Associations of co-exposure to metals with serum uric acid and hyperuricemia: A cross-sectional study

Shunli Jiang

   The First Affiliated Hospital of Shenzhen University

Shuang Zhou

   Huazhong University of Science and Technology

Huimin Liu

   Huazhong University of Science and Technology

Cheng Peng

   Huazhong University of Science and Technology

Xu Zhang

   Huazhong University of Science and Technology

Hao Zhou

   Huazhong University of Science and Technology

Zhihong Wang (✉ zhihongwangsz@126.com)

   The First Affiliated Hospital of Shenzhen University   https://orcid.org/0000-0001-9153-964X

Qing Lu

   Huazhong University of Science and Technology

Research

Abstract

While lead exposure is associated with hyperuricemia, there is scarce evidence about whether other metals are associated with serum uric acid (SUA) levels and hyperuricemia, and whether joint effects among metals existed. We conducted a cross-sectional study in 1950 eligible participants with 20 metals measured in urine. We used multivariable linear and logistic regression models to investigate the associations of metals exposure with SUA levels and hyperuricemia risk. We found that urinary vanadium and arsenic concentrations were associated with increased SUA levels in both sexes while urinary selenium concentrations were inversely associated with SUA levels in males. Each doubling of vanadium, arsenic, and selenium concentrations was associated with an adjusted odds ratio of 1.17 (95% CI: 1.03, 1.33), 1.22 (95% CI: 0.99, 1.50), and 0.67 (95% CI: 0.50, 0.88) for hyperuricemia in males, respectively. In addition, under the exposure of vanadium and arsenic, only if high selenium content existed, no significantly increased SUA levels and hyperuricemia risk in both sexes can be found. Vanadium and arsenic exposure were suggested to be associated with elevated SUA levels and hyperuricemia risk with sex difference while high selenium status might counteract their detrimental effects.

Introduction

Uric acid (UA) is the end product of purine metabolism in humans. UA has as powerful antioxidant properties as ascorbic acid and accounts for nearly half of the antioxidant capacity in plasma. However, it can as well be deleterious pro-oxidant, resulting in vascular smooth muscle cell proliferation and endothelial dysfunction [1]. Excessive UA production or reduced urate excretion leads to hyperuricemia and gout. In the last decade, the prevalence of hyperuricemia was 13% and 20% in China and America, respectively, with an increasing trend [2, 3]. Furthermore, hyperuricemia plays a crucial role in the development and prognosis of hypertension, hyperlipidemia, insulin resistance, and other cardiovascular diseases [4, 5]. Given the augmenting prevalence and severe complications, it is necessary to explore potential risk factors of hyperuricemia and seek solutions to reduce serum UA (SUA) levels.

Although the evidence was somewhat inconclusive, exposure to metals had been linked to hyperuricemia and gout [6–8]. The associations of lead exposure with hyperuricemia and gout have been well-documented in both the occupational exposure group and the general population [6, 7, 9–11]. In the context of lead exposure, due to the increased transformation of xanthine oxidoreductase to xanthine oxidase (XO), excessive hypoxanthine was catabolized to xanthine then to UA, resulting in elevated SUA content [12]. In addition, the nephrotoxicity of lead, such as reduced glomerular filtration rate, tubular atrophy and hyperplasia, was associated with increased tubular reabsorption and decreased excretion of urate [6, 13, 14]. Furthermore, chronic lead exposure might disrupt the renin-angiotensin system, neutralize endothelium-derived nitric oxide, and reduce the renal blood flow, predisposing individuals to an acquired urate excretion defect [6, 14].

The association of arsenic exposure with SUA levels is inconsistent. In some animal experiments, the administration of arsenic was associated with increased UA levels while others found opposite associations [15–18]. An intervention experiment in Korea shown that total arsenic concentrations, particularly dimethylarsinate, increased rapidly after short-term seafood consumption, but SUA levels were not changed [19]. However, in the National Health and Nutrition Examination Survey (NHANES) 2003–2010 dataset, urinary total arsenic and dimethylarsinate concentrations were found to be associated with increased SUA levels and the odds of hyperuricemia in male population [8].

Postulated essential elements might reduce the risk of having hyperuricemia. In a study using a semi-quantitative food frequency questionnaire to evaluate dietary magnesium intake, an inverse association of magnesium intake with the prevalence of hyperuricemia was suggested in the male population [20]. According to the dietary intake results of NHANES 2001–2014, dietary zinc intake was associated with reduced risk of hyperuricemia in both sexes [21].

Unexpectedly, although the myriad beneficial effects of selenium intake have received extensive attention, no epidemiological research concerning selenium with hyperuricemia or gout can be found in electronic databases.

In summary, we found that researches about metals exposure with SUA and hyperuricemia were scarce and inconclusive. Furthermore, epidemiological studies usually focused on a single metal, the nature of simultaneously exposed to multiple metals and the joint effects of metals were underappreciated [22]. Therefore, we conducted this cross-sectional study to explore the associations of multiple metals exposure with SUA levels as well as the odds of hyperuricemia in both sexes. Additionally, the joint effects of co-exposure to metals were evaluated.

Methods

Study design and participants

The study data were obtained from our ongoing observational study in Wuhan, which had been previously described in detail [22, 23]. We launched this study from 2016 in the physical examination center of Wuhan Union Hospital with the purpose of investigating the potential adverse effects of environmental contaminants on human health. At the beginning of this study, we excluded individuals with cardiovascular diseases (e.g., coronary heart disease, myocardial infarction, heart failure), stroke, diabetes, renal failure, hyperthyroidism, hypothyroidism, and cancers. Until the end of 2018, a total of 2285 participants were enrolled. After excluding individuals without data on SUA (n = 181), without sufficient urine volume for metals determination (n = 107), and without complete information on covariates (n = 47), 1950 (85.34%) participants were included in the subsequent analysis. All participants provided written informed consent. The study was approved by the Ethics and Human Subject Committee of Tongji Medical College, Huazhong University of Science and Technology.

Urine sample collection and metals determination

After a detailed explanation and demonstration, single morning midstream urine samples > 20 mL were collected from each participant. All the urine samples were gathered between 09:00 a.m. and 11:00 a.m. to reduce diurnal variability.

Urinary concentrations of 20 metals (aluminum, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, arsenic, selenium, rubidium, strontium, cadmium, cesium, barium, mercury, thallium, lead, and uranium) were measured on an inductively coupled plasma mass spectrometer (Agilent 7700X, Agilent Technologies Inc., USA), according to the previously described protocol [22, 24]. Briefly, an aliquot of 500 μL of urine supernatant was acidified with the pure nitric acid solution overnight. After that, samples were equilibrated to room temperature then diluted to 5.0 mL. The resulting samples were under ultrasound for 30 min before being injected into the instrument for analysis. A series of quality control methods were performed to guarantee the validity of our data as follows. Standard reference material (SRM) 2670a (Toxic Elements in Urine) was applied to confirm the accuracy of our method by comparing the measured concentrations with the certified values and the reference values [22]. Furthermore, tuning solution, reagent blanks, procedural blanks, SRM 1640 (Trace Elements in Natural Water), and spiked urine samples were utilized to assess instrument daily performance, potential laboratory contaminants, and the real-time precision of the method. The spiked recovery rates for these metals ranged from 90.00–110.00%, except for mercury (83.64%) and chromium (87.87%). The limits of detection (LOD) for these metals ranged from 0.003 μg/L to 0.267 ug/L. The detection rates (> LOD) for all metals were > 98%, and a value of LOD/√2 was assigned to samples with urinary metal concentrations below LOD.

Urine creatinine concentrations were analyzed to adjust for urine dilution on an automatic biochemical analyzer (Mindray BS200, Mindray Medical International Co., Ltd., China). Urinary metal concentrations were expressed as μg/g

creatinine (μg/g Cr) in the primary analyses and results.

SUA measurement and hyperuricemia definition

SUA levels were measured on a Beckman Chemistry Analyzer (AU5831, Beckman Coulter Inc., USA) using a UA kit (Kyowa Medex Co., Ltd., Shanghai, China), according to the uricase method. The intra-assay and inter-assay coefficients of variation both were less than 3.00%. Individuals were diagnosed as having hyperuricemia if their SUA levels were ≥ 416 μmol/L (7 mg/dL) for males and ≥ 357 μmol/L (6 mg/dL) for females, a self-reported physician diagnosis, or using allopurinol medications [25].

Covariate data collection

Data on sociodemographic variables (e.g., age, sex, education, income), smoking status, alcohol consumption, health history, medication use, and exercise frequency were collected by a well-trained investigator in a face-to-face interview, using a semi-structured questionnaire. Height, weight, and blood pressure levels were measured on calibrated and validated devices by qualified medical personnel. Participants' biochemical data such as cholesterol, serum creatinine were obtained from the physical examination reports. Body mass index (BMI, kg/m^2) and the estimated glomerular filtration rate (eGFR, calculated by CKD-EPI equation) were calculated, hyperlipidemia and hypertension status were defined accordingly [26−28].

Statistical analysis

Statistical analysis was conducted separately for males and females, considering the significant difference in their SUA levels. General characteristics among participants were presented as numbers (percentage) for categorical variables, mean ± standard deviation for normally distributed variables, and median (interquartile range) for non-normally distributed variables. Differences in these variables were calculated by Student's *t*-test, Mann-Whitney *U* test, and chi-square test, according to variable types and distributions.

The associations of urinary metals concentrations with the difference in SUA levels and the risk of having hyperuricemia were estimated by the multivariable linear and logistic regression model, respectively. Urinary metals concentrations were right-skewed while log2 transformed values fit the normal distribution. Thus, log2 transformed values were applied in the models. Many biological matrixes such as urine, plasma, and whole blood have been used to appraise different metals' exposure levels. For example, urine has been proposed as the best matrix for representing the long term exposure levels of arsenic and cadmium while whole blood is an appropriate matrix for characterizing iron exposure [29, 30]. Compared with other biological matrixes, noninvasive urine samples are easy-to-access thus used more frequently in large-scale epidemiological studies. However, due to the variability of urinary metals, a single urine sample might lead to exposure misclassification [31]. Considering these aspects, we selected urinary vanadium, cobalt, arsenic, and selenium in the primary analyses according to our laboratory's previous experiments and the two principles: a) metals' concentrations in urine have significant correlations ($p_{correlation}$ < 0.05) with those in whole blood and plasma; b) fair to good reproducibility (intra-class correlation coefficient > 0.40) in repeated urine samples (Supplementary Table S1) [30, 32]. Statistical results about the rest of 16 metals were represented in Supplementary Materials.

A variable was considered in the model if it caused at least a 10% change of the estimated exposure-effect [odds ratio (OR) or regression coefficient] or had biological relevance with the outcome [33]. Diuretics and seafood intake are linked with the development of hyperuricemia; thus we designed questions to collect relevant information. However, participants only could provide one or two names of the drugs that they were using. Besides, as a typical inland area (Wuhan, the capital city of Hubei province in central China), participants in our study reported a very low frequency and irregular intake of seafood, which could not be accurately classified and quantified. Hence, the two factors were not

included in the final models. Among female adults, only 10 (1.1%) had a history of smoking. Among females with alcohol consumption, 69 were current-drinker, and only 2 were former-drinker. Therefore, when we explored the associations in females, smoking status and pack-years of smoking were not included, and drinking status was dichotomized into non-drinker and drinker (current and former drinker) in the model.

We concurrently added the four metals in the model to simulate the co-exposure situation. Variance inflation factor was applied to check for multicollinearity [34]. The maximum variance inflation factor was less than 2, indicating no significant multicollinearity. The subset of metals (vanadium, arsenic, and selenium) which was significantly associated with the outcomes in the co-exposure model underwent further investigation. According to the median value of each metal, we divided our participants into high exposure and low exposure group. After that, we evaluated the joint effects of each two metals by examining a four-category variable (low/low, low/high, high/low and high/high group) in the adjusted model.

We performed a series of sensitivity analyses to test the robustness of our results. First, we repeated our primary analyses after excluding urine samples with extreme creatinine values (creatinine < 0.3 g/L, or > 3.0 g/L) [35]. Second, considering the debatable effectiveness of creatinine adjustment, we applied urine specific gravity to correct urinary metal concentrations [36]. Third, elder participants (age $\geq$ 80) and those with severe obesity (BMI $\geq$ 30 kg/m^2) were susceptible to environmental pollutants and prone to have underlying diseases. Thus, they were individually excluded. Fourth, hypertension, hyperlipidemia, and renal function are risk factors for hyperuricemia; they might enhance metals' effects on hyperuricemia [37]. Besides, diuretics, β-blockers, angiotensin-converting enzyme inhibitors, and non-losartan angiotensin II antagonists inhibited urate excretion while calcium-channel blockers and losartan had uricosuric effects [37]. Therefore, participants with hypertension (no matter using antihypertensive drugs or not), hyperlipidemia, or low eGFR (< 90 mL/min/1.73 m^2) were separately excluded from our analyses. Fifth, Maesaka et al. indicated that individuals with SUA below 2 mg/dL might be ascribed to genetic or acquired maladjustments [38]. Consequently, they were also excluded. Besides, in order to exclude lead exposure's effect on the association between other metals and outcomes, we further adjusted lead concentrations in the models.

We performed all these statistical analyses on the Statistical Package for the Social Sciences (SPSS), version 22.0 (IBM SPSS Institute, Inc., New York, USA). A two-tailed p-value < 0.05 was regarded as statistically significant.

Results

Characteristics of the study population

Table 1 shows that male participants in the study were younger than females, and they were prone to have high BMI, high SUA, and low eGFR levels. The prevalence of hyperlipidemia, hypertension, and hyperuricemia in males was significantly higher than that in females (all $p < 0.001$). A total of 421 (21.6%) participants were diagnosed as hyperuricemia, and 72.9% of them were male adults. Participants with hyperuricemia had high BMI and low eGFR levels; they were predisposed to be smokers and drinkers; they were more likely to have hyperlipidemia and hypertension (all $p < 0.001$). Urinary vanadium, cobalt, arsenic, and selenium concentrations in females were significantly higher than those in males (all $p < 0.001$). Participants with hyperuricemia had significantly lower urinary cobalt and selenium concentrations (both $p < 0.001$).

Table 1
General characteristics and urinary metal concentrations among the study population (N = 1950).a

Variable	Total population (N = 1950)	Sex characteristic			Disease characteristic		
		Male (N = 1043)	Female (N = 907)	p-value[b]	Non-yperuricemia (N = 1529)	Hyperuricemia (N = 421)	p-value[b]
Sex, male, N (%)	1043 (53.5)	1043 (100.0)	0 (0.00)	-	736 (48.1)	307 (72.9)	< 0.001
Age, year	53 ± 10	52 ± 9	59 ± 10	< 0.001	53 ± 10	53 ± 11	0.923
BMI, kg/m^2	23.5 ± 2.9	24.2 ± 2.8	22.7 ± 2.8	< 0.001	23.1 ± 2.8	25.0 ± 2.9	< 0.001
Smoking status, N (%)							
Non-smoker	1495 (76.7)	598 (57.3)	897 (98.9)		1218 (79.7)	277 (65.8)	
Current smoker	344 (17.6)	334 (32.0)	10 (1.1)	< 0.001	226 (14.8)	118 (28.0)	< 0.001
Former smoker	111 (5.7)	111 (10.7)	0 (0.0)		85 (5.6)	26 (6.2)	
Drinking status, N (%)							
Non-drinker	1276 (65.4)	440 (42.2)	836 (92.2)		1045 (69.0)	221 (52.5)	
Current drinker	635 (32.6)	566 (54.3)	69 (7.6)	< 0.001	439 (28.7)	196 (46.5)	< 0.001
Former drinker	39 (2.0)	37 (3.5)	2 (0.2)		35 (2.3)	4 (1.0)	
Pack-years of smoking	4.9 ± 11.7	9.1 ± 14.7	0.1 ± 1.4	< 0.001	4.4 ± 11.3	6.8 ± 13.0	< 0.001
Exercise, N (%)							
< 1 time/week	643 (33.0)	321 (30.8)	322 (35.5)		507 (33.2)	136 (32.3)	
1−3 times/week	565 (29.0)	306 (29.3)	259 (28.6)	0.068	443 (29.0)	122 (29.0)	0.934
> 3 times/week	742 (38.0)	416 (39.9)	326 (35.9)		579 (37.8)	163 (38.7)	
Education, N (%)							
< high school	221 (11.3)	122 (11.7)	99 (10.9)		171 (11.2)	50 (11.9)	
high school	370 (19.0)	208 (19.9)	162 (17.9)	0.379	303 (19.8)	67 (15.9)	0.194
> high school	1359 (69.7)	713 (68.4)	646 (71.2)		1055 (69.0)	304 (72.2)	

Variable	Total population (N = 1950)	Sex characteristic			Disease characteristic		
		Male (N = 1043)	Female (N = 907)	p-value[b]	Non-yperuricemia (N = 1529)	Hyperuricemia (N = 421)	p-value[b]
Income, RMB, yuan/month, N (%)							
< 5000	673 (34.5)	322 (30.9)	351 (38.7)		541 (35.4)	132 (31.3)	
5000–10000	970 (49.7)	553 (53.0)	417 (46.0)	0.001	752 (49.2)	218 (51.8)	0.297
>10000	307 (15.7)	168 (16.1)	139 (15.3)		236 (15.4)	71 (16.9)	
eGFR, mL/min/1.73 m^2	95.2 ± 13.7	92.4 ± 13.8	98.5 ± 12.8	< 0.001	96.5 ± 12.47	90.3 ± 16.5	< 0.001
eGFR < 90, N (%)	576 (29.5)	377 (36.1)	199 (21.9)	< 0.001	391 (25.6)	185 (43.9)	< 0.001
Hyperlipidemia, N (%)	403 (20.7)	242 (23.2)	161 (17.8)	0.003	252 (16.5)	151 (35.9)	< 0.001
Hypertension, N (%)	451 (23.1)	309 (29.6)	142 (15.7)	< 0.001	310 (20.3)	141 (33.5)	< 0.001
Uric acid, μmol/L	334 ± 88	378 ± 83	284 ± 64	< 0.001	301 ± 59	456 ± 66	< 0.001
Hyperuricemia, N (%)	421 (21.6)	307 (29.4)	114 (12.6)	< 0.001	0 (0.0)	421 (100.0)	-
Metals concentrations, μg/g creatinine							
V (vanadium)	1.1 (0.4, 2.2)	1.0 (0.4, 1.9)	1.3 (0.5, 2.5)	< 0.001	1.1 (0.4, 2.2)	1.2 (0.4, 2.2)	0.788
Co (cobalt)	0.2 (0.1, 0.4)	0.2 (0.10, 0.2)	0.3 (0.2, 0.5)	< 0.001	0.2 (0.1, 0.4)	0.2 (0.1, 0.3)	< 0.001
As (arsenic)	23.4 (16.4, 34.1)	22.4 (15.8, 31.5)	25.1 (16.9, 36.5)	< 0.001	23.7 (16.4, 34.2)	22.8 (16.7, 32.9)	0.672
Se (selenium)	19.4 (14.2, 26.2)	17.8 (13.5, 22.9)	21.4 (15.5, 29.8)	< 0.001	19.7 (14.4, 26.7)	18.1 (13.5, 23.0)	< 0.001

[a] Continuous variables were presented as mean ± standard deviation or median (interquartile range), according to its distribution; categorical variables were presented as numbers (percentage). Data were complete for all variables, except for 10 missing information about hyperlipidemia.

[b] p-values were calculated by Student's t-test, Mann-Whitney U test, or chi-square test for different variables according to its type and distribution.

Metals exposure and SUA levels

High urinary vanadium concentrations were associated with elevated SUA levels in the total population and both sexes, after adjustment for potential confounders (model 1) and other three metals (model 2) (Table 2). In model 2, doubling of urinary vanadium concentrations was associated with a 4.76 μmol/L [95% confidence interval (CI): 0.84, 8.68] and 3.01 μmol/L (95% CI: − 0.04, 6.05) increased SUA levels in males and females, respectively. No significant association of cobalt with SUA could be found in the total population and both sexes. In both sexes, arsenic was positively associated with SUA levels. The adjusted increase in SUA levels with a doubling of urinary arsenic concentrations was 8.00 μmol/L (95% CI: 1.60, 14.39) in males and 4.85 μmol/L (95% CI: 0.23, 9.47) in females. In addition, selenium in model 2 was associated with a 5.12 μmol/L (95% CI:0.52, 9.73) and 14.07 μmol/L (95% CI: 5.43, 22.70) decreased SUA levels in the total and male population.

Table 2

The difference [95% confidence interval (CI)] in serum uric acid levels (mol/L) with a 2-fold increase in urinary metals.

μ						
Metals	Total		Male		Female[c]	
	Coefficient (95% CI)	*p*-value	Coefficient (95% CI)	*p*-value	Coefficient (95% CI)	*p*-value
V						
Model 1[a]	**4.07 (1.78, 6.36)**	**0.001**	**4.09 (0.54, 7.64)**	**0.024**	**3.45 (0.61, 6.28)**	**0.017**
Model 2[b]	**4.23 (1.75, 6.72)**	**0.001**	**4.76 (0.84, 8.68)**	**0.017**	3.01 (−0.04, 6.05)	0.053
Co						
Model 1	−0.85 (−3.39, 1.69)	0.513	0.48 (−3.78, 4.75)	0.824	−0.44 (−3.49, 2.62)	0.780
Model 2	−2.04 (−4.70, 0.61)	0.131	−0.01 (−4.64, 4.62)	0.997	−1.49 (−4.64, 1.66)	0.354
As						
Model 1	**5.29 (1.77, 8.80)**	**0.003**	5.48 (−0.06, 11.03)	0.053	**5.47 (1.23, 9.71)**	**0.012**
Model 2	**5.54 (1.63, 9.45)**	**0.006**	**8.00 (1.60, 14.39)**	**0.014**	**4.85 (0.23, 9.47)**	**0.040**
Se						
Model 1	−1.13 (−5.27, 3.01)	0.593	−5.79 (−13.09, 1.51)	0.120	1.26 (−3.34, 5.87)	0.590
Model 2	**−5.12 (−9.73, −0.52)**	**0.029**	**−14.07 (−22.70, −5.43)**	**0.001**	−1.29 (−6.26, 3.68)	0.611

Abbreviations: V, vanadium; Co, cobalt; As, arsenic; Se, selenium.

[a] Model 1 adjusted age, sex, BMI, smoking status, pack-years of smoking, alcohol consumption, exercise frequency, education attainment, income level, eGFR, hyperlipidemia, and hypertension. Model 1 for males and females did not adjust sex.

[b] Model 2 adjusted all covariates in model 1 and other metals levels. Model 2 for males and females did not adjust sex.

[c] Model 1 and 2 for females did not adjust smoking status and pack-years of smoking owing to the few numbers of smokers, and alcohol consumption was dichotomized into non-drinker and drinker (current and former drinker) in the models.

We found positive associations of aluminum, manganese, barium, and uranium with SUA levels in males, and zinc with SUA levels in females (Supplementary Table S3). Intriguingly, doubling of urinary strontium concentrations was associated with a 5.87 μmol/L (95% CI:1.20, 10.53) decreased SUA levels in males, whereas it was associated with a 4.46 μmol/L (95% CI:0.24, 8.69) increased SUA levels in females. A borderline significant association of urinary lead concentrations with elevated SUA levels (2.13, 95% CI: − 0.04, 4.30) was observed in the total population.

Metals exposure and hyperuricemia risk

The associations of the four metals with hyperuricemia risk were similar to them with SUA levels, but with some differences (Table 3). In model 2, doubling of urinary vanadium concentrations was associated with a 1.14-fold (95% CI: 1.03, 1.26) and 1.17-fold (95% CI: 1.03, 1.33) increased risk of having hyperuricemia in the total and male population, respectively. Urinary cobalt concentrations had no significant association with hyperuricemia risk. Urinary arsenic concentrations were suggested to be associated with increased risk of hyperuricemia in the total (OR = 1.15, 95% CI: 0.98, 1.34) and male population (OR = 1.22, 95% CI: 0.99, 1.50). As for selenium, we found a significantly reduced risk of having hyperuricemia (OR = 0.67, 95% CI: 0.50, 0.88) in the male population. Besides, positive associations of aluminum, manganese, and uranium exposure with the odds of hyperuricemia in the total and male population were found. Significant associations of urinary barium and lead concentrations with hyperuricemia risk in the male population also were suggested (Supplementary Table S4).

Table 3
Odds ratios [95% confidence interval (CI)] for hyperuricemia with a 2-fold increase in urinary metals.

Metals	Total		Male		Female[c]	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
V						
Model 1[a]	**1.14 (1.04, 1.25)**	**0.007**	**1.16 (1.03, 1.30)**	**0.011**	1.10 (0.93, 1.29)	0.269
Model 2[b]	**1.14 (1.03, 1.26)**	**0.009**	**1.17 (1.03, 1.33)**	**0.013**	1.08 (0.90, 1.29)	0.398
Co						
Model 1	0.999(0.90, 1.11)	0.987	1.08 (0.95, 1.23)	0.255	0.95 (0.80, 1.12)	0.525
Model 2	0.97 (0.87, 1.08)	0.539	1.07 (0.93, 1.23)	0.352	0.92 (0.77, 1.09)	0.330
As						
Model 1	**1.15 (1.001, 1.33)**	**0.049**	1.17 (0.98, 1.39)	0.083	1.16 (0.91, 1.48)	0.228
Model 2	1.15 (0.98, 1.35)	0.077	1.22 (0.99, 1.50)	0.053	1.13 (0.86, 1.48)	0.377
Se						
Model 1	0.97 (0.82, 1.15)	0.735	0.87 (0.69, 1.10)	0.259	1.09 (0.83, 1.42)	0.546
Model 2	0.85 (0.71, 1.03)	0.104	**0.67 (0.50, 0.88)**	**0.004**	1.03 (0.77, 1.38)	0.829

Abbreviations: V, vanadium; Co, cobalt; As, arsenic; Se, selenium.

[a] Model 1 adjusted age, sex, BMI, smoking status, pack-years of smoking, alcohol consumption, exercise frequency, education attainment, income level, eGFR, hyperlipidemia, and hypertension. Model 1 for males and females did not adjust sex.

[b] Model 2 adjusted all covariates in model 1 and other metals levels. Model 2 for males and females did not adjust sex.

[c] Model 1 and 2 for females did not adjust smoking status and pack-years of smoking owing to the few numbers of smokers, and alcohol consumption was dichotomized into non-drinker and drinker (current and former drinker) in the models.

Metals interaction analysis

We explored the joint effects of each two metals in a four-category model with the low/low exposure group as the reference (Tables 4 and 5). High vanadium exposure was associated with increased SUA levels in the female population, no matter arsenic concentrations were high or low. Compared with the low vanadium and low selenium group in females, although no significant joint effect was found, SUA levels increased by 16.36 μmol/L (95% CI:3.44, 29.27) in the high vanadium and low selenium group, while no significant increase can be found in the high vanadium and high selenium group (8.32 μmol/L, 95% CI: − 1.72, 18.35). Furthermore, despite the 95% CI contained the null reference value, we found reduced effect of arsenic on SUA when selenium levels were high. Similar situations existed in the associations of metals exposure with the odds of hyperuricemia. However, the effect of vanadium exposure on hyperuricemia was more pronounced in males, no matter under high or low arsenic exposure levels.

Table 4

The difference [95% confidence interval (CI)] in serum uric acid levels (mol/L) with the combined categories of urinary metals.a

μ									
Metals[b]	Total			Male			Female		
	Coefficient (95% CI)	p_{value}	p_{int}[c]	Coefficient (95% CI)	p_{value}	p_{int}	Coefficient (95% CI)	p_{value}	p_{int}
V + As									
L (V) + L (As)	1.00 (Reference)	-		1.00 (Reference)	-		1.00 (Reference)	-	
L (V) + H (As)	1.58 (−7.44, 10.61)	0.731	0.844	−1.16 (−14.78, 12.47)	0.867	0.756	6.67 (−4.81, 18.14)	0.254	0.395
H (V) + L (As)	**11.58 (2.32, 20.84)**	**0.014**		9.05 (−4.72, 22.81)	0.198		**12.56 (0.58, 24.53)**	**0.040**	
H (V) + H (As)	**11.89 (3.87, 19.92)**	**0.004**		10.95 (−1.26, 23.15)	0.079		**12.33 (2.16, 22.50)**	**0.018**	
V + Se									
L (V) + L (Se)	1.00 (Reference)	-		1.00 (Reference)	-		1.00 (Reference)	-	
L (V) + H (Se)	−4.32 (−13.53, 4.88)	0.357	0.981	−9.57 (−23.68, 4.55)	0.184	0.447	1.94 (−9.59, 13.47)	0.741	0.239
H (V) + L (Se)	**12.66 (3.30, 22.01)**	**0.008**		9.04 (−4.25, 22.34)	0.182		**16.36 (3.44, 29.27)**	**0.013**	
H (V) + H (Se)	**8.17 (0.30, 16.05)**	**0.042**		7.07 (−4.96, 19.09)	0.249		8.32 (−1.72, 18.35)	0.104	
As + Se									
L (As) + L (Se)	1.00 (Reference)	-		1.00 (Reference)	-		1.00 (Reference)	-	
L (As) + H (Se)	−1.72 (−10.86, 7.43)	0.713	0.975	−4.85 (−18.78, 9.07)	0.494	0.752	1.67 (−9.91, 13.24)	0.778	0.492
H (As) + L (Se)	4.15 (−4.96, 13.26)	0.371		2.48 (−10.66, 15.61)	0.711		8.68 (−3.61, 20.98)	0.166	
H (As) + H (Se)	2.23 (−5.57, 10.04)	0.575		0.76 (−11.15, 12.66)	0.901		4.67 (−5.22, 14.56)	0.355	

μ

Abbreviations: V, vanadium; Co, cobalt; As, arsenic; Se, selenium; H, high exposure; L, low exposure, divided by the median concentration of the metal.

[a] Model for the difference of uric acid with the combined categories of urinary metals adjusted age, sex, BMI, smoking status, pack-years of smoking, alcohol consumption, exercise frequency, education attainment, income level, eGFR, hyperlipidemia, and hypertension. Model for males and females did not adjust sex. Model for females did not adjust smoking status and pack-years of smoking owing to the few numbers of smokers, and alcohol consumption was dichotomized into non-drinker and drinker (current and former drinker) in the model.

[b] L, Lower than the median of the urinary metal in total participants; H, higher than the median of the urinary metal in total participants.

[c] p_{int}, p-value for interaction of the combined metals by adding the two metals and the interaction of them into the aforementioned model.

Table 5
Odds ratios [95% confidence interval (CI)] for hyperuricemia with the combined categories of urinary metals.a

Metals[b]	Total			Male			Female		
	OR (95% CI)	p_{value}	p_{int} [c]	OR (95% CI)	p_{value}	p_{int}	OR (95% CI)	p_{value}	p_{int}
V + As									
L (V) + L (As)	1.00 (Reference)	-		1.00 (Reference)	-		1.00 (Reference)	-	
L (V) + H (As)	1.18 (0.82, 1.70)	0.371	0.184	1.01 (0.64, 1.57)	0.980	0.686	1.77 (0.92, 3.41)	0.090	0.069
H (V) + L (As)	**1.72 (1.2, 2.46)**	**0.003**		**1.72 (1.11, 2.66)**	**0.014**		1.73 (0.89, 3.37)	0.104	
H (V) + H (As)	**1.45 (1.05, 2.00)**	**0.026**		**1.52 (1.03, 2.26)**	**0.036**		1.36 (0.75, 2.46)	0.311	
V + Se									
L (V) + L (Se)	1.00 (Reference)	-		1.00 (Reference)	-		1.00 (Reference)	-	
L (V) + H (Se)	0.76 (0.51, 1.12)	0.164	0.625	0.62 (0.38, 1.01)	0.055	0.236	1.08 (0.55, 2.11)	0.827	0.471
H (V) + L (Se)	**1.47 (1.03, 2.10)**	**0.034**		1.49 (0.98, 2.26)	0.063		1.45 (0.72, 2.90)	0.298	
H (V) + H (Se)	1.27 (0.93, 1.74)	0.135		1.37 (0.93, 2.01)	0.112		1.11 (0.63, 1.94)	0.715	
As + Se									
L (As) + L (Se)	1.00 (Reference)	-		1.00 (Reference)	-		1.00 (Reference)	-	
L (As) + H (Se)	1.04 (0.72, 1.49)	0.843	0.279	0.92 (0.59, 1.44)	0.719	0.753	1.32 (0.69, 2.52)	0.405	0.124
H (As) + L (Se)	1.27 (0.90, 1.79)	0.180		1.15 (0.76, 1.74)	0.503		1.75 (0.90, 3.40)	0.100	
H (As) + H (Se)	0.997 (0.73, 1.36)	0.987		0.96 (0.66, 1.41)	0.833		1.15 (0.65, 2.05)	0.634	

Metals[b]	Total			Male			Female		
	OR (95% CI)	p_{value}	p_{int}[c]	OR (95% CI)	p_{value}	p_{int}	OR (95% CI)	p_{value}	p_{int}

Abbreviations: V, vanadium; Co, cobalt; As, arsenic; Se, selenium; H, high exposure; L, low exposure, divided by the median concentration of the metal.

[a] Model for the difference of uric acid with the combined categories of urinary metals adjusted age, sex, BMI, smoking status, pack-years of smoking, alcohol consumption, exercise frequency, education attainment, income level, eGFR, hyperlipidemia, and hypertension. Model for males and females did not adjust sex. Model for females did not adjust smoking status and pack-years of smoking owing to the few numbers of smokers, and alcohol consumption was dichotomized into non-drinker and drinker (current and former drinker) in the model.

[b] L, Lower than the median of the urinary metal in total participants; H, higher than the median of the urinary metal in total participants.

[c] p_{int}, p-value for the interaction of the combined metals by adding the two metals and the interaction of them into the aforementioned model.

Sensitivity analysis

The magnitude and direction of these associations remained unchanged in the majority of sensitivity analyses (Supplementary Table S5-S20). However, when excluding participants with low eGFR (n = 576), the association of vanadium exposure with SUA in females became non-significant. Intriguingly, when excluding participants with low eGFR, inverse associations of cobalt with SUA levels in the total population and cobalt with hyperuricemia risk in females were observed. Furthermore, excluding participants with hypertension (n = 451) slightly blunted the association of vanadium exposure with the risk of hyperuricemia while other associations still were robust.

Discussion

To the best of our knowledge, this is the first study to evaluate the associations of exposure to multiple metals with SUA levels and the risk of having hyperuricemia. Herein, we found that vanadium and arsenic exposure were associated with increased SUA levels and hyperuricemia risk, especially in males. Selenium content might be associated with decreased SUA levels and hyperuricemia risk in males. Furthermore, co-exposure to vanadium and arsenic was associated with greatly increased SUA levels and hyperuricemia risk, while high selenium status perhaps could partly counteract their effects.

Vanadium is the 21st most abundant element in the earth's crust and is ubiquitously distributed in the soil, water, and atmosphere. Natural processes and accelerated anthropogenic activities such as combusting fossil fuels, mining, and widespread industrial utilization aggravate the contamination situation of vanadium [39]. In our study, all participants had detectable vanadium concentrations in urine, revealing the extensive vanadium exposure in their daily life. Kidneys are the primary organs where vanadium is accumulated [40]. Experimental studies demonstrated that high vanadium exposure caused granular and vacuolar degeneration in renal tubular and glomerulus epithelial cells, which could lead to urate underexcretion [41, 42]. Furthermore, vanadium compounds inhibited superoxide dismutase and glutathione peroxidase (GSH-Px) activity of scavenging hydroxyl radicals, thus further worsening renal function and restricting urate excretion [41]. Moreover, vanadium not only induced the secretion of pro-inflammatory cytokines (interleukin-6 and interleukin-8) but itself could be a pro-inflammatory agent to upregulate the expression of cyclooxygenase-2, or stimulate mitogen-activated protein kinase cascades and the nuclear factor-κB signal, resulting in renal oxidative damage and urate excretion reduction [43–45]. Meanwhile, high oxidative stress status in the body will mobilize the

antioxidant system to produce more UA for redox balance [46]. In the context of vanadium exposure, increased UA production and decreased urate excretion might lead to high SUA levels.

Evidence about arsenic exposure with UA in epidemiological studies and experimental research still was disagreement, which might be partly due to the disparate purine metabolism in humans (loss of urate oxidase activity) and other mammals [8, 18, 47, 48]. Arsenic could bind to the molybdenum center in XO, thus retarding the catabolism of xanthine to UA via inhibiting the activity of XO, leading to a reduction in SUA levels [17]. Moreover, arsenic exposure, trivalent arsenicals in particular, depleted UA by generating reactive oxygen species (ROS) [49]. The two aspects of arsenic reduced the production and increased the consumption of UA. Nevertheless, arsenic-triggered lipid peroxidation in kidneys caused tubular injury, glomerulus sclerosis, and glomerulus collapse, leading to reduced urate excretion [50]. Furthermore, similar to lead, arsenic-damaged proximal convoluted tubule may strengthen the reabsorption of urate. In summary, arsenic exposure not only reduced the UA production, depleted the anti-oxidative UA, but blocked the excretion and strengthed the reabsorption of urate. Whether arsenic exposure was associated with hyperuricemia might depend on its total effects.

Selenium has anti-oxidative and anti-inflammatory effects [51]. We found that urinary selenium concentrations were not only inversely associated with SUA and hyperuricemia but could partly counteract the hazardous effects of vanadium and arsenic. GSH-Px widely exists in the body and plays a pivotal role in ROS metabolism. The synthesis of GSH-Px in kidneys requires selenium as an essential cofactor [51]. High selenium status promoted the capacity of GSH-Px to neutralize lead, vanadium, and arsenic-induced ROS. Accordingly, less UA would be produced to maintain redox balance. In addition, selenium could reduce internal arsenic contents via the excretion of arsenic-selenium compounds [52]. Moreover, selenium could improve renal function, accelerate the excretion of toxic metals and UA mainly by its anti-oxidative ability [53, 54]. Therefore, selenium supplements might contribute to reducing SUA levels and hyperuricemia risk.

We found positive associations of urinary aluminum, barium, lead, and uranium concentrations with SUA levels and hyperuricemia risk. Oxidative stress and subsequent renal injury were the mutual toxic mechanisms of these heavy metals, and to some extent, resulting in the increase of SUA [55–57]. Besides, in our study, we noticed that essential metal manganese in urine was associated with increased SUA levels in males. Similarly, a small-sample occupational study indicated that manganese exposure led to low UA concentrations in urine, indicating high UA accumulation in serum [58]. As regard to zinc, Zhang et al. found that dietary zinc intake was inversely associated with the risk of hyperuricemia in both sexes, but our results indicated that urinary zinc concentrations were associated with increased SUA levels in females [21]. There might exist no conflict in the two results. The human body has no storage of zinc that could be immediately mobilized to fill up the depletion. The excessive zinc concentrations in urine might be the consequence of disrupted zinc homeostasis and perhaps represented zinc deficiency in the body [59]. Zinc deficiency might lead to elevated SUA levels while zinc supplements could mitigate this situation. We found beneficial effects of cobalt on hyperuricemia in females with high eGFR. Cobalt, as the vital component of Vitamin B12 (cobalamin), might affect UA production by controlling the generation of tetrahydrofolic acid in the purine metabolism [60]. However, more evidence is needed to support this theory. As for the opposite association of strontium with SUA in males and females, additional investigation is deserved to preclude chances and explain the mechanism.

Low eGFR, hypertension, and diuretics are the risk factors of hyperuricemia [37]. Moreover, renal function and diuretics have impacts on urate and metals excretion [55]. In the sensitivity analysis, we excluded individuals with low eGFR (< 90 mL/min/1.73 m^2) and individuals with hypertension no matter using antihypertensive or not. However, these stringent exclusion criteria only slightly weakened the association of vanadium with hyperuricemia in males while other associations were still robust. These analyses revealed that damaged renal function could only explain part of

the associations between metals exposure and the changes in SUA levels. There might be other more specific and effective mechanisms underlying these associations.

Sex difference existed in our results. Though vanadium, cobalt, arsenic, and selenium concentrations were higher in females, most associations were still more significant in males. The mean eGFR value in males (92.4 mL/min/1.73 m^2) was significantly lower than that in females (98.5 mL/min/1.73 m^2). Low eGFR in males was associated with low urinary metals excretion, thus accumulated metals in the body would cause extra damage [55]. Meanwhile, low eGFR reduced urate excretion and increased the risk of having hyperuricemia. Besides, male participants in our study had a high prevalence of smoking, drinking, hypertension, and hyperlipidemia. All these adverse factors might enhance metals' impacts on hyperuricemia. Furthermore, compared with males, females physiologically had more antioxidant gene expression and possessed more metabolic capability to mitigate heavy metals' deleterious impacts on UA metabolism [61, 62]. Moreover, the risk profile of hyperuricemia was different. Females with hyperuricemia were more due to diuretics use while males were more owing to inherent genetic variants [63, 64]. These differences in males and females help explain the sex-specific effects of metals, but more hypothesis-driven researches focusing on this topic are needed.

We evaluated the associations of metals exposure with SUA levels and hyperuricemia risk in the present study. Other strengths of this study included large sample size, standardized and validated measurements of urinary metals, and multiple sensitivity analyses. However, the cross-sectional study design restricted the causality of the associations. Nevertheless, given the well-documented association of lead exposure with hyperuricemia risk and the similarity among metals, it was more reasonable to hypothesize that metals exposure changed SUA levels, not vice versa. Second, although we adjusted for most confounders in our analyses, the associations might still be slightly influenced by residual confounding. However, since our results remained robust in different sensitivity analyses, reasons preceded chances in the associations. Further studies should take genetic variants (e.g., SLC2A9, ABCG2), dietary factors (seafood, beer, and red meat), and detailed drug use into consideration [37]. Third, our study was launched in a physical examination center, selection bias might restrict the extrapolation of our findings. Considering the exploratory intention of this study, such a study design helps to increase the participation rate and contribute to high-standard quality control in data collection. Fourth, inorganic arsenic is more toxic than organic arsenic; pentavalent vanadium tends to be more deleterious than trivalent vanadium [8, 39]. Future studies should take the species of these metals into account. Fifth, we only measured metals concentrations in one urine sample, potential non-differential exposure misclassification might dilute the risk estimates. Hence, in prospective studies, using repeated urine samples and other biological matrixes to character metals exposure levels are recommended to confirm our findings.

Conclusions

Collectively, we found that vanadium and arsenic exposure were significantly associated with increased SUA levels and hyperuricemia risk with sex difference. Meanwhile, high selenium content not only was suggested to be inversely associated with SUA levels and hyperuricemia risk, but might could partly counterbalance vanadium and arsenic-induced detrimental effects. More hyperuricemia patients might benefit from the interventional management of selenium supplements. Prospective cohort studies and experimental researches are needed to confirm these associations and elucidate the underlying mechanisms.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics and Human Subject Committee of Tongji Medical College, Huazhong University of Science and Technology.

Consent for publication

Not available.

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no potential conflicts of interest.

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Authors' contributions

SLJ, ZHW, and QL contributed to study design. SLJ, SZ, HML, XZ, CP, and HZ contributed to data acquisition. SLJ, ZHW, and QL contributed to data analysis. SLJ, ZHW, and QL wrote the manuscript. All authors reviewed the manuscript and approved the publication.

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