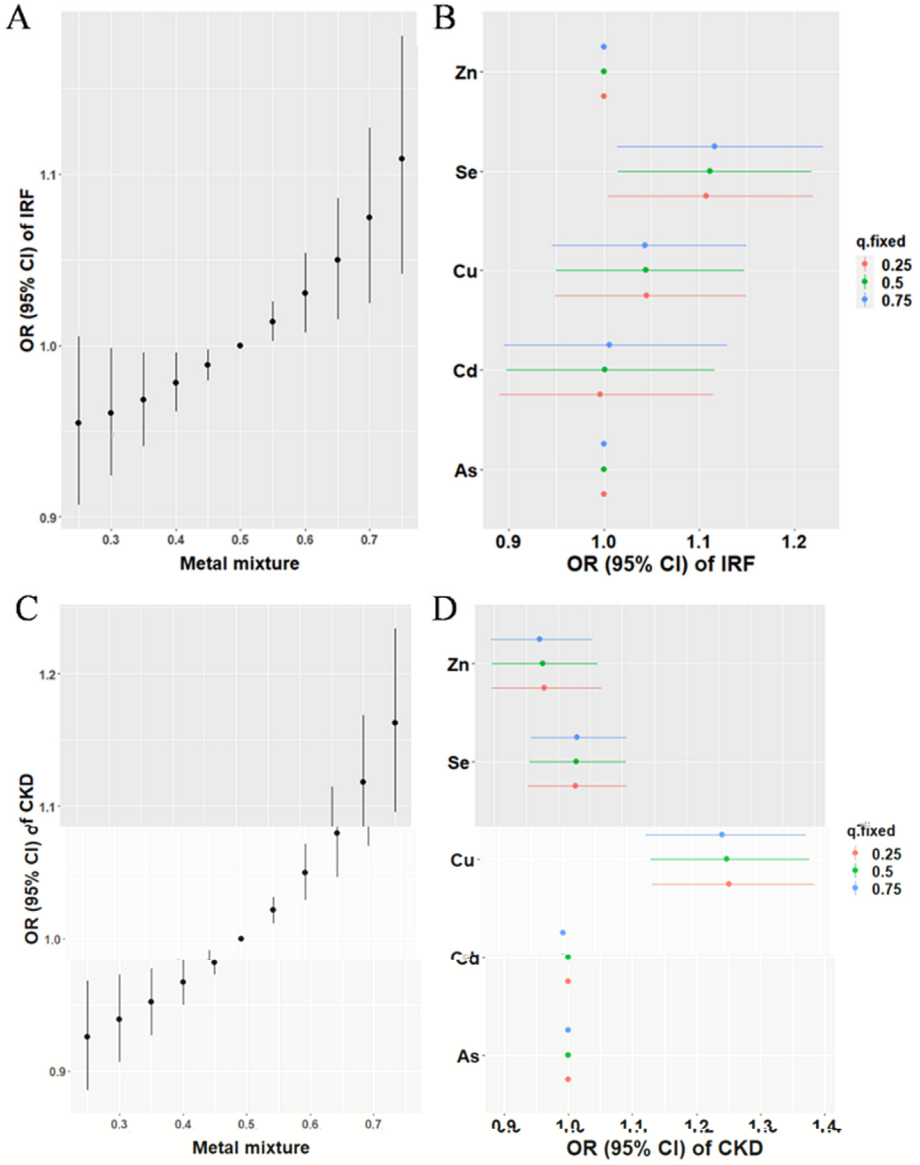
4. D c

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



F . 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.

CRed T a c b a e e

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Da a a a ab

Data will be made available on request.

Dec a a c e e

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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A e d A. S e e a da a

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Re e ce

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