Exposure to Cadmium, Lead, Mercury and Arsenic and Uric Acid Levels: Results from NHANES 2007-2016

Wenhui Gao
Jilin University
Li Tong
Jilin University
Saisai Zhao
Jilin University
Lina Jin (jinln@jlu.edu.cn)
Jilin University https://orcid.org/0000-0002-8961-2809

Research Article

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Abstract

Background: Mechanisms underlying abnormal uric acid (UA) levels from exposure to heavy metals have not been not fully elucidated, especially in the context of mixtures.

Objectives: To identify major heavy metals affected UA levels with a mixture exposure concept in the association model.

Methods: 4794 adults from 2007-2016 National Health and Nutrition Examination Survey (NHANES) were involved. Serum UA (SUA) and SUA/SCr were used to estimate the UA levels, and cadmium (Cd), lead (Pb), mercury (Hg) and arsenic (As) in blood and/or urinary were evaluated in the study. We assessed the associations between heavy metals and UA levels using linear regression and Bayesian kernel machine regression (BKMR).

Results: The median [P_{25}, P_{75}] SUA/SCr and SUA level were 6.22[5.27, 7.32] and 0.83[0.72, 0.98], respectively. There was no difference for SUA/SCr by gender, (men: 6.25[5.39, 7.29]; women: 6.17[5.17, 7.36], P=0.162), but men had higher SUA than women (men: 0.95[0.85, 1.05]; women: 0.72[0.64, 0.82], P<0.001). Blood Pb (β_{men} = 0.651 and β_{women} =1.014) and urinary Cd (β_{men} = 0.252 and β_{women} = 0.613) were positively associated with SUA/SCr, and urinary Pb (β_{men} = -0.462 and β_{women} = -0.838) was inversely associated with SUA/SCr in multivariate linear regression analysis, but urinary As (β_{men}= 0.351) was positively associated with SUA/SCr only in men. BKMR showed that higher concentrations of exposure to a mixture of heavy metals was positively associated with higher UA levels, where Cd, Pb and urinary As contributed most to the overall mixture effect in men, while Pb and urinary Cd in women.

Conclusions: Our study provided the first evidence that mixtures of metals are associated with the UA levels. Increased concentrations of metals, particularly blood Pb, urinary Cd and As (only in men) may increase the levels of UA.

1. Introduction

Uric acid (UA) is the final product of purine oxidation catabolism, and mainly excreted in urine. Serum uric acid (SUA) is believed to be an important indicator to evaluate kidney health and hyperuricemia (Feig et al., 2008; Gao et al., 2021; Sanders et al., 2019), and associated with cardiovascular mortality and all-cause mortality (Culleton et al., 1999; Hu et al., 2019; Tseng et al., 2018; Zhao et al., 2013). Increased SUA is believed as a biomarker of inflammatory cytokine activation, insulin resistance and oxidative stress (Liu et al., 2021; Lyngdoh et al., 2011; Mazidi et al., 2018), and may be involved in the occurrence and development of many diseases, such as gout, cancer and neurological diseases (Fini et al., 2012; Strasak et al., 2007; Tana et al., 2018). Further, the excretion of UA is highly dependent on renal function, and about 75% UA is excreted by the kidney daily (Fathallah-Shaykh and Cramer, 2014; Rumora et al., 2020), thus kidney plays important roles in maintaining the homeostasis of UA and SUA (Rumora et al., 2020). Serum creatinine (SCr) is widely interpreted as a measure of renal function, and abnormal SCr is associated with the increasing risk of cardiovascular diseases (Irie et al., 2006; Perrone et al., 1992). There is emerging evidence

that SUA to SCr ratio (SUA/SCr) is a standardized SUA indicator for renal function, which can reflect endogenous UA level better (Gu et al., 2017; Levey et al., 1988; Tao et al., 2020), and SUA/SCr is reported to be associated with β cell function, metabolic syndrome and chronic kidney disease (Al-Daghri et al., 2017; Li et al., 2018), and is a new indicator to predict metabolic disease and all-cause mortality (Al-Daghri et al., 2017; Mazidi et al., n.d.).

SUA, as an antioxidant, may be involved in the oxidative stress caused by heavy metal exposures (Kovacik et al., 2019), and multiple metals have been widely detected in the environment in daily life, such as ambient air, drinking water, food, medications, and consumer products (Wu et al., 2016). Many studies have evaluated the associations between SUA and exposure to single metals, such as cadmium (Cd), lead (Pb), mercury (Hg) and arsenic (As) (del Razo et al., 2003; Krishnan et al., 2012; Kuo et al., 2015; Park and Kim, 2011; Sun et al., 2017). The Pb and Hg in blood were positively associated with SUA, while Cd in blood was inversely associated with SUA and the risk of hyperuricemia in women in a cross-sectional study in Korea (Park and Kim, 2011). Another study in eastern China found that no association between blood Pb and SUA, but a significantly positive association between blood Cd and SUA and the risk of hyperuricemia in men (Sun et al., 2017). Krishnan E et al. showed that low levels of Pb exposure were positively correlated with SUA levels, while Hg and Cd showed no correlation with SUA (Krishnan et al., 2012). It was suggested that As might inhibit xanthine oxidase, resulting in a decrease in UA levels (del Razo et al., 2003), while Kuo CC et al. showed that the urinary As exposure was associated with higher SUA levels and an increased prevalence of hyperuricemia in men (Kuo et al., 2015). Thus the relationship between exposure to single heavy metals and SUA is limited and conflicting.

Meanwhile, humans are exposed to a mixture of multiple heavy metals, where they occur simultaneously and often with complex correlation structures and interactions (Carpenter et al., 2002; Gao, 2021). Thus it is necessary to consider the impact of exposure to a mixture of heavy metals on UA, because the effect of single exposure was reported to be different from that in its mixture (Billionnet et al., 2012; Zanobetti et al., 2014), and multiple heavy metals exposure may exhibit synergistic or antagonistic effects on UA (Carpenter et al., 2002). Furthermore, the joint effects of multiple heavy mental exposures on UA have never been assessed.

Hence, we aimed to evaluate the association between multiple heavy metals that commonly exposed in blood and urine (i.e., Cd, Pb, Hg, As) and UA. The objectives of the current study are (1) to access the individual effects of exposure to single heavy metals on SUA/SCr and SUA and (2) to evaluate the joint effects of exposure to a mixture of multiple heavy metals on SUA/SCr and SUA using Bayesian kernel machine regression (BKMR) models (Bobb et al., 2014).

2. Materials And Methods

2.1 Study population

The National Health and Nutrition Examination Survey (NHANES) program is a series of multistage, ongoing, complex surveys designed by the National Center for Health Statistics to assess the health and nutritional status of the non-institutionalized civilian population in the U.S. The survey ethics review board

of the CDC approved the NHANES procedures and protocols, and all participants provided written informed consent.

In this study, 5 cycles of NHANES data (2007-2008, 2009-2010, 2011-2012, 2013-2014 and 2015-2016) were combined. A total of 29,201 adults of 20 years old and over completed the NHANES 2007–2016 in-home interview and the medical evaluation at the mobile examination center. Firstly, we excluded the individuals who received diuretics and uric acid medications (n=4,044), considering that these drugs may bring bias to the study. Secondly, we excluded the participants with missing SUA (n=2,416) and SCr (n=3), and those with missing values on exposures of heavy metals (n=15,278) and major covariates (including race, educational level, ratio of family income to poverty (PIR), cigarette smoking, alcohol drinking, fish eaten during the past 30 days, BMI, cotinine, history of hypertension, diabetes and gout) (n=2,666). Finally, 4,794 participants (including 2,452 men and 2,342 women) were enrolled in our study.

2.2 Measurement of exposures

The measurements of all the exposures of interest (whole blood Cd, Pb and Hg as well as spot urine Cd, Pb, Hg and As) were tested by inductively coupled plasma-dynamic reaction mass spectrometry (ICP-DRC-MS) at the CDC's National Center for Environmental Health. Values of concentrations below the limit of detection (LOD) were imputed value of LOD/. Detailed information on laboratory quality assurance and monitoring are available at https://www.cdc.gov/nchs/nhanes/index.htm.

2.3 Serum Uric acid and other biochemical parameters

SUA and SCr were detected on a Beckman UniCel ® DxC800 Synchron or a Beckman Synchron LX20 (Beckman Coulter, Inc., Brea, CA, USA). SUA was assessed using a timed endpoint method, and SCr was analyzed using the Jaffe rate method. Serum cotinine was measured by using an isotope-dilution high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometric (ID HPLC-APCI MS/MS) method.

2.4 Covariates

All statistical models were adjusted for the following a priori identified potential confounders based on the literature: age (years), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American and other Hispanic), educational level (less than high school, high school, or more than high school), PIR (≤1.30, 1.31-3.50, ≥3.51), smoking (no: <100 cigarettes in life; yes: ≥100 cigarettes in life), drinking (no: <12 alcohol drinks in life; yes: ≥12 alcohol drinks in life), fish eaten during the past 30 days (yes, no), gout (yes, no), diabetes (yes, no), hypertension (yes, no), BMI (computed as weight in kilograms divided by height in meters squared, kg/m^2), natural log-transformed serum cotinine (ng/mL), eGFR (calculated using the CKD-EPI equation, mL/min/1.73 m^2).

Gout was defined as individuals with self-reported physician diagnosed gout. Diabetes was defined as individuals with self-reported physician diagnosis, or medication use or hemoglobin A1c was greater than or equal to 6.5% or fasting (8 – 24 h) plasma glucose was greater than or equal to 126 mg/dL. Hypertension

was defined as individuals with self-reported physician diagnosed hypertension, or antihypertensive medication use or blood pressure ≥ 140/90 mmHg.

2.5 Statistical analysis

Descriptive statistics were calculated for all demographic and other characteristics of the study subjects by gender, respectively. The continuous variables are expressed in median [P_{25}, P_{75}] and compared by Mann–Whitney U test. The categorical variables are presented as counts and percentages and compared by Chi-square test. We followed the NHANES analytical reporting guidelines and accounted for the complex survey design, which assigns weights to individual participants to correct for oversampling of certain subgroups.

All heavy metal exposures were initially natural log–transformed, and the association between heavy metal exposures and SUA/SCr (SUA) was evaluated by linear regression models. Each heavy metal was firstly evaluated as separated predictors in linear regression, and then all the seven multiple heavy metals, where race/ethnicity, age, education, PIR, smoking, drinking, serum cotinine, fish eaten during the past 30 days, BMI, eGFR, gout, diabetes, and hypertension were adjusted. Variance Inflation Factor (VIF) was used to address the concerns about the effect of multicollinearity on linear regression results. BKMR model, a new semi-parametric statistical method, was used to flexibly evaluate the joint effects of the multiple contaminant mixtures using a kernel function (Bobb et al., 2014). In sensitivity analyses, the BKMR analyses were repeated by including participants with suitable urine samples concentration (urinary creatinine concentrations: 30 – 300 mg/dL) according to the World Health Organization guidelines for studies of adults with occupational exposures (International Program on Chemical Safety. and World Health Organization., 1996).

All analyses were conducted with SPSS (version 24.0; IBM® SPSS® Statistics, Armonk, NY, USA) and R (version3.5.1; R Foundation for Statistical Computing), and a two- tailed $P < 0.05$ was considered statistically significant. BKMR was implemented with the R packages “bkmr” (version 0.2.0) (Bobb et al., 2018).

3. Results

3.1 Characteristics of study population

The characteristics of the participants was shown in Table 1, where the median [P_{25}, P_{75}] age of the study participants was 44 [31, 57] years, with approximately similar distribution for both genders. But there are significantly statistical difference between genders in SUA, SCr, and majority of covariates, thus all the following analysis were by genders.

3.2 Distributions and correlations for multiple heavy metals

The lowest, 5^{th}, 25^{th}, 50^{th},75^{th}, 95^{th} percentiles and highest values of blood Cd, Pb, Hg and urinary Cd, Pb, Hg, As for men and women were summarized in Table 2. There were significantly statistical differences between genders in blood Cd, Pb, urinary Cd, Pb, As, but blood Pb, Hg and urinary Pb, Hg, As in men were

higher than those of women, while blood Cd and urinary Cd in men were lower than those of women. Further, the level of heavy metals in blood were higher than the corresponding ones in urinary.

Figure 1A & 2A also illustrate the Spearman rank correlation coefficients (r_s) between metal concentrations among men and women, respectively. Metals were weakly to highly correlated with each other, where r_s ranged -0.03 to 0.79 in men, and -0.02 to 0.66 in women, with blood Pb and urinary Pb having the highest correlation (r_s = 0.79 in men and 0.66 in women).

3.3 Multivariable linear regression analyses

Single metal linear regression analyses and multiple metals linear regression analyses were used to assess the associations between heavy metals and SUA/SCr (SUA). In general, blood Pb and urinary Cd were positively associated with SUA/SCr in both single and multivariate regression analysis, and urinary Pb was inversely associated with SUA/SCr only in multivariate analysis (Table 3). No associations between Hg (blood and urinary) and SUA/SCr were found in multivariate analysis. Similar results were also found in SUA (supplementary Table S1).

3.3.1 Associations between heavy metals and UA levels in single metal model

The single metal model showed that blood Pb (β = 0.454, P < 0.001), Hg (β = 0.140, P = 0.034), urinary Cd (β = 0.205, P = 0.001) and As (β = 0.159, P = 0.005) were positively associated with SUA/SCr level. While in sex-stratified analysis, urinary As (β = 0.278, P < 0.001) was positively associated with SUA/SCr levels only in men. Blood Pb and urinary Cd showed significantly positive associations with SUA/SCr levels both in men (blood Pb: β = 0.284, P = 0.034, urinary Cd: β = 0.159, P = 0.040) and in women (blood Pb: β = 0.470, P = 0.003, urinary Cd: β = 0.269, P = 0.004).

3.3.2 Associations between heavy metals and UA levels in multiple metals model

The multiple metals model showed that there were negative associations between SUA/SCr levels and blood Cd ($\beta_{overall}$ = -0.237, P = 0.022) and urinary Pb ($\beta_{overall}$ = -0.720, P <0.001; β_{men} = -0.462, P = 0.003; β_{women} = -0.838, P <0.001), whereas positive associations were found between SUA/SCr levels and blood Pb ($\beta_{overall}$ = 0.987; β_{men} = 0.651, P = 0.002; β_{women} = 1.014, P <0.001), urinary Cd ($\beta_{overall}$ = 0.461, P <0.001; β_{men} = 0.252, P = 0.027; β_{women} = 0.613, P <0.001) and urinary As ($\beta_{overall}$ = 0.206, P = 0.006; β_{men} = 0.351, P <0.001).

3.4 BKMR analyses

Firstly, we assessed the relative importance of metals, indicated by posterior inclusion probabilities (PIPs), an indicator for the importance of mixture components.

Urinary As was estimated to have the highest PIP (1.000), followed by blood Pb (0.926) and urinary Pb (0.868) in men, while blood Pb, urinary Cd and Pb were estimated to have the highest PIP (1.000) in women (Supplementary Table S2).

Secondly, we evaluated the association between all metals and UA levels, where the association was evaluated as the expected change in UA when values for all seven metals changed simultaneously from their median values to a particular quantile. As shown in Figure 1B and Supplementary Figure S3B, we found an increasing trend in the UA levels with the jointly increasing percentiles of all metals in men. Similar trend was found in women (Figure 2B & Supplementary Figure S4B).

Further, an exposure-response relationship of each metal with UA was also fitted respectively to assess the potential nonlinearity of the exposures, when the other metals were fixed at their 50^{th} percentile. Urinary Pb was inversely associated with SUA/SCr, whereas blood Pb and urinary Cd were positively associated with SUA/SCr both in men and women. Blood Cd showed inverse and urinary As showed positive associations with SUA/SCr levels in men, but not in women (Figure 1C & 2C).

Finally, the component-specific exposure-outcome relationships and potential exposure-exposure interactions were examined, where the UA changes were studied with a single metal increasing from the 25^{th} percentile to the 75^{th} percentile, when all the other metals were fixed at the 25^{th}, 50^{th}, and 75^{th} percentile. Blood Cd and urinary Pb showed significantly negative effects on SUA/SCr, whereas blood Pb, urinary Cd and As performed significantly negative effects in men (Figure 1D). Specifically, a change in blood Cd and Pb (blood Pb, urinary Cd and As) from their 25^{th} percentile to 75^{th} percentile was significantly associated with a decreased (increased) level of SUA/SCr, when the other six metals were set at the 25^{th}, 50^{th}, and 75^{th} percentiles, respectively. Similar trend was found in urinary Cd and As. In women (Figure 2D), urinary Pb showed a significantly negative effect on SUA/SCr, whereas blood Pb and urinary Cd displayed significantly negative effects. A change in urinary Pb (blood Pb, urinary Cd) from their 25^{th} percentile to 75^{th} percentile were significantly associated with a decreased (increased) level of SUA/SCr, when the other six metals were set at the 25^{th}, 50^{th}, and 75^{th} percentiles, respectively.

We further investigated the potential interactions between metals, and no interactions were identified, as indicated by the finding that all of the metals' confidence intervals encompassed zero (supplementary Figure S2). Moreover, similar results were also found in the associations between metals and SUA (supplementary Figure S3 and S4).

3.5 Sensitivity analyses

We further excluded 510 participants, whose urinary creatinine concentrations <30 mg/dL or >300 mg/dL, and found that the results were consistent with the analysis aforesaid (Figure S5 – S8).

4. Discussion

In this study, we evaluated the effects of individual and exposure to a mixture of Cd, Pb, Hg and As on UA. We found that the heavy metal mixtures were positively associated with UA levels, where blood Pb and urinary Cd were positively associated with SUA/SCr, while urinary Pb was inversely associated, and no associations between Hg (blood and urinary) and SUA/SCr were found. Further, there were potential

differences in the associations of urinary As by genders, where urinary As was positively associated with SUA/SCr only in men. Finally, similar results were also found in SUA levels.

UA may provide information on the effects of contaminants in the environment on the organism, as a serum biochemical parameter and a marker of oxidative status (Kovacik et al., 2019). On one hand, the oxidative stress was a sensitive endpoint for metal toxicity, which could produce and promote reactive oxygen species (ROS), including hydrogen or the radical peroxide, superoxide and nitric oxide, leading to cellular damage (Parris and Adeli, 2002) while UA can provide a secondary defense against ROS, as endogenous antioxidants (Sies, 1997). On the other hand, many enzymes may be involved in the process of oxidative stress, while they may be effected by different heavy metals, for example, Cd can affect the activity of superoxide dismutase, while Pb affects the function of various antioxidant enzymes (Abarikwu et al., 2017; Gupta, 2014; Kovacik et al., 2019). Thus persistent and comprehensive metal exposure may affect the antioxidant ability of blood (Kovacik et al., 2019), and the study of joint effects of metals are of great importance to understand the impact of correlated exposures that may act synergistically or antagonistically on health outcomes (Wang et al., 2020).

The exposure of Pb seems to be the strongest influencing factor both in SUA/SCr and SUA levels, and even in both gender in our study. Pb is an environmental pollutant with renal toxicity, and several studies have proposed that Pb adversely affects renal function such as tubular fibrosis, tubular atrophy and tubulointerstitial nephropathy through vascular system (Barbosa et al., 2005; Lai et al., 2008) However, abnormal changes in UA levels are often associated with adverse renal outcomes like renal tubulopathy, which further alters the toxic effects of purine metabolizing nucleoproteins, thus the effect of Pb on UA levels can also be explained by the nephrotoxic mechanism of Pb (Niamane et al., 2002; Weaver et al., 2005). A study showed that occupational exposure to Pb induced activity of xanthine oxidase activity and increased UA levels (Kasperczyk et al., 2013) Other studies reported the similar results: the concentration of blood Pb was independently and positively associated with UA levels, conversely to the associations between urinary Pb and UA (Dai et al., 2015, 2019; Krishnan et al., 2012; Sanders et al., 2019). However, the mechanism driving this different association is still unclear, and one of the possible reasons was that blood Pb and urinary Pb levels reflected recent and recent months of exposure respectively, and might have different metabolic and excretory toxicological characteristics, and UA levels might be more affected by recent Pb exposure (Barbosa et al., 2005)

Cd is also a nephrotoxic heavy metal, and the earliest sign of Cd induced renal damage is proteinuria (Atsdr, 2012; Nordberg et al., 2009; Roels et al., 1991). A primary mechanism for Cd toxicity was depletion of glutathione and alteration of sulfhydryl homeostasis, which indirectly increased oxidative stress (Valko et al., 2005; Yiin et al., 1999). Meanwhile, Cd induced renal proximal tubular injury, salt retention, and volume overload which might increase the level of UA (Varoni et al., 2003). Previous animal experiments established renal toxicity models and found that eGFR decreased after Cd administration, further leading to increased SUA levels (Valko et al., 2005; Yiin et al., 1999). In our study, urinary Cd was positively associated with SUA/SCr in both gender, while low exposure of blood Cd reduced SUA/SCr in men. One possible explanation for the inverse association that found only in men was the high exposure to Cd in cigarettes smoking, and that serum cotinine levels were much higher in men than in women in this study, while a cross-sectional

study of US adults showed a stronger association of blood Cd compared with urine Cd with serum cotinine (Tellez-Plaza et al., 2008). Moreover, the study noted that metallothionein was a low-molecular-weight metal-binding protein induced by Cd exposure that played an important role in Cd metabolism and toxicokinetic, and by binding Cd, metallothionein might protect the kidneys and other organs from the toxic effects of Cd (Nordberg et al., 1992; Tellez-Plaza et al., 2008). In addition, we did not find any significant association between Cd and SUA in men, either blood Cd or urinary Cd. Thus SUA/SCr ratio seemed to be more sensitive than SUA as a biomarker in understanding the association between UA and heavy metals.

Population studies on the effects of As and Hg exposures on UA are limited. Consistent with our study, Kuo CC et al. found a positive association between urinary As and men's SUA levels (Kuo et al., 2015). Sinha M et al. reported that oxidative stress is an important mechanism of As caused kidney damage (Sinha et al., 2008), and Saxena PN et al. also suggested that As exposure may lead to hyperuricemia secondary to renal dysfunction (Saxena et al., 2009). The mechanism of gender difference in the association between As and UA levels is still unclear, where sex hormones may be involved. An animal model study showed that As may reduce serum levels of testosterone by affecting the hypothalamic-pituitary-testicular axis in adult rats (Jana et al., 2006), and another study of 1,365 general adult men showed that higher UA levels were associated with lower total testosterone (Gao et al., 2017). Another animal study found that oral administration of mercuric chloride increased SUA levels in rabbits (Ali et al., 2019), and a cross-sectional study from the Korea National Health and Nutrition Examination Survey (KNHANES) showed that blood Hg level was positively associated with UA levels in women (Park and Kim, 2011). Thus the associations between As, Hg and UA still need further investigations.

Using a large, nationally representative database to assess individual and joint effects of exposure to heavy metals on UA is a major strength of the present study. Secondly, present study introduced SUA/SCr levels as a noval index into the study and revealed that there was a significant positive association between SUA/SCr levels and metal mixtures. Thirdly, given that diuretics and UA medications were important factor that it may affect the concentration of metals and also affect actual UA levels, we excluded the individuals who received these medications. In addition, limited epidemiological researches are available on the sex-specific associations between heavy metal exposures and UA levels, and we conducted the analyses stratified by gender which was helpful for us to recognize that different hormone regulation system might influence the metal association with UA levels. Finally, BKMR model was used to quantify and visualize the potential nonlinearities and non-additive effects of metal mixtures to UA.

However, its cross-sectional design meant that it was not possible to be considered as causality. In addition, the study relied on UA and metal concentrations assessment at a single time point. Finally, residual confounding or unmeasured confounding by environmental factors such as air pollution could be possible.

5. Conclusion

Exposures to a mixture of multiple heavy metals were positively correlated with UA, where blood Pb and urinary Cd were positively associated with SUA/SCr, and urinary Pb was inversely associated. Urinary As was positively associated with UA only in men, and no associations between Hg (either blood or urinary)

and SUA/SCr were found. These results provided new insights into the impact of environmental stressors on UA and highlighted the significance of using SUA/SCr levels (and not only SUA levels) to evaluate the effect of individual and the joint effects of Cd, Pb, Hg, and As and their mixture on UA. Further experimental as well as large prospective cohort studies are recommended to verify the observed relationship and to explore the underlying biological mechanisms of different heavy metals.

Declarations

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Author contribution

Wenhui Gao: Data curation, Conceptualization, Methodology, Software, Formal analysis, Validation, Writing - Original draft preparation, Writing - review & editing. **Li Tong:** Writing - Review & Editing, Investigation, Resources, Supervision. **Saisai Zhao:** Writing - Review & Editing, Resources, Data curation. **Lina Jin:** Writing - Review & Editing, Supervision, Conceptualization, Project administration.

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Availability of data and materials

The data that support the findings of this study are openly available in https://www.cdc.gov/nchs/nhanes/. Information from NHANES is made available through an extensive series of publications and articles in scientific and technical journals. For data users and researchers throughout the world, survey data are available on the internet and on easy-to-use CD-ROMs.

Ethics approval and consent to participate

All studies involving human participants were approved by the institutional review committee, and were performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All participants signed written informed consent, and the National Center for Health Statistics (NCHS) ethics review committee approved the study protocol.

Consent for publication

All the authors have reviewed and approved the manuscript for publication.

Competing interests

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

Contributor Information

Wenhui Gao, Email: gaowh20@mails.jlu.edu.cn;

Li Tong, Email: tongli20@mails.jlu.edu.cn;

Saisai Zhao, Email: sszhao20@mails.jlu.edu.cn;

Lina Jin, Email: jinln@jlu.edu.cn.

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Tables

Table 1. Characteristics of Participants in the NHANES 2007–2016, with age 20 years old and over by Gender (n(%)/median [P_{25}, P_{75}]).

Characteristics	Overall (n=4,794)	Men(n=2,452)	Women(n=2,342)	*P*
Age (years)	44(31, 57)	44(31, 56)	45(31, 58)	0.098
Race				0.057
Non-Hispanic White	2,091(67.2)	1,064(66.1)	1,027(68.2)	
Non-Hispanic Black	894(10.0)	478(9.6)	416(10.5)	
Mexican American	793(9.0)	403(9.9)	390(8.2)	
Other Hispanic and other race/multiracial	1,016(13.7)	507(14.4)	509(13.1)	
Educational level				0.002
Below high school	1,162(16.3)	614(17.6)	548(15.0)	
High school	1,078(22.5)	592(24.5)	486(20.6)	
Above high school	2,554(61.2)	1,246(57.9)	1,308(64.4)	
Ratio of family income to poverty (PIR)				0.681
≤1.30	1,494(21.5)	1,820(21.0)	1,480(21.9)	
1.31-3.50	1,820(35.8)	955(36.4)	865(35.3)	
≥3.51	1,48042.7)	759(42.6)	721(42.8)	
Cigarette smoking				<0.001
No	2,151(45.2)	1,295(50.9)	856(39.6)	
Yes	2,643(54.8)	1,157(49.1)	1,486(60.4)	
Alcohol drinking				<0.001
No	3,517(78.3)	2,053(86.5)	1,464(70.1)	
Yes	1,277(21.7)	399(13.5)	878(29.9)	
Fish eaten during the past 30 days				0.309
No	1,429(29.2)	754(30.2)	675(28.2)	
Yes	3,365(70.8)	1,698(69.8)	1,667(71.8)	
Hypertension				<0.001
No	3,173(70.2)	1,566(67.1)	1,607(73.3)	
Yes	1,621(29.8)	886(32.9)	735(26.7)	
Diabetes				0.026
No	4,101(89.2)	2,066(87.9)	2,035(90.6)	
Yes	693(10.8)	386(12.1)	307(9.4)	
Gout				0.007
No	4,668(98.1)	2,359(97.5)	2,309(98.8)	
Yes	126(1.9)	93(2.5)	33(1.2)	
Body mass index (BMI, kg/m^2)	27.32[24.06, 31.83]	27.57[24.65, 31.21]	26.98[23.41, 32.40]	0.074
Cotinine (ng/mL)	0.04[0.01, 11.3]	0.07[0.02, 72.09]	0.03[0.01, 0.61]	<0.001
eGFR (mL/min/1.73 m^2)	98.33[84.15, 111.90]	97.84[84.15, 110.12]	98.93[84.13, 113.42]	0.028
Serum uric acid (SUA, mg/dL)	5.30[4.40, 6.30]	6.00[5.20, 6.80]	4.60[3.80, 5.30]	<0.001
Serum creatinine (SCr, mg/dL)	0.83[0.72, 0.98]	0.95[0.85, 1.05]	0.72[0.64, 0.82]	<0.001
Serum uric acid to creatinine ratio (SUA/SCr)	6.22[5.27, 7.32]	6.25[5.39, 7.29]	6.17[5.17, 7.36]	0.162

Table 2. The lowest, 5th, 25th, 50th, 75th, 95th percentiles and highest values of Cd, Pb, Hg and As in blood and urinary in NHANES 2007-2016.

Metals	Above LOD (%)[a]	*Z*	*P*[b]	Percentiles						
				Lowest	5th	25th	50th	75th	95th	Highest
In whole blood, ug/L										
Cd		8.513	<0.001							
Men	80.46			0.07	0.11	0.17	0.28	0.55	1.50	6.88
Women	79.59			0.07	0.14	0.23	0.35	0.58	1.60	8.67
Pb		-12.687	<0.001							
Men	99.92			0.34	0.50	0.88	1.40	2.19	4.29	33.67
Women	99.95			0.22	0.36	0.62	0.95	1.49	2.91	23.60
Hg		-0.659	0.512							
Men	89.60			0.16	0.20	0.45	0.85	1.74	6.01	50.81
Women	89.24			0.18	0.20	0.45	0.84	1.56	4.36	24.30
In urine, ug/L										
Cd		2.632	0.011							
Men	92.65			0.03	0.04	0.11	0.22	0.43	1.12	5.15
Women	93.17			0.03	0.04	0.11	0.23	0.46	1.25	6.94
Pb		-7.259	<0.001							
Men	98.41			0.06	0.11	0.30	0.54	0.94	2.12	52.30
Women	96.50			0.05	0.08	0.22	0.40	0.70	1.55	49.60
Hg		-0.736	0.464							
Men	84.71			0.05	0.08	0.15	0.33	0.72	2.01	12.19
Women	83.69			0.04	0.06	0.13	0.32	0.71	2.37	54.25
As		-4.617	<0.001							
Men	98.98			0.88	1.72	4.19	8.47	18.03	71.96	822.60
Women	98.63			0.85	1.36	3.44	6.89	14.48	54.66	1269.00

[a] LOD, limits of detection.

[b] Mann–Whitney U test between the gender.

Table 3. Adjusted *β* [95% *CI*] from single metal linear regression models and multiple metals linear regression models of SUA/SCr level stratified by gender.

Metals	Overall (n=4,794)		Men(n=2,452)		Women(n=2,342)	
	β [95% *CI*]	*P*	*β* [95% *CI*]	*P*	*β* [95% *CI*]	*P*
Single metal linear regression models [a,b]						
log_e blood Cd (ug/L)	0.041 [-0.135, 0.218]	0.640	-0.069 [-0.301, 0.163]	0.554	0.272 [0.020, 0.524]	0.035
log_e blood Pb (ug/L)	0.454 [0.256, 0.652]	<0.001	0.284 [0.022, 0.545]	0.034	0.470 [0.163, 0.777]	0.003
log_e blood Hg (ug/L)	0.140 [0.011, 0.269]	0.034	0.138 [-0.008, 0.283]	0.063	0.169 [-0.011, 0.349]	0.066
log_e urinary Cd (ug/L)	0.205 [0.092, 0.319]	0.001	0.159 [0.008, 0.310]	0.040	0.269 [0.091, 0.447]	0.004
log_e urinary Pb (ug/L)	0.029 [-0.088, 0.147]	0.620	0.095 [-0.049, 0.239]	0.192	-0.086 [-0.278, 0.107]	0.377
log_e urinary Hg (ug/L)	0.057 [-0.032, 0.147]	0.207	0.062 [-0.066, 0.191]	0.336	0.059 [-0.094, 0.212]	0.443
log_e urinary As (ug/L)	0.159 [0.051, 0.268]	0.005	0.278 [0.152, 0.403]	<0.001	0.041 [-0.121, 0.204]	0.613
Multiple metals linear regression models [a,c]						
log_e blood Cd (ug/L)	-0.237 [-0.439, -0.035]	0.022	-0.258 [-0.542, 0.025]	0.073	-0.152 [-0.459, 0.154]	0.325
log_e blood Pb (ug/L)	0.987 [0.760, 1.213]	<0.001	0.651 [0.255, 1.047]	0.002	1.014 [0.627, 1.401]	<0.001
log_e blood Hg (ug/L)	0.003 [-0.146, 0.152]	0.971	-0.006 [-0.187, 0.174]	0.943	0.080 [-0.140, 0.300]	0.469
log_e urinary Cd (ug/L)	0.461 [0.262, 0.660]	<0.001	0.252 [0.030, 0.474]	0.027	0.613 [0.331, 0.894]	<0.001
log_e urinary Pb (ug/L)	-0.720 [-0.915, -0.525]	<0.001	-0.462 [-0.757, -0.167]	0.003	-0.838 [-1.170, -0.505]	<0.001
log_e urinary Hg (ug/L)	0.007 [-0.126, 0.139]	0.920	-0.048 [-0.218, 0.123]	0.579	0.032 [-0.174, 0.239]	0.756
log_e urinaryAs (ug/L)	0.206 [0.060,	0.006	0.351 [0.199,	<0.001	0.055	0.609

	0.351]	0.504]	[-0.159, 0.269]

β: partial regression coefficient; *CI*: confidence interval.

[a] Adjusted for age, race/ethnicity, education, PIR, smoking, drinking, serum cotinine, fish eaten during the past 30 days, BMI, eGFR, gout, diabetes, and hypertension. [b] Each metal predicts SUA/SCr outcome separately.

[c] All metals are included together in the same model.

Figures

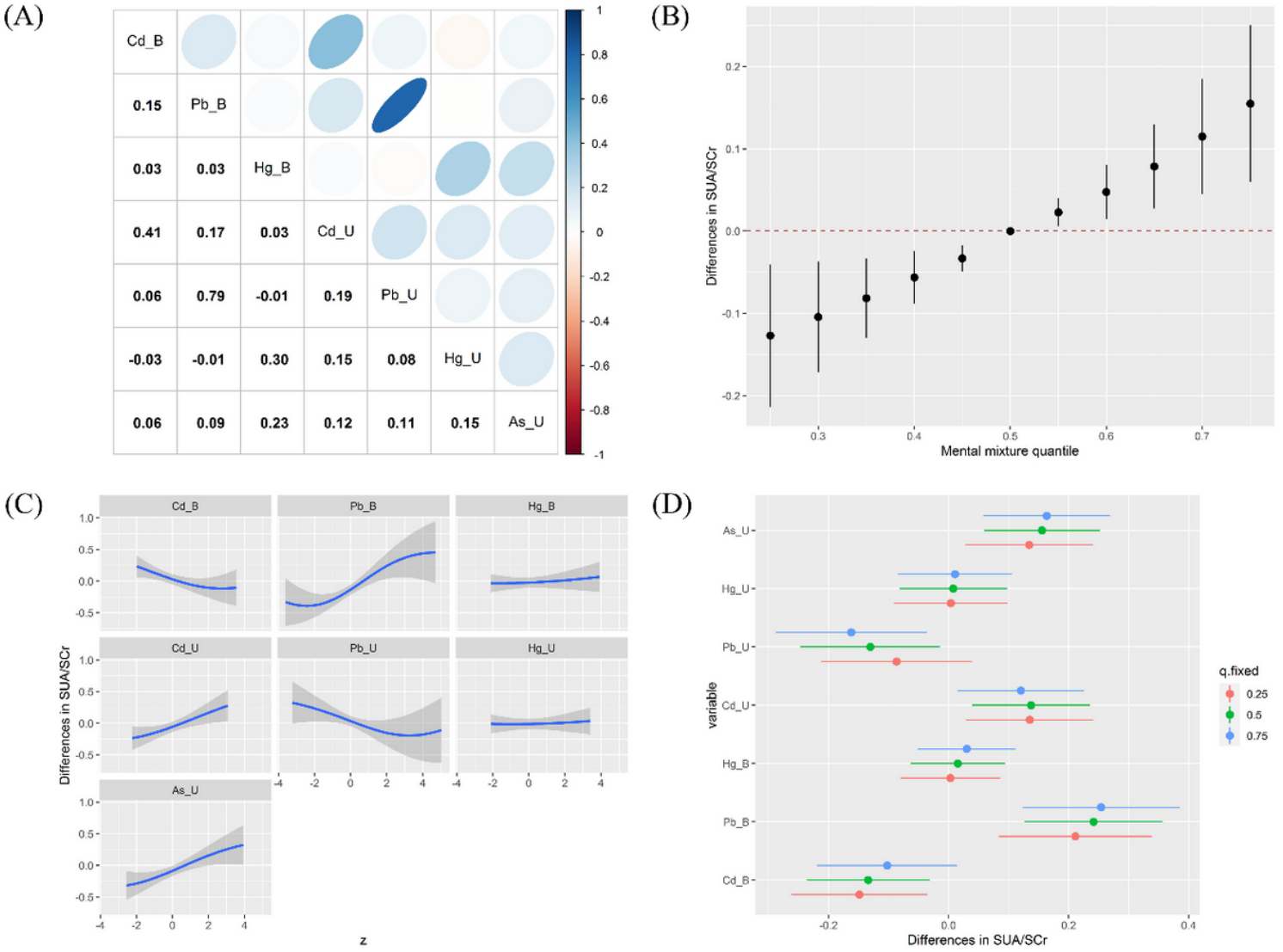

Figure 1

The BKMR analysis for the associations of SUA/SCr and multiple metals in men, where suffix "_U" indicates the metals in urinary and "_B" in blood. (A) Spearman's correlation matrix for metals; (B) Joint effects of exposure to a mixture of multiple heavy metals on SUA/SCr, comparing various percentiles of the mixture to the median (50th percentile); (C) Univariate exposure-response function and 95% confidence bands for each metal with the other metals fixed at the median; (D) Single metal effect on SUA/SCr comparing the upper

quartile to the lower quartile level of a particular metal while fixing the other metals at the 25th, 50th, and 75th percentile.

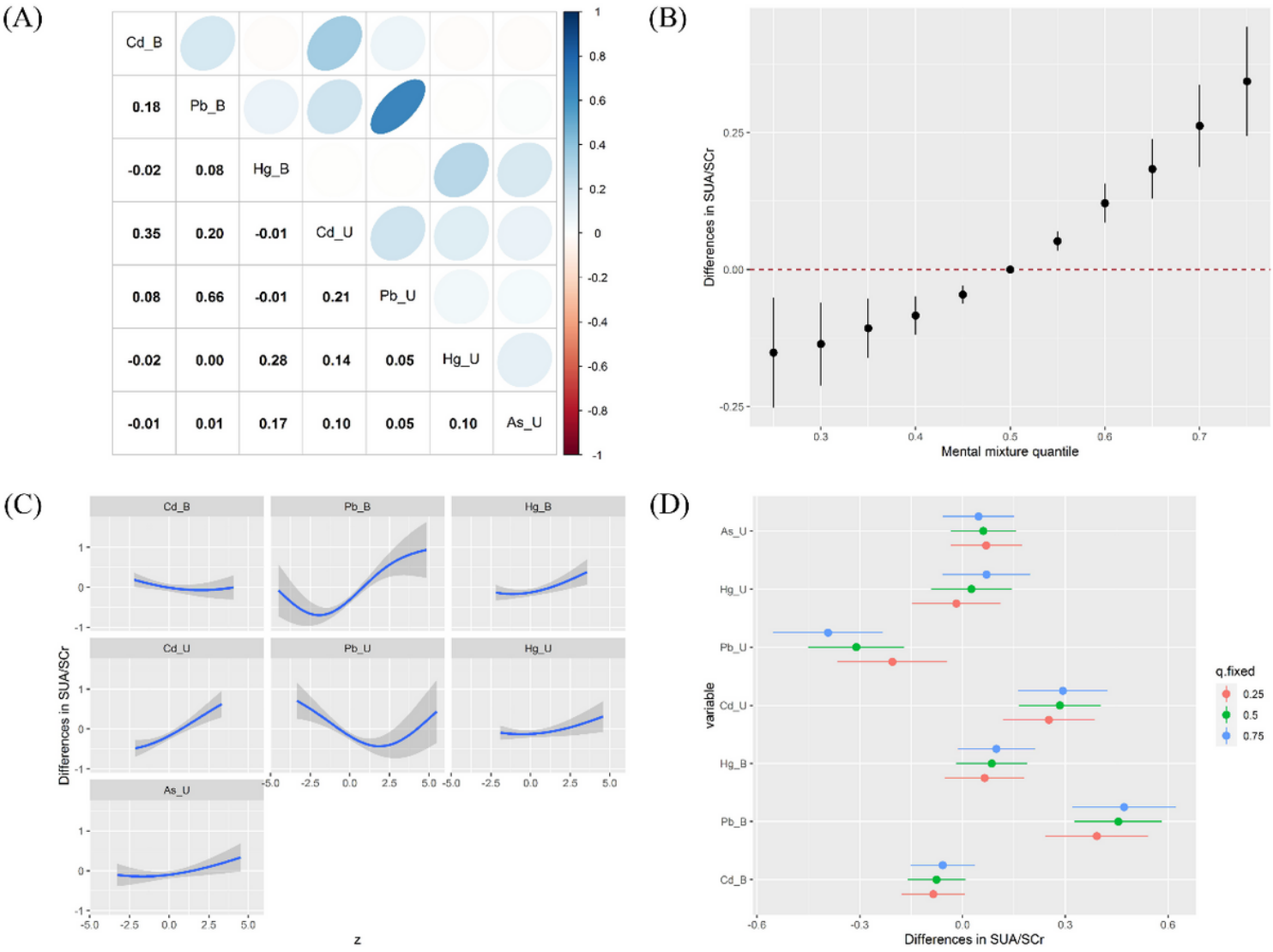

Figure 2

The BKMR analysis for the associations of SUA/SCr and multiple metals in women, where suffix "_U" indicates the metals in urinary and "_B" in blood. (A) Spearman's correlation matrix for metals; (B) Joint effects of exposure to a mixture of multiple heavy metals on SUA/SCr, comparing various percentiles of the mixture to the median (50th percentile); (C) Univariate exposure-response function and 95% confidence bands for each metal with the other metals fixed at the median; (D) Single metal effect on SUA/SCr comparing the upper quartile to the lower quartile level of a particular metal while fixing the other metals at the 25th, 50th, and 75th percentile.

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