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

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Abstract
Mechanisms underlying abnormal uric acid (UA) levels from exposure to toxic metals/metalloids have not been fully elucidated, especially in the context of mixtures. The aim was to identify major toxic metals/metalloids that affected UA levels with a mixture exposure concept in the association model. From 2007–2016 National Health and Nutrition Examination Survey (NHANES), 4794 adults were involved. Serum UA (SUA) and SUA to serum creatinine ratio (SUA/SCr) were used to estimate the UA levels, and cadmium (Cd), lead (Pb), mercury (Hg), and arsenic (As) in the blood and/or urine were evaluated in the study. We assessed the associations between toxic metals and UA levels using linear regression and Bayesian kernel machine regression (BKMR). 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 (\(\beta_{\text{men}}=0.651\) and \(\beta_{\text{women}}=1.014\)) and urinary Cd (\(\beta_{\text{men}}=0.252\) and \(\beta_{\text{women}}=0.613\)) were positively associated with SUA/SCr, and urinary Pb (\(\beta_{\text{men}}=-0.462\) and \(\beta_{\text{women}}=-0.838\)) was inversely associated with SUA/SCr in multivariate linear regression analysis. However, urinary As (\(\beta_{\text{men}}=0.351\)) was positively associated with SUA/SCr only in men. BKMR showed that higher concentrations of exposure to a mixture of toxic metals were 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. Our study provided the first evidence that mixtures of metals are associated with the UA levels. Increased concentrations of metals, mainly blood Pb, urinary Cd, and As (only in men) may increase the level of UA.

Keywords Bayesian kernel machine regression (BKMR) · Mixtures · Toxic metals/metalloids · Joint effects · Uric acid

Introduction
Uric acid (UA) is the final product of purine oxidation catabolism and is mainly excreted in the urine. Serum uric acid (SUA) is believed to be an essential indicator in evaluating kidney health and hyperuricemia [1–3] and is associated with cardiovascular mortality and all-cause mortality [4–7]. Increased SUA is believed as a biomarker of inflammatory cytokine activation, insulin resistance, and oxidative stress [8–10] and may be involved in the occurrence and
development of many diseases, such as gout, cancer, and neurological disorders [11–13]. Furthermore, the excretion of UA is highly dependent on renal function, and about 75% UA is excreted by the kidney daily [14, 15]. Thus, kidney plays an essential role in maintaining the homeostasis of UA and SUA [15]. Serum creatinine (SCr) is widely interpreted as a measure of renal function, and abnormal SCr is associated with an increasing risk of cardiovascular diseases [16, 17]. 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 [18–20], and SUA/SCr is reported to be associated with β cell function, metabolic syndrome, and chronic kidney disease [21, 22] and is a new indicator to predict metabolic disease and all-cause mortality [22, 23].

SUA, as an antioxidant, may be involved in the oxidative stress caused by toxic metal exposures [24], and multiple toxic metals/metalloids (hereafter, simply referred to as “metals”) have been widely detected in the environment in daily life, such as in ambient air, drinking water, food, medications, and consumer products [25]. Many studies have evaluated the associations between SUA and exposure to single metals, such as cadmium (Cd), lead (Pb), mercury (Hg), and arsenic (As) [26–30]. The Pb and Hg in blood were positively associated with SUA. In contrast, Cd in blood was inversely associated with SUA and the risk of hyperuricemia in women in a cross-sectional study in Korea [29]. Another study in eastern China found no association between blood Pb and SUA, but a significantly positive association between blood Cd and SUA and the risk of hyperuricemia in men [28]. 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 [26]. It was suggested that As might inhibit xanthine oxidase, resulting in a decrease in UA levels [30], 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 [27]. Thus, the relationship between exposure to single toxic metals and SUA is limited and conflicting.

Meanwhile, humans are exposed to a mixture of multiple toxic metals, occurring simultaneously and often with complex correlation structures and interactions [31, 32]. Thus, it is necessary to consider the impact of exposure to a mixture of toxic metals on UA, because the effect of single exposure was reported to be different from that in its mixture [33, 34], and multiple toxic metal exposure may exhibit synergistic or antagonistic effects on UA [31]. Furthermore, the joint effects of multiple toxic metals exposures on UA have never been assessed.

Hence, we aimed to evaluate the association between multiple nephrotoxic metals that are 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 toxic metal on SUA/SCr and SUA and (2) to evaluate the joint effects of exposure to a mixture of multiple toxic metals on SUA/SCr and SUA using Bayesian kernel machine regression (BKMR) models [35].

Materials and Methods

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 USA. 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 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 = 4044), considering that these drugs may be a bias to the study. Secondly, we excluded the participants with missing SUA (n = 2416) and SCr (n = 3) and those with missing values on exposures to toxic metals (n = 15,278) and significant covariates (including race, educational level, the 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 = 2666). Finally, 4794 participants (including 2452 men and 2342 women) were enrolled in our study (Fig. S1).

Measurement of Exposures

The measurements of all the exposures of interest (whole blood Cd, Pb, and Hg and spot urine Cd, Pb, Hg, and As) were tested by inductively coupled plasma-dynamic reaction mass spectrometry (ICP-DRC-MS) on an ELAN® 6100 DRC Plus or ELAN® DRC II (PerkinElmer Instruments, Headquarter Office, 710 Bridgeport Ave., Shelton, CT 06,484–4794) at the CDC’s National Center for Environmental Health. Values of concentrations below the limit of detection (LOD) were imputed values of LOD/√2. Detailed information on laboratory quality assurance and monitoring is available at https://www.cdc.gov/nchs/nhanes/index.htm.
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 using an isotope-dilution high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometric (ID HPLC-APCI MS/MS) method.

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/m²), natural log-transformed serum cotinine (ng/mL), and eGFR (calculated using the CKD-EPI equation, mL/min/1.73 m²).

Gout was defined as individuals with a self-reported physician-diagnosed gout. Diabetes was defined as individuals with a self-reported physician diagnosis, 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 a self-reported physician diagnosis, medication use, or blood pressure ≥140/90 mmHg.

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 [P25, P75] and compared by the Mann-Whitney U test. The categorical variables are presented as counts and percentages and compared by the 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 toxic metal exposures were initially natural log-transformed, and the association between metal exposures and SUA/SCr (SUA) was evaluated by linear regression models. Each metal was firstly considered as separated predictor in linear regression, and then all the seven multiple 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 [35]. We conducted several sensitivity analyses. First, the BKMR analyses were repeated by excluded 510 participants whose urinary creatinine concentrations were <30 mg/dL or >300 mg/dL [36] and found that the results were consistent with the main findings (Figs. S5–S8). Second, we repeated the analyses further, taking fish eaten during the past 30 days as a stratified variable, and found that the results were consistent across subgroups, and the association between total urinary As and SUA/SCr also stayed in the same direction across subgroups (Tables S3 and S4 and Figs. S9 and S10).

There is a significantly statistical difference between genders in SUA, SCr, and the majority of covariates; thus, all the following analyses were by genders. 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) [37].

Results

Characteristics of the Study Population

A total of 4794 participants with complete data were included in this study. The survey-weighted descriptive statistics are presented in Table 1. The median [P25, P75] age of the male and female was 44 [31, 56] and 45 [31, 58] years, respectively. Significant differences were observed in educational level, cigarette smoking, alcohol drinking, alcohol consumption, hypertension, diabetes, gout, cotinine, eGFR, SUA, and SCr between male and female (all P < 0.05). The male had higher level of BMI, cotinine, SUA, and SCr and were more likely to be a hypertensive, diabetic, and gout.

Distributions and Correlations for Multiple Toxic Metals

The lowest, 5th, 25th, 50th,75th, 95th percentiles, and highest values of blood Cd, Pb, Hg, and urinary Cd, Pb, Hg, and As for men and women are summarized in Table 2. There were significant statistical differences between genders in blood Cd, Pb, urinary Cd, Pb, and As,
but blood Pb, Hg, and urinary Pb, Hg, and As in men were higher than women. In contrast, blood Cd and urinary Cd in men were lower than those of women. Furthermore, the level of toxic metals in the blood was higher than the corresponding ones in the urinary.

Figures 1A and 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 from $-0.03$ 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).

**Multivariable Linear Regression Analyses**

Single metal linear regression analyses and multiple metal linear regression analyses were used to assess the associations between metals and SUA/SCr (SUA). Blood Pb and urinary Cd were positively associated with SUA/SCr in both single and multivariate regression analyses, 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).

**Associations Between 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. Furthermore, 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).

**Associations Between Metals and UA Levels in Multiple Metals Model**

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

**BKMR Analyses**

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

| Metals | Above LOD (%)<sup>a</sup> | Z<sup>b</sup> | Percentiles | Lowest | 5<sup>th</sup> | 25<sup>th</sup> | 50<sup>th</sup> | 75<sup>th</sup> | 95<sup>th</sup> | Highest |
|--------|--------------------------|-------------|-------------|---------|------------|------------|------------|------------|------------|---------|
| Cd     | 80.46                    | 8.513       | <0.001      | 0.07    | 0.11       | 0.17       | 0.28       | 0.55       | 1.50       | 6.88    |
| Pb     | 79.59                    | 12.687      | <0.001      | 0.34    | 0.50       | 0.88       | 1.40       | 2.19       | 4.29       | 33.67   |
| Hg     | 99.92                    | 0.659       | 0.512       | 0.16    | 0.20       | 0.45       | 0.85       | 1.74       | 6.01       | 50.81   |
| Total Hg | 89.60                  | 2.632       | 0.011       | 0.03    | 0.04       | 0.11       | 0.22       | 0.43       | 1.12       | 5.15    |
| As     | 93.17                    | 7.259       | <0.001      | 0.06    | 0.11       | 0.30       | 0.54       | 0.94       | 2.12       | 52.30   |
| Total As | 96.50                  | 0.736       | 0.464       | 0.05    | 0.08       | 0.22       | 0.40       | 0.70       | 1.55       | 49.60   |

<sup>a</sup> LOD limits of detection

<sup>b</sup> Mann-Whitney U test between the gender

| Metals | Above LOD (%)<sup>a</sup> | Z<sup>b</sup> | Percentiles | Lowest | 5<sup>th</sup> | 25<sup>th</sup> | 50<sup>th</sup> | 75<sup>th</sup> | 95<sup>th</sup> | Highest |
|--------|--------------------------|-------------|-------------|---------|------------|------------|------------|------------|------------|---------|
| Cd     | 80.46                    | 8.513       | <0.001      | 0.07    | 0.11       | 0.17       | 0.28       | 0.55       | 1.50       | 6.88    |
| Pb     | 79.59                    | 12.687      | <0.001      | 0.34    | 0.50       | 0.88       | 1.40       | 2.19       | 4.29       | 33.67   |
| Hg     | 99.92                    | 0.659       | 0.512       | 0.16    | 0.20       | 0.45       | 0.85       | 1.74       | 6.01       | 50.81   |
| Total Hg | 89.60                  | 2.632       | 0.011       | 0.03    | 0.04       | 0.11       | 0.22       | 0.43       | 1.12       | 5.15    |
| As     | 93.17                    | 7.259       | <0.001      | 0.06    | 0.11       | 0.30       | 0.54       | 0.94       | 2.12       | 52.30   |
| Total As | 96.50                  | 0.736       | 0.464       | 0.05    | 0.08       | 0.15       | 0.33       | 0.72       | 2.01       | 12.19   |

**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
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. The association was assessed 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 Fig. 1B and Supplementary Fig. S3B, we found an increasing trend in the UA levels with the jointly increasing percentiles of all metals in men. A similar trend was found in women (Fig. 2B and Supplementary Fig. S4B).

Furthermore, 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 50th 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 total urinary As showed positive associations with SUA/SCr levels in men, but not in women (Figs. 1C and 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 25th percentile to the 75th percentile when all the other metals were fixed at the 25th, 50th, and 75th percentile (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 quantile to the lower quantile level of a particular metal while fixing the other metals at the 25th, 50th, and 75th percentile.

Fig. 1 The BKMR analysis for the associations of SUA/SCr and multiple metals in men, where the 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 toxic metals on SUA/SCr, comparing various percentiles of the mixture to the median.
percentiles, respectively. A similar trend was found in urinary Cd and As. In women (Fig. 2D), urinary Pb showed a significantly adverse effect on SUA/SCr, whereas blood Pb and urinary Cd displayed significantly adverse effects. A change in urinary Pb (blood Pb, urinary Cd) from their 25th percentile to 75th percentile was significantly associated with a decreased (increased) level of SUA/SCr, when the other six metals were set at the 25th, 50th, and 75th 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 Fig. S2). Moreover, similar results were also found in the associations between metals and SUA (Supplementary Figs. S3 and S4).

**Discussion**

In this study, we evaluated the effects of individual exposure to a mixture of Cd, Pb, Hg, and As on UA. We found that the toxic metal mixtures were positively associated with UA levels, where blood Pb and urinary Cd were positively associated with SUA/SCr. In contrast, urinary Pb was inversely associated, and no associations between Hg (blood and urinary) and SUA/SCr were found. Furthermore, there were potential differences in the associations
of total urinary As by genders, where total 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 [24]. On the 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 [38], while UA can provide a secondary defense against ROS, as endogenous antioxidants [39]. On the other hand, many enzymes may be involved in the process of oxidative stress, while they may be affected by different toxic metals; for example, Cd can affect the activity of superoxide dismutase, while Pb adversely affects renal function such as tubular fibrosis, tubular atrophy, and tubulointerstitial nephropathy through the vascular system [43, 44]. 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 impact of Pb on UA levels can also be explained by the nephrotoxic mechanism of Pb [45, 46]. A study showed that occupational exposure to Pb induced xanthine oxidase activity and increased UA levels [47]. Other studies reported similar results: the concentration of blood Pb was independently and positively associated with UA levels, conversely to the associations between urinary Pb and UA [2, 26, 48, 49]. However, the mechanism driving this different association is still unclear. 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. UA levels might be more affected by recent Pb exposure [44].

Cd is also a nephrotoxic heavy metal, and the earliest sign of Cd-induced renal damage is proteinuria [50–52].
A primary mechanism for Cd toxicity was the depletion of glutathione and alteration of sulfhydryl homeostasis, which indirectly increased oxidative stress [53, 54]. Meanwhile, Cd-induced renal proximal tubular injury, salt retention, and volume overload might increase the level of UA [55]. Previous animal experiments established renal toxicity models and found that eGFR decreased after Cd administration, further increasing SUA levels [53, 54]. In our study, urinary Cd was positively associated with SUA/Scr in both genders, while low exposure to blood Cd reduced SUA/Scr in men. One possible explanation for the inverse association that was found only in men was the high exposure to Cd in cigarette smoking and that serum cotinine levels were much higher in men than in women in this study. In contrast, a cross-sectional survey of US adults showed a stronger association between blood Cd and urine Cd with serum cotinine [56]. 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 [56, 57]. 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.

Arsenic is a metalloid widely found in groundwater and in the food chain. Humans are exposed to different forms of arsenic, including inorganic and organic compounds [58]. In our study, it was not possible to determine the route of arsenic exposure or the species of arsenic that comprised the exposure because only a spot urine sample was collected for arsenic measurement. Consistent with our research, Kuo CC et al. found a positive association between urinary As and men’s SUA levels [27]. Sinha M et al. reported that oxidative stress is an essential mechanism of As caused kidney damage [59]. Saxena PN et al. also suggested that As exposure may lead to hyperuricemia secondary to renal dysfunction [60]. 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 [61], and another survey of 1365 general adult men showed that higher UA levels were associated with lower total testosterone [62]. However, organic arsenic and its species such as arsenobetaine and arsenocholine are considered less toxic; inorganic arsenic and its metabolites dimethylarsinate (DMA) and methylarsonate (MA) are highly toxic [58]. Unfortunately we could not evaluate the association between arsenic metabolism and uric acid as inorganic arsenic, MA and DMA, species that are essential to understand arsenic metabolism, had high LODs in NHANES [27].

Population studies on the effects of Hg exposures on UA are limited. An animal study found that oral administration of mercuric chloride increased SUA levels in rabbits [63], 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 [29]. Thus, the associations between Hg and UA still need further investigations.

Using an extensive, nationally representative database to assess individual and joint effects of exposure to toxic metals on UA is a major strength of the present study. Secondly, the present study introduced SUA/Scr levels as a novel index into the research and revealed that there was a significant positive association between SUA/Scr levels and metal mixtures. Thirdly, given that diuretics and UA medications were an essential factor that 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 toxic metals 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 impossible to be considered causality. More prospective studies are needed to validate our findings. Second, the study relied on UA and metal concentrations assessment at a single time point. Third, we did not detect the major sources and exposure routes of metals that are considered critical for toxicity of different metals. Fourth, we did not evaluate the effect of seafood-derived arsenicals (i.e., arsenobetaine) on total arsenic concentrations. Future studies need to further adjusted for arsenobetaine as an objective biomarker of seafood intake in order to evaluate the association for arsenic that is not derived from seafood. Finally, although many potential confounders were adjusted, residual confounding or unmeasured confounding by environmental factors such as air pollution could be possible.

**Conclusion**

Exposures to a mixture of multiple toxic metals were positively correlated with UA, where blood Pb and urinary Cd were positively associated with SUA/Scr, and urinary Pb was inversely associated. Total urinary As was positively associated with UA only in men. 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 and large prospective cohort studies are recommended to verify the observed relationship and to explore the underlying biological mechanisms of different toxic metals.

Supplementary Information  The online version contains supplementary material available at https://doi.org/10.1007/s12011-022-03309-0.

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Data Availability  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.

Declarations

Competing interests  The authors declare no competing interests.

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