Sex-specific associations of urinary metals with renal function: A cross-sectional study in China

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Abstract

Background: Extensive studies revealed the association between heavy metals and CKD. Compared with single meta, the mixtures metals reflect metals exposure scenarios in real life and deserves attention. While the mechanism of action of the metal mixture on renal function is still undefined.

Methods: A cross-sectional study involving 2775 participants was conducted. Urinary concentrations of heavy metals were measured by inductively coupled plasma mass spectrometry, and the estimated glomerular filtration rate (eGFR) for renal function was calculated. The association of metals with eGFR was estimated by linear regression. Interaction of the metal mixture was used to evaluate by using a Bayesian nuclear machine regression model (BKMR).

Results: In linear regression, urinary As ($\beta = 2.723$, $P<0.05$) and Pb ($\beta = 3.081$, $P<0.05$) were positively correlated with eGFR in total population. In BKMR model, the mixture of five metals had a positive joint effect on eGFR levels, and Pb (PIP = 0.996) contributed the most to the eGFR levels. Pb was significantly and positively associated with eGFR levels in total participants and women. As was significantly and positively associated with eGFR levels in women. Pb displayed a significant and positive effect when all the other metals were fixed at 25th, 50th, and 75th percentiles.

Conclusions: To the best of our knowledge All five metals mixed exposure was positively associated with eGFR, while Pb was demonstrated more important effects than the other four metals in the mixture, especially in women.

1. Introduction

Chronic kidney disease (CKD) is a public health problem of great concern in China even world. Cross-sectional studies on CKD have shown the high prevalence of CKD in China, especially in rural and specific geographical areas [1]. CKD imposes a huge burden on the health and economy of many countries and regions. The Chinese burden of disease reported that CKD remains one of the leading causes of death, with 264 years of life lost per 100,000 population [2]. It increases the risk of end-stage renal disease, cardiovascular disease, and cognitive impairment [3], with high complications and mortality. Increasing evidence suggests an association between environmental compounds and chronic kidney function [4]. The general population is exposed to various environmental pollutants through drinking water or diet, which accumulate in the body for a long time and then have health problems [5].

Heavy metal pollution is currently an important environmental issue because heavy metal ions are difficult to degrade. The kidneys, as the main organ of excretory substances, are more susceptible to contamination by heavy metals. eGFR is commonly used to estimate the burden of kidney disease [6]. Several epidemiological investigations found an association between arsenic (As), cadmium (Cd), lead (Pb), manganese (Mn) and chromium (Cr) and eGFR to demonstrate that metal exposure impairs renal function [7–10]. Arsenic (As), cadmium (Cd) and lead (Pb) are known as nephrotoxic metals, and they can increase the level of oxidative stress in the body, which play a vital role in CKD [11–12]. Manganese

(Mn) and Chromium (Cr) are essential nutrients that required for various biochemical and physiological function, deficiencies or excesses of these elements can have adverse effects on the body [13–14]. In addition, Mn and Cr can produce oxidative stress [14–15]. Moreover, the pollutants in the environment are mostly mixtures, and general public are chronically exposed to multiple metals that coexist in the environment [16]. Compare with single metal, it is particularly important to study the effects of multiple metals on renal function.

The Bayesian kernel machine regression (BKMR) was used to estimate the health effects of multi-pollutant mixtures. This model can estimates joint health effects of simultaneous exposure to multiple concurrent risk factors and the exposure-response functions that included both nonlinear and non-additive effects [17]. The model is currently used by many scholars to evaluate the health effects of environmental mixed pollutant exposure [18–19]. In this study, we used the BKMR model to analyze the association between metals and eGFR.

2. Method

2.1. Study population

Our data were from Gongcheng Ecology and Longevity Research and Application Project, a prospective cohort study in Gongcheng Yao Autonomous County, Guangxi, China. A total of 4356 local middle-aged and elderly people over the age of 30 were initially invited and provided baseline blood samples, urine samples, and questionnaire information between December 2018 and November 2019. All participants completed both questionnaires and clinical examinations. A total of 2775 subjects were included in the present study after excluding the following: a) those who failed to complete the questionnaire or did not provide blood or urine samples; b) cancer or tumors; c) eGFR < 60 mL/min/1.73 m^2; d) and those with missing covariate information. Sample collection and questionnaire survey were conducted with participants who had given written informed consent. This study was approved by the Medical Ethics Committee of Guilin Medical University (No. 20180702- 3).

2.2. Urinary metal determination

Midstream urine samples were collected and stored at -80°C in the laboratory until required for metal detection. Inductively coupled plasma–mass spectrometer (ICP-MS, NEXION350; PerkinElmer, Inc., USA) was used to measure the urinary concentrations of the metals: Pb, Cd, As, Cr, and Mn.Urine samples and dilute nitric acid were diluted 1:9 and acidified overnight. Blank solutions of samples and reagents were determined under the operating conditions of the measurement standard series. Each sample was analyzed thrice and the average value was taken. Seronorm™ Trace Elements Urine Level-1 and Level-2 (Sero AS, Billingstad, Norway) were used for internal quality control. The two standard reagents were measured once in every 30 samples. The recovery rate of standard addition was controlled at 80–120%. The limits of detection (LODs) were 0.0072, 0.0037, 0.0117, 0.0018, and 0.0009 μg/L for Cr, Mn, As, Cd, and Pb, respectively. Samples with a concentration below LOD were replaced by LOD /√2. The creatinine

of the sample results was corrected using creatinine correction method in accordance with limit requirements.

2.3. Estimation of kidney function

Glomerular filtration rate (GFR) was estimated by age, sex, race, and serum creatinine levels. Studies showed the CKD-EPI creatinine equation is more accurate than the MDRD Study equation [20]. Therefore, the CKD-EPI formula was used to calculate eGFRas follows:

$$eGFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018 \text{ [if female]}$$

Where SCr is the serum creatinine concentration (in mg/dL), and age. When the subjects are men, $\kappa = 0.9$ and $\alpha = -0.411$; when the subjects are women, $\kappa = 0.7$ and $\alpha = -0.329$. Min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.

2.4. Data collection and covariates

A standardized and structured questionnaire was used to obtain the information, particularly age, ethnicity (Yao or other ethnic groups), education level (≤ 6 years or > 6 years), smoking history (yes or no), and alcohol consumption (yes or no). Smoking was defined as currently smoking at least one cigarette per day. Alcohol consumption was defined as drinking at least 50 g of alcohol or more once a month. Body mass index (BMI) was calculated by dividing the weight by height squared (kg/m^2).

2.5. Statistical analysis

Descriptive statistics were calculated for all demographic and clinical characteristics of the study subjects. Continuous variables are expressed as mean (SD) or median (IQR). Categorical variables are presented as numbers and percentages. The Wilcoxon rank–sum test was used to analyze the distribution of urine metals in different subgroups. Pearson's correlation coefficients were calculated between urinary metals and eGFR. The levels of metals were subjected to log10 (lg) transformation to reduce their skewness.

Linear regression models were used to assess the relationship between the five metals as individual predictors and eGFR. Urinary metal concentrations were included in the model as a continuous variable for quartiles. Covariates included gender, age, ethnicity, education, BMI, smoking, alcohol drinking were selected and adjusted in the model were those reported in previous studies [1]. This model assessed the effect of co-exposure of the five metals on renal function.

BKMR was used to estimate the over-all associations of multi-metals exposure with the eGFR and investigate the possible interaction and non-linear dose-response for these five correlated metals and eGFR accounting for uncertainty [17]. We presented the posterior inclusion probability (PIP) of each metal calculated by the BKMR model to identify the most important metal in the mixture. The PIP can be thought of as a measure of variable importance, in which higher values (closer to 1) indicate higher importance, and lower values (closer to 0) indicate lower importance.

Given the significant differences in serum creatinine concentrations between men and women, analyses were conducted separately in accordance with sex [6]. All data were analyzed using SPSS 20.0 software (SPSS Inc., Chicago, IL) and R (4.0.4 revised). Main associations from linear regression, multiple metals linear regression, and BKMR were considered statistically significant at a $P < 0.05$.

3. Results

3.1. Characteristics of participants

A total of 2775 participants included 1018 men and 1757 women with a mean age of 56.76 ± 12.20 years and a mean eGFR of 93.57 ± 17.31ml/min/1.73 m^2 (Table 1). Table 2 shows that the distribution of urinary Cr, Mn, As, Cd, and Pb is different in gender and different smoking status groups. The distribution of all metals in women was greater than that in men.

Table 1

General characteristics of the study population.[a]

Variables	Total(n = 2775)	Man(n = 1018)	Woman(n = 1757)	*P-value*[b]
Age, years	56.76 ± 12.20	58.28 ± 11.94	55.87 ± 12.26	**< 0.001**
Ethnicity				**0.004**
Yao	2077(74.8)	798(78.4)	1279(72.8)	
Other	695(0.8)	220(4.3)	478(6.1)	
Education				**< 0.001**
≤ 6 years	1733(62.5)	500(49.1)	1233(70.2)	
> 6years	1042(37.5)	518(50.9)	524(29.8)	
Smoking status				**< 0.001**
yes	500(18.0)	489(48.0)	11(0.6)	
no	2275(82.0)	529(52.0)	1746(99.4)	
Drinking status				**< 0.001**
yes	882(31.80)	467(45.9)	331(18.8)	
no	1893(68.2)	551(54.1)	1426(81.2)	
BMI	22.67 ± 3.27	22.95 ± 3.18	22.51 ± 3.31	**0.001**
Scr mg/dL	0.77 ± 0.16	0.91 ± 0.14	0.69 ± 0.11	**< 0.001**
Ucr mg/dL	0.13 ± 0.07	0.15 ± 0.07	0.11 ± 0.06	**< 0.001**
eGFR ml/min/1.73 m^2	93.57 ± 17.31	90.88 ± 22.25	95.13 ± 13.42	**< 0.001**

Note: Abbreviations: BMI, body mass index; Scr, creatinine in serum; Ucr, creatinine in urine; eGFR, estimated glomerular filtration rate.

[a] The data was presented as n (n%), mean ± SD (standard deviation), median(25th, 75th)

[b]p-value in bold < 0.05.

Table 2

Concentrations of Cr, Mn, As, Cd, and Pb in urinary samples of different population characteristics.[a]

	Cr (μg/g, creatinine)	Mn (μg/g, creatinine)	As (μg/g, creatinine)	Cd (μg/g, creatinine)	Pb (μg/g, creatinine)
Total(n = 2775)	0.47(0.25, 0.77)	0.62(0.25, 1.44)	41.33(30.93, 56.03)	2.35(1.40, 3.77)	0.39(0.25, 0.59)
Sex					
Man(n = 1018)	0.42(0.24, 0.66)	0.40(0.16, 0.87)	37.85(28.07, 50.34)	2.35(1.40, 3.77)	0.36(0.23, 0.54)
Woman(n = 1757)	0.52(0.27, 0.84)	0.78(0.34, 1.77)	43.88(32.66, 59.74)	2.69(1.67, 4.24)	0.41(0.27, 0.63)
P-value	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**

[a] The data was presented as median(25th, 75th).Urinary metal has been corrected for urinary creatinine.

[b]p-value in bold < 0.05.

3.2. Correlation analysis between metals

Pearson's correlation coefficients indicated correlations between each pair of metals. Weak correlations were detected between Mn and eGFR (r = − 0.08), As and eGFR (r = − 0.06), and Cd and eGFR (r = − 0.08) in total population (P < 0.05). Positive correlation was observed among the five metals (r_s values ranging from 0.16 to 0.45, P < 0.05). Similar results were observed in sex group. (Fig. S1).

3.3. Associations between urinary metals and eGFR in generalized linear regression model

The single metal model (model 1) found that urinary As (β = 2.723, P < 0.05) and Pb (β = 3.081, P < 0.05) was positively correlated with eGFR in the total population. urinary Cr (β = 1.069, P < 0.05), Mn (β = 0.809, P < 0.05), As (β = 3.467, P < 0.05) and Pb (β = 3.181, P < 0.05) were positively correlated with eGFR in the women. No significant correlation was found between Cd and eGFR. (Table 3)

Table 3
Associations between urinary metals and FPG levels determined using estimated changes from single metal and multiple metals linear regression models.

Metal (μg/g, creatinine)	Model 1 [a]		Model 2 [b]	
	β (95%CI)	*P-value*	β (95%CI)	*P-value*
Total				
lgCr	0.701(-0.18, 1.582)	0.119	-0.121(-1.121, 0.879)	0.812
lgMn	0.624(-0.093, 1.341)	0.088	0.243(-0.546, 1.032)	0.546
lgAs	2.723(0.29, 5.157)	**0.028**	1.645(-1.016, 4.305)	0.226
lgCd	1.463(-0.327, 3.253)	0.109	-0.189(-2.194, 1.816)	0.854
lgPb	3.081(1.725, 4.438)	**< 0.001**	2.863(1.354, 4.372)	**< 0.001**
Man				
lgCr	-0.016(-2.126,2.093)	0.988	-0.739(-3.144,1.666)	0.547
lgMn	0.246(-1.319,1.811)	0.758	0.056(-1.689,1.8)	0.95
lgAs	1.431(-4.296,7.157)	0.624	0.002(-6.283,6.287)	1.00
lgCd	2.201(-1.95,6.352)	0.298	1.34(-3.404,6.083)	0.58
lgPb	2.727(-0.543,5.997)	0.102	2.703(-0.927,6.333)	0.144
Woman				
lgCr	1.069(0.334,1.804)	**0.004**	0.243(-0.589,1.075)	0.567
lgMn	0.809(0.174,1.444)	**0.013**	0.298(-0.395,0.991)	0.399
lgAs	3.467(1.419,5.515)	**0.001**	2.676(0.446,4.906)	**0.019**
lgCd	0.965(-0.56,2.491)	0.215	-1.046(-2.73,0.639)	0.224
lgPb	3.181(2.053,4.309)	**< 0.001**	2.794(1.538,4.05)	**< 0.001**

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; lg log10 transformed

[a] Model 1: Single metal linear regression models, adjusted for and/or sex, and/or age, ethnicity, education, BMI, smoking, drinking.

[b] Model 2: Multiple metals linear regression models, adjusted for Model 1, and Cr, Mn, As, Cd, and Pb were fitted simultaneously.

In model 2, after adjusting the other metals in multivariate metals model, urinary As in women (β = 2.676, P < 0.05) was significant positively associated with eGFR. Urinary Pb in the total population (β = 2.863, P < 0.05), women (β = 2.794, P < 0.05) were significant positively associated with eGFR. (Table 3)

3.4. Bayesian kernel machine regression analyses

We further conducted BKMR model to analysis the global correlation analysis of the metal mixtures. The PIP values of each metal exposure obtained from the model were summarized in Table 4. Given the highest PIP from Pb in the total population (PIP = 0.966),women (PIP = 1.000).

Table 4
PIP for conditional inclusion into eGFR by using the BKMR model.

	Cr	Mn	As	Cd	Pb
Total	0.003	< 0.001	< 0.001	< 0.001	0.966
Man	0.011	0.005	< 0.001	0.009	0.006
Woman	< 0.001	< 0.001	0.002	< 0.001	1.000
Data were estimated using the Bayesian kernel machine regression while adjusted for and/or sex, and/or age, ethnicity, education, BMI, smoking, drinking.					
Abbreviations: PIP, posterior inclusion probability; eGFR, estimated glomerular filtration rate; BKMR, Bayesian kernel machine regression					

In BKMR model, as shown in Fig. 1, we conducted the overall association analysis of the mixture. In total population, we found a joint association of the metals mixture with eGFR levels. When all metals were above their 50th, the metals mixture showed a significantly positive association with the eGFR levels, in contrast, a significant negative association was observed when metals concentrations were all below their 50th, as compared to that when all metals were at the 50th percentile (The 50th percentile of each metal was Cr 0.47 μg/g, creatinine, Mn 0.62 μg/g, creatinine, As 41.33 μg/g, creatinine, Cd 2.35 μg/g, creatinine, Pb 0.39 μg/g, creatinine). Similar results were observed in woman population.

Furthermore, We investigated potential nonlinear exposure–response relationships when the concentrations of other metals were kept at corresponding median concentrations. As shown in Fig. 2, Urinary As and Pb have correlation with eGFR in total population and women. The single metal exposure-response relationship was basically consistent with the results of the single metals linear regression model.

As shown in Fig. 3, when the other five metals were set to p25, p50, or p75, a positive correlation between Pb and eGFR was observed in the total population (estimate: from 1.00 to 1.02), and woman population (estimate: From 0.967 to 0.997). However, no such significant association was found for the other four metals.

The bivariate exposure–response function is shown in Fig. S3. No interaction effect was found among the five metals.

4. Discussion

In this study, we comprehensively evaluated the relationship of urinary Cr, Mn, As, Cd, and Pb contents with eGFR levels and explored potential metal interactions among participants using the BKMR model. The BKMR study results as follows: the mixture of five metals had a positive combined effect on eGFR levels, and Pb (PIP = 0.966) contributed the most to the eGFR levels. Furthermore, Pb and As were positively correlated with eGFR levels in women. Cr, Mn, As, Cd, and Pb showed no significant correlation with eGFR when analyzed as a mixture of contaminants rather than as a single contaminant.

Pb is a nephrotoxic metal that can be harmful at even extremely low doses. Pb nephrotoxicity presents with proximal renal tubular nephropathy, glomerulosclerosis, interstitial fibrosis, and associated functional deficits. Moreover, Pb also can enter the mitochondria in renal proximal tubular cells, thereby impairing oxidative metabolism in the kidney [21]. The effect of Pb on the kidney has also been reported in many studies. Hui-Ju Tsai et al found that high concentrations of blood Pb were associated with the occurrence of proteinuria and the reduction of eGFR [22]. A perspective study showed that low concentrations of blood Pb can cause a decrease in eGFR, increasing the risk of CKD [23]. Blood Pb that increased the risk of decreased proteinuria and eGFR was also found in the study by a joint analysis [7]. Nevertheless, the results of the association between urinary Pb and eGFR are inconsistent. A decrease in eGFR with increasing urinary Pb was found in a cross-sectional study in Taiwan [24]. Xiao Chen et al [25] found a positive association between urinary lead and renal effect biomarkers such as urinary microalbuminuria, urinary N-acetyl-β-D-glucosaminidase and urinary total protein, but no significant correlation with eGFR. In the BKMR model, we found a significant positive correlation between urinary Pb and eGFR. A study in the United States found that urinary Pb discharge increased with increasing eGFR [26]. Rufeng Jin et al [27] also found that the urinary excretion rate of metals increased with increasing levels of eGFR, in which eGFR is more susceptible to Pb. Some studies believe that this is a poor hyperfiltration, which leads to subsequent adverse renal reactions. In an animal experiment, rats showed a positive correlation between GFR and blood lead within one month of lead exposure, thereafter decreased significantly [21, 28]. Some studies also regard this as a reverse causality prediction [26, 27, 29]. Most metals are excreted by renal excretion and should be reduced after impaired renal function. Thus, eGFR decreases and filtration of metals decreases, resulting in a decrease in urine and increased metal levels in the blood.

Mn and Cr are essential trace element, but little attention has been paid to their renal effects. A cross-sectional study of Chinese people over 90 years found the dose-response relationship between manganese and eGFR consistent with the trace element dose effect curve, the U-type curve [30]. A cross-sectional study in Korea found that low blood Mn concentrations (1.28 μg/dL in the participants with renal dysfunction) can increase the risk and prevalence of renal dysfunction [31]. Jingli Yang et al. [32] also found plasma Mn (median concentration, 9.34 μg/L) and urinary Mn (median concentration, 0.106 μg/g, creatinin) were positive correlation with eGFR. In this study, urinary Mn was positively associated with eGFR in women, and the urinary Mn levels was 0.78 μg/g, creatinine. Some studies of renal function in occupational Cr exposure found negative or equivocal results [14]. In our study, we found that

significantly positively associated between urinary Cr and eGFR in women. A few studies have found a negative correlation between urinary chromium and eGFR [24, 10], but others have not found a significant correlation between urinary chromium and eGFR [22]. Due to the limitations of cross-sectional study design, it is not possible to elucidate the causal relationship between chromium and kidneys, which requires more research to confirm our findings. At present, whether chromium is a trace element necessary for humans is still controversial, but the effect of chromium-induced oxidative stress on the body should be worth noting.

In the BKMR model, we found that As had a significant positive correlation with eGFR, and Cd had no significant association with eGFR. Cd and As are known nephrotoxic heavy metals [11]. Significant associations between these heavy metals and eGFR has been rarely observed, and more have demonstrated the association between heavy metals and albuminuria, α1-microglobulin and other indicators [8, 24, 38, 39]. A few studies demonstrated that exposure to Cd or As exerted toxicity through an oxidative stress process, that generation of ROS, reduced levels of glutathione, decrease in superoxide dismutase, and induction of DNA adduct, which would aggravate the development of kidney disease [40–41].

Interestingly, we found that eGFR-associated metals were mostly different between men and women. First, urinary metal concentrations were higher in women than in men. This is due to the lower iron storage in women, which leads to the up regulation of the intestinal divalent metal transporter (DMT1), increasing the absorption of other metals [42]. On the other hand, we found that women's eGFR was more susceptible to the effects of metals, especially Pb. Studies have shown that metals affect metabolic disorders in the body or induce the upregulation of inflammatory biomarkers, leading to an increased risk of diseases such as cardiovascular disease, diabetes and hypertension, especially in postmenopausal women. For example, Estradiol (E2) disorder may be a risk factor for metabolic diseases in postmenopausal women, while E2 is susceptible to Pb interference [43]. The mean age of the women in this study was 55.87 years, so the majority were postmenopausal women, and this population was more susceptible to metal effects. Furthermore, serum creatinine is limited by age and sex, so urinary metal excretion may also be influenced by gender [6]. Although the current study cannot clearly explain the sex-specific effects on the relationship between urinary metals and eGFR, we should focus more on sex differences-related health effects, especially the role of hormones in sex differences.

Our study has several advantages. First, BKMR analysis was used to analyze the single and combined effects of metals and to assess the metal interactions that may occur at the eGFR level. Second, we performed different stratified analyses, which helped us realize that different metal exposure environments may affect the relationship between metal and eGFR levels. However, our study’s limitations cannot be ignored. First, the present study was a cross-sectional study, and the determination of the causal relationship between metal exposure and eGFR was not possible. Second, some measurements may be affected by certain factors. For instance, creatinine may be affected by drugs and intestinal bacteria [44], which may exhibit extreme variation. Thus, we were unable to rule out the possibility of false-positive or false-negative results. Finally, considering that our results were obtained

only from the excretion of these metals in the urine, we cannot rule out the possibility of false-positive results. Therefore, the correlations we found require further investigation.

5. Conclusion

In the present study, urinary Cr, Mn, As and Pb may be associated with eGFR. The mixture of five metals had a positive combined effect on eGFR levels, and eGFR levels are more susceptible to Pb. Sex-specific was also found in the association between heavy metals and renal function. Our findings should serve to remind health researchers and the government of the importance of environmental policies and legislative changes to improve human health. Future follow-up studies are necessary to verify the causal relationships among heavy metals and CKD.

Declarations

Sample CRediT author statement

Yinxia Lin: Conceptualization, Methodology, Data curation, Software, Writing – original draft, Writing – review & editing. **Jiansheng Cai, Qiumei Liu:** Conceptualization, Methodology, Data curation, Software, Writing – review & editing. **Xiaoting Mo, Min Xu, Junling Zhang, Shuzhen Liu, Chunmei Wei:** Field management, Sampling, Investigation, Data curation. **Yanfei Wei, Shenxiang Huang, Tingyu Mai, Dechan Tan:** Sampling, Investigation, Data curation. **Huaxiang Lu, Tingyu Luo, Ruoyu Gou:** Sampling, Investigation. **Zhiyong Zhang, Jian Qin:** Resources, Supervision, Writing – review & editing. All authors have given approval to the final version of the manuscript.

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Declaration of competing interest

The authors declare that there is no conflict of interests.

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Figures

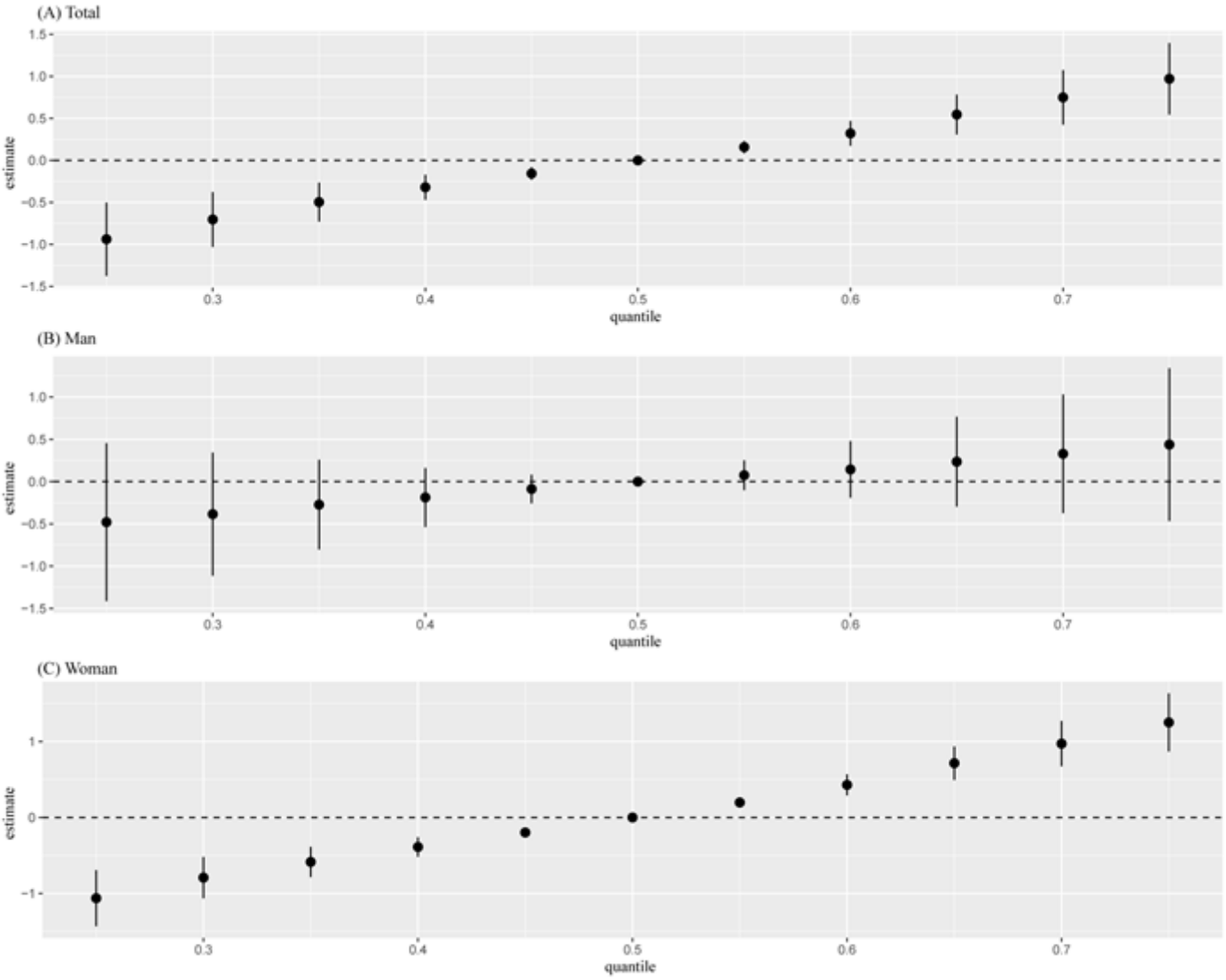

Figure 1

Overall effect of the mixture estimates and 95% credible interval. (A) Total, (B) Man, (C) Woman. Data were estimated by Bayessian Kermel Machine Regression, while adjusting for age, sex, BMI, smoking, drinking, education and ethnicity.Univariate exposure-response functions and 95% credible intervals (shaded areas) for each metal with the other metals holding at the median.

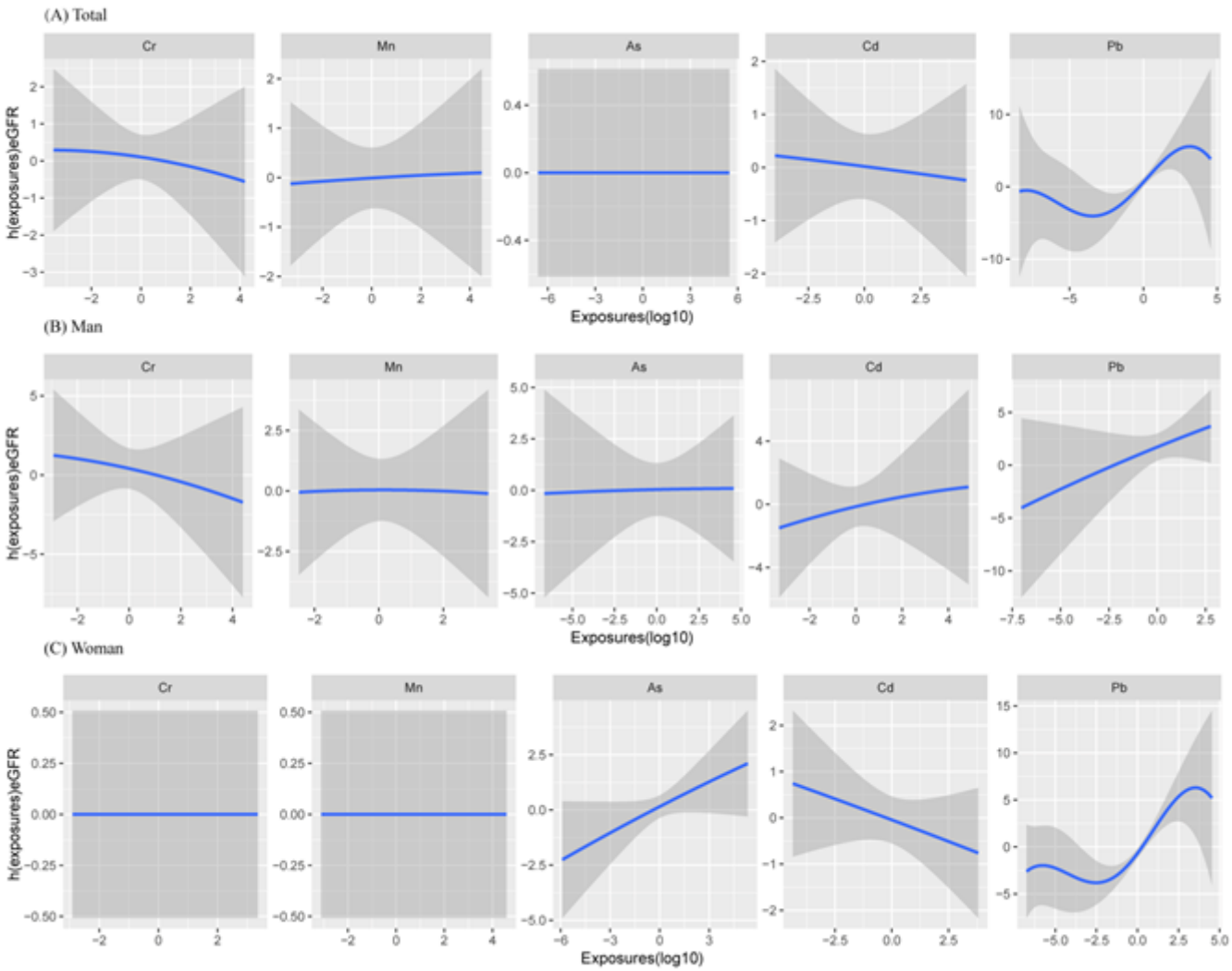

Figure 2

Effects of single metal on eGFR. (A) Total, (B) Man, (C) Woman. Data were estimated by Bayessian Kermel Machine Regression, while adjusting for age, sex, BMI, smoking, drinking, education and ethnicity. Univariate exposure-response functions and 95% credible intervals (shaded areas) for each metal with the other metals holding at the median.

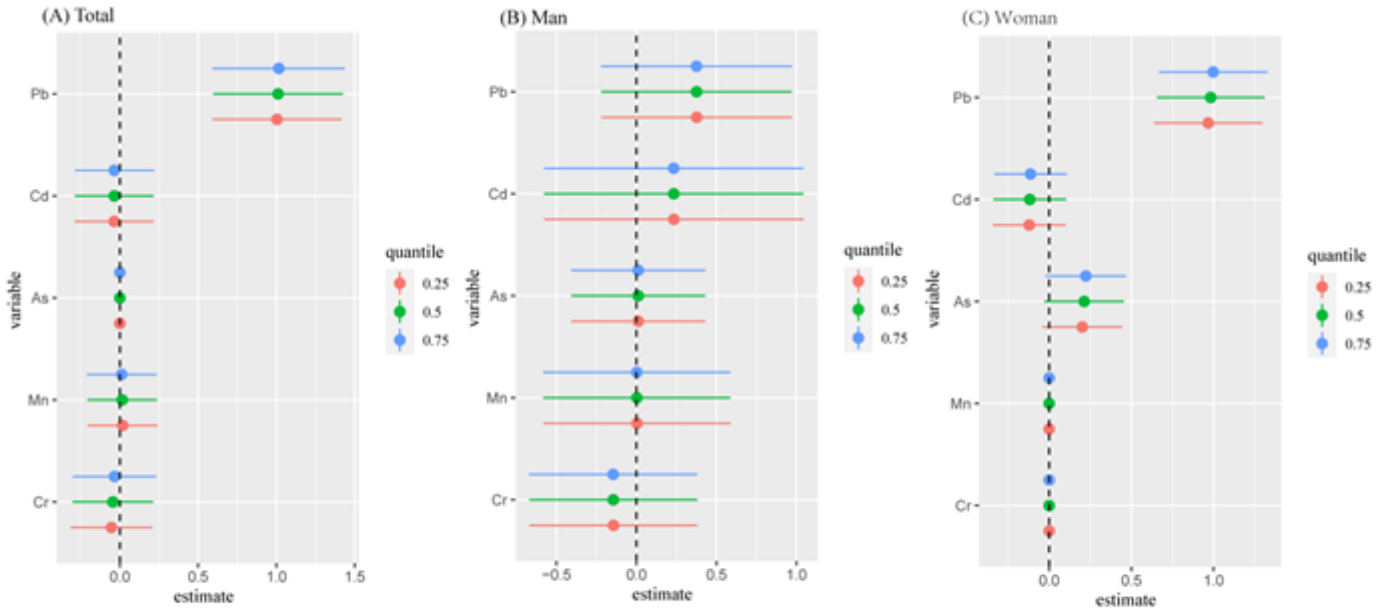

Figure 3

Association (estimate and 95% credible intervals) of each metal increased from the 25th percentile to the 75th percentile with eGFR was observed when other metals in the mixture have been fixed at the 25th, 50th, and 75th percentiles. Estimate can be interpreted as the contribution of predictors to the response. (A) Total, (B) Man, (C) Woman. Data were estimated using the Bayesian kernel machine regression, while adjusting for age, sex, BMI, smoking, drinking, education and ethnicity.

Supplementary Files

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