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Association of urinary metal profiles with serum uric acid: a cross-sectional study of traffic policemen in Wuhan, China

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ABSTRACT

Objectives Serum uric acid (SUA) is both a strong antioxidant and one of the key risk factors of cardiovascular diseases (CVDs). We aimed to investigate the associations of urinary metal profile with SUA in traffic policemen in Wuhan, China.

Design A cross-sectional study was carried out in traffic policemen.

Setting A seriously polluted Chinese city.

Participants A total of 186 traffic policemen were recruited in this study. About 56 of them worked in the logistics department and the other 130 maintained traffic order or dealt with traffic accidents on the roads. All these subjects had worked as a policeman for at least 1 year.

Main outcome measures SUA.

Results The significantly negative association of lead with SUA was consistent between single-metal and multiple-metal models (p=0.004 and p=0.020, respectively). Vanadium, chromium and tin were reversely associated with SUA levels in the single-metal models after false discovery rate (FDR) adjustment (all $P_{\_FDR} < 0.05$). One IQR increase in vanadium, chromium, tin and lead was associated with 26.9 µmol/L (95% CI −44.6 to −9.2; p=0.003), 27.4 µmol/L (95% CI −46.1 to −8.8; p=0.004), 11.2 µmol/L (95% CI −18.9 to −3.4; p=0.005) and 16.4 µmol/L (95% CI −27.6 to −5.2; p=0.004) decrease in SUA, respectively. Significant interaction between smoking and vanadium on decreased SUV was found ($p_{\text{for interaction}} = 0.007$ and $p_{\_FDR} = 0.028$).

Conclusions Urinary vanadium, chromium, tin and lead were negatively associated with SUA. Vanadium and cigarette smoking jointly affected SUA levels. Further studies are needed to replicate these findings and to investigate the potential mechanisms.

Strengths and limitations of this study

- This is the first study with concise design to investigate the effect of urinary metals on serum uric acid (SUA) of traffic policemen in a seriously polluted Chinese city.
- For each participant SUA and 23 urinary metals were measured, with emphasis on the relationship between them.
- The cross-sectional design might prevent us to identify the causal associations between metal profiles and SUA.
- A relatively small sample size might reduce the statistical power.

INTRODUCTION

Accompanied with rapid urbanisation, heavy metal pollution has long become a critical problem which is increasingly serious in China.[1] Heavy metal exposure occurs mainly by inhalation and ingestion, leading to various oxidative stress related diseases.[2] Kidney is the primary route of metal excretion. For example, the majority of absorbed chromium is excreted into urine by glomerular filtration, or bound to a low-molecular organic transporter.[3] Urinary concentrations of most metals reflect previous exposure within several hours or decades.[4]

Oxidative stress is a biological process, resulting from an imbalance between pro-oxidants and antioxidants. Previous evidence found that oxidative stress might mediate numerous diseases, involving cardiovascular diseases (CVDs), diabetes, atherosclerosis, cancer, chronic inflammation and others due to the metal exposure.[2] Serum uric acid (SUA), the end-product of endogenous and dietary purine metabolism, is a strong antioxidant present in high levels in the serum of humans.[5] It plays an important role in inhibiting lipid peroxidation and in scavenging reactive oxygen species (ROS).[6] However, uric acid (UA) also represents one of the key risk factors for CVDs and hypertension, conditions associated with oxidative stress. Previous evidence showed that increased UA, even within the normal range, is a risk factor for the incidence and mortality due

to CVDs including coronary heart disease (CHD), heart failure and atrial fibrillation.[7] Hyperuricaemia also independently increased risks for cardiovascular events.[8] Thus, the investigation of environmental factors affecting UA levels is benefit for prevention and treatment of hyperuricaemia, CVDs and other diseases which related to oxidative stress. However, the evidence of the association between heavy metals and SUA is limited and still far from conclusive. Previous reports found that blood lead was positively related to SUA[9] and prevalence of hyperuricaemia and gout[10] of adult residents both in China and Europeans, even in the range of acceptable concentrations. Similar results were observed between urine arsenic and UA to civilians of the USA.[11] But for the other metals, few reports were found.

Road transportation is part of the most vital sources of heavy metal pollution because the combustion of liquid fuels, vehicular abrasion and the weathering of track or road materials can release fine particles containing heavy metals into the air.[12 13] In China, traffic policemen work at the main road intersections to maintain traffic order or to cope with traffic accidents on the road with high vehicle flows. They are exposed chronically to a relatively high level of heavy metal pollution. Thus, heavy metals are significant health risk factors for outdoor workers, especially to traffic policemen.[14–16] In this current study, we performed a cross-sectional study to investigate the roles of urinary metal profile in SUA of 186 traffic policemen in China.

METHODOLOGY

Study participants

A total of 199 traffic policemen were recruited from a traffic police brigade in Wuhan (Hubei, China) on November 2016. Subjects with missing data covariates (n=4), and without adequate urine sample volume for metals assays (n=9) were all excluded from the current analysis. Finally, the remaining 186 subjects were enrolled for further analysis. About 56 of them worked in the logistics department and the other 130 maintained traffic order or dealt with traffic accidents on the roads. All these subjects were between 20 and 60 years and had worked as a policeman for at least 1 year. They had no malignant tumour, gout or kidney diseases. None of them used antioxidant against uric acid.

Each subject was interviewed one-by-one and face-to-face to collect information on demographic characteristics, smoking status, alcohol consumption, body weight and height, physical activity, disease history and occupational history by means of a standardised occupational questionnaire. The interview was performed by trained interviewers.

For each subject, a 2 mL-venous blood sample was drawn into an EDTA-K2 anticoagulant vacuum tube and 40 mL of morning urine samples were collected into sterile cylindrical tubes. All samples were stored at −80°C freezers and analysed within half a year after sampling.

Patient and public involvement

The physical examination and laboratory test results were mailed to all participants.

Determination of urinary metals

We measured 23 urinary metals including aluminium, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, arsenic, selenium, rubidium, strontium, molybdenum, cadmium, tin, antimony, barium tungsten, thallium, lead and uranium by inductively coupled plasma mass spectrometry which was described in detail in our previous study.[17] In brief, thawed urine samples (3.0 mL) were mixed with 67% (v/v) HNO_3 (15.0 µL) and stored at 5°C overnight. Then those samples were distilled at room temperature (2 hours) and a 1.0 mL of the sample was diluted to one-fifth with 1.2% (v/v) HNO_3 (Optima grade, Fisher, Belgium). The samples were then measured by an Agilent 7700x inductively coupled plasma mass spectrometer with an octopole-based collision/reaction cell (Waldbronn, USA). Standard reference materials (2670a and 1640a) and reference or information values from the National Institute of Standards and Technology, and spiked pooled sample were used for quality control.

Determination of SUA, urinary creatinine and covariates

SUA and urinary creatinine were measured by the centre's laboratory with fully automated clinical chemistry analyser (Toshiba TBA 120FR, Toshiba Medical Systems, Otawara-shi, Tochigi, Japan).

Participants, who had smoked at least one cigarette per day for more than half a year, were classified as former or current smokers. Otherwise they were defined as non-smokers according to the occupational questionnaire. We defined those who had drunk at least once a week for more than half a year no matter currently or formerly as drinkers (only one former drinker), else they were defined as non-drinkers. Physical activity was dichotomised as yes (every exercise lasted 20 min or more per half-month) or no.

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Pack-years = (packs smoked per day) × (years as a smoker). Number of cigarettes per day was the current rate of smoking or the rate of smoking before they quitted smoking.

Statistical analyses

Relationships between metals were investigated by partial correlation tests adjusted for age and gender. A one-sample Kolmogorov-Smirnov test was used to test the normality of SUA. The distribution of SUA met the assumption of normality for the general linear modelling (p=0.759, online supplementary figure S1). Thus, the general linear models were used to reveal associations between urinary metals and SUA with adjustment for age, gender, smoking, pack-years, number of cigarettes per day, drinking, physical activity, employment duration, seafood intake, urinary creatinine, BMI, hypertension, diabetes and CHD. Hypertension, diabetes and CHD were

diagnosed by a physician. A full linear regression model with forward selection that included significant metals (vanadium, chromium, tin and lead) and the covariates mentioned above was established to identify statistically independent impact of multiple metals on outcome (SUA). This model selected the metals that predicted the SUA with $p<0.05$.

As smoking is an important source of heavy metals in human, we performed stratified analysis according to smoking status by general linear models. These models were limited to the metals that were significantly associated with SUA in the single-metal models. We further explored the interaction effects between the significant metals and smoking on SUA in the general linear models.

All effect estimates were shown as changes per IQR increase of the metals on SUA. All statistical analysis was carried out using SPSS V.12.0 software. A two-sided p value<0.05 was considered significant. False discovery rate (FDR) adjustment was used for multiple comparisons and FDR<0.05 was defined as the significance level.

RESULTS

General characteristics, levels of urinary creatinine, SUA and urinary metals of study participants

The demographic characteristics of the participants were summarised in table 1. The means of age, employment duration, BMI were 43.20±8.07 years, 22.02±10.43 years and 24.8±3.0 kg/m^2, respectively. More men (83.9%) than women (16.1%) were included in this project. The mean of number of cigarettes per day and pack-year were 14.6±9.2 and 16.98±13.15 in former and current smokers. The proportions of subjects who performed physical activity, having CHD, hypertension or diabetes were 65.6%, 2.2%, 15.6% and 1.6%, respectively. The mean levels of urinary creatinine and SUA were 11.3±7.2 mmol/L and 332.0±94.8 µmol/L, respectively. The frequency of seafood intake is 1.2±0.2 servings/week. The characteristics of workers on the roads and those in the logistics department were also separately showed in table 1 in detail. There were more

Table 1 General characteristics, urinary creatinine and SUA of participants

	Mean±SD or per cent		
Variables	**Workers in the logistics department**	**Workers on the roads**	**Combined group**
Sample size	56	130	186
Age (years, mean±SD)	42.30±8.47	43.59±7.90	43.20±8.07
Gender (%)			
Male	53.6	96.9	83.9
Female	46.4	3.1	16.1
Employment duration (years, mean±SD)	22.40±10.31	21.12±10.76	22.02±10.43
Smoking (%)			
Never	76.8	38.5	50.0
Former	5.4	4.6	4.8
Current	17.9	56.9	45.2
No of cigarettes per day	13.9±6.5	14.7±9.5	14.6±9.2
Pack-years (mean±SD)	13.31±8.36	17.53±13.68	16.98±13.15
Drinking (%)			
No	73.2	60.0	64.0
Yes	26.8	40.0	36.0
BMI (kg/m^2, mean±SD)	23.3±2.6	25.5±3.0	24.8±3.0
Physical activity (%)			
No	28.6	36.9	34.4
Yes	71.4	63.1	65.6
Frequency of seafood intake (servings/week, mean±SD)	1.2±0.3	1.2±0.2	1.2±0.2
Coronary heart disease (%)	0	3.1	2.2
Hypertension	10.7	17.7	15.6
Diabetes	1.8	1.6	1.6
Urinary creatinine (mmol/L, mean±SD)	8.5±6.6	12.4±7.2	11.3±7.2
SUA (µmol/L, mean±SD)	298.4±91.6	346.4±92.8	332.0±94.8

BMI, body mass index; SUA, serum uric acid.

men and smokers, and higher levels of urinary creatinine and SUA in workers on the roads than those in the logistics department.

The limits of quantification (LOQ) for the urinary metals were in the range from 0.0004 to 0.3934 µg/L (online supplementary table S1). For measurements below LOQ, half of LOQ was used as default value. The distributions of the 23 urinary metals were showed in online supplementary table S2. Chromium, iron, tin and tungsten concentrations were <LOQ in 4.30%, 3.23%, 2.69% and 1.79% of samples, respectively. Higher concentrations of metals were found in workers on the roads than those in the logistics department.

Partial correlation tests adjusting for age and gender found that most of the metals were positively and significantly related to each other except for manganese, cobalt, nickel and tungsten (all p<0.05, online supplementary table S3).

Associations between urinary metal concentrations and SUA levels

In the single-metal generalised linear models adjusted for age, gender, smoking, pack-years, number of cigarettes per day, drinking, physical activity, employment duration, seafood intake, urinary creatinine, BMI, hypertension, diabetes and CHD, vanadium, chromium, tin and lead were negatively associated with SUA levels after FDR adjustment for multiple comparisons (all $p_{\_FDR} < 0.05$, table 2). One IQR increase in vanadium, chromium, tin and lead was associated with 26.9 µmol/L (95% CI −44.6 to −9.2; p=0.003), 27.4 µmol/L (95% CI −46.1 to −8.8; p=0.004), 11.2 µmol/L (95% CI −18.9 to −3.4; p=0.005) and 16.4 µmol/L (95% CI −27.6 to −5.2; p=0.004) decrease in SUA, respectively. These associations remained significant in workers on the roads but not in those in the logistics department.

The estimate based on the model that included multiple significant metals showed that an IQR increase in urinary lead was associated with a 13.2 µmol/L (95% CI −24.2 to −2.1; p=0.020, table 2) decrease in SUA, which was in consistent with results from the single-metal models. This association was also found in workers on the roads (β=−25.7, 95% CI −42.8 to −8.5; p=0.004, table 2) but not in those in the logistics department.

The potential collinearity within vanadium, chromium, tin and lead was assessed.[18] There was no strong collinearity between lead and the other metals. (all condition indexes<10 and all variance proportions<0.90, online supplementary table S4).

Interactions of smoking and metals on SUA

Results from smoking-stratified analysis were shown in table 3. Vanadium, chromium, tin and lead were significantly and negatively associated with SUA concentrations in smokers, with adjustment for age, gender, drinking, physical activity, employment duration, seafood intake, urinary creatinine, BMI, hypertension, diabetes and CHD, but not in non-current smokers (table 3). The interaction between smoking and vanadium on SUV was statistically significant ($p_{\text{for interaction}} = 0.007$ and $p_{\_FDR} = 0.028$, table 3). The interaction results from pack-years and number of cigarettes per day stratified analysis where pack-years and number of cigarettes were binary variables were similar and the data were not shown.

DISCUSSION

In the current cross-sectional study, we revealed the associations of the urinary metal profile with SUA of 186 traffic policemen in Wuhan, China. The concentrations of vanadium, chromium, tin and lead were negatively associated with SUA levels, even after FDR adjustment for multiple testing based on single-metal models. The associations of lead with SUA levels were consistent between single-metal and multiple-metal models. Vanadium and smoking affected SUA levels jointly. To the best of our knowledge, this is the first study to investigate the effect of urinary metal profiles on SUA levels of Chinese traffic policemen.

Lead, chromium and vanadium are all traffic-related metals.[19 20] Lead was well known and most widely studied occupational and environmental toxin. Previous studies found that blood lead levels were independently associated with increased SUA and hyperuricaemia risk in cross-sectional studies.[9 10 21] However, little information is available for the associations of urinary lead concentrations with SUA. Urinary lead reflects recent exposure.[22] We found that the concentration of urinary lead was independently and negatively associated with SUA, conversely to the previously published associations between blood lead and UA.[9 10 21] The underlying mechanism is unidentified. Oxidative stress is one of the key initial event in the toxicity of metals.[23 24] UA, an endogenous antioxidant, has strong capacity to scavenge toxic reactants and protects cells against oxidants.[25] We assumed that the ROS induced by metals might consume SUA. In other words, heavy metals might induce oxidative stress which resulted in low levels of SUA.

In addition, lead nephrotoxicity is believed to be significantly related with interstitial fibrosis, tubular atrophy, decreased glomerular filtration and nephritis.[21 26] The positive association of urinary lead and inverse association of blood lead with glomerular filtration rate were observed in a cross-sectional, national survey,[27] indirectly providing an explanation for the different associations of blood and urinary lead concentrations with SUA. It is speculated that impaired renal function might reduce the total filtration of heavy metals and consequently lead to decreased levels of metals in the urine and increased levels in the blood. Further mechanism studies are needed in the future.

Chromium and vanadium are trace metals and play a crucial role in carbohydrate, lipid and protein metabolism in limited concentrations.[19 28] Both of them are mainly excreted through the kidneys and their urinary levels reflected recent exposure.[3 29] Previous evidence showed that chromium and vanadium played

Table 2 Effects of 1-IQR increase in metal levels on SUA levels

Urinary metals	Workers in the logistics department		Workers on the roads		Combined group	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
Single-metal models†						
Aluminium	17.7 (–6.6 to 42.0)	0.152	–2.0 (–13.1 to 9.0)	0.718	0.5 (–9.2 to 10.2)	0.919
Titanium	7.3 (–25.9 to 40.4)	0.668	–14.6 (–35.7 to 6.4)	0.173	–10.7 (–27.7 to 6.2)	0.214
Vanadium	9.8 (–20.9 to 40.5)	0.532	–39.1 (–60.8 to 17.5)	**<0.001***	–26.9 (–44.6 to 9.2)	**0.003***
Chromium	23.7 (–10.6 to 58.0)	0.175	–43.3 (–66.1 to 20.6)	**<0.001***	–27.4 (–46.1 to 8.8)	**0.004***
Manganese	–4.4 (–30 to 21.1)	0.734	2.3 (–4.3 to 8.8)	0.501	1.7 (–4.4 to 7.8)	0.584
Iron	–9.5 (–31.6 to 12.5)	0.396	1.4 (–6.8 to 9.6)	0.739	0.7 (–6.6 to 8.0)	0.852
Cobalt	0.0 (–4.3 to 4.3)	0.994	3.1 (–1.1 to 7.4)	0.149	2.2 (–1 to 5.5.0)	0.178
Nickel	–1.1 (–7.4 to 5.1)	0.720	–0.9 (–3.8 to 2.0)	0.543	–0.6 (–3.1 to 2.0)	0.662
Copper	52 (6.9 to 97.2)	0.024	–12.4 (–34 to 9.2)	0.262	–6.4 (–23.7 to 10.9)	0.468
Zinc	5.2 (–28.0 to 38.3)	0.761	1.1 (–18 to 20.1)	0.911	0.9 (–15 to 16.7)	0.916
Arsenic	–2.3 (–13.1 to 8.5)	0.679	–3.5 (–14.6 to 7.6)	0.537	–3.9 (–11.6 to 3.8)	0.326
Selenium	–1.8 (–42.3 to 38.7)	0.929	–2.5 (–17.5 to 12.4)	0.742	–2.1 (–15.3 to 11.0)	0.751
Rubidium	46.0 (8.3 to 83.7)	0.017	–32.9 (–57.5 to 8.4)	0.009	–15.3 (–35.9 to 5.4)	0.147
Strontium	–12.2 (–38.2 to 13.7)	0.355	–10.5 (–27.2 to 6.1)	0.214	–12.4 (–25.6 to 0.8)	0.066
Molybdenum	2.5 (–25.1 to 30.1)	0.859	–14.2 (–36.1 to 7.7)	0.203	–4.9 (–22.0 to 12.2)	0.571
Cadmium	5.5 (–26.9 to 37.8)	0.740	–3.5 (–21.3 to 14.4)	0.703	–2.4 (–17.7 to 12.9)	0.757
Tin	8.3 (–16.5 to 33.1)	0.511	–13.3 (–21.7 to 4.9)	**0.002***	–11.2 (–18.9 to 3.4)	**0.005***
Antimony	7.8 (–12.9 to 28.6)	0.460	–33.1 (–57.5 to 8.7)	0.008	–13.8 (–30.6 to 3)	0.108
Barium	–6.5 (–23.7 to 10.7)	0.460	5.8 (–8.6 to 20.1)	0.432	2.5 (–8.8 to 13.9)	0.662
Tungsten	–0.2 (–3.7 to 3.3)	0.908	–1.1 (–5.2 to 3.0)	0.597	–0.7 (–3.6 to 2.2)	0.651
Thallium	2.8 (–40.3 to 45.9)	0.898	–23.2 (–44 to 2.4)	0.028	–17.2 (–35.1 to 0.7)	0.059
Lead	–18.6 (–36.8 to 0.5)	0.044	–30.1 (–43.9 to 16.3)	**<0.001***	–16.4 (–27.6 to 5.2)	**0.004***
Uranium	4.9 (–12.2 to 22.1)	0.575	–10.2 (–25.6 to 5.1)	0.190	–4.6 (–15.8 to 6.7)	0.425
Multiple-metal model‡						
Lead	–	–	–25.7 (–42.8 to 8.5)	0.004	–13.2 (–24.2 to2.1)	0.020

The bold values are statistically significant after FDR adjustment.
*$P_{FDR} < 0.05$.
†Generalised linear models adjusted for age, gender, smoking, pack-years, no. of cigarettes per day, drinking, physical activity, employment duration, seafood intake, urinary creatinine, body mass index, hypertension, diabetes and coronary heart disease.
‡Linear regression model included four significant metals (vanadium, chromium, tin, lead) and covariates mentioned above and selected these metals that predicted the outcome (SUA) with p<0.05.
SUA, serum uric acid.

a protective role against CVDs.[30–32] Low chromium concentration is reported to relate with increased CVD risk factors including low density lipoprotein cholesterol, triglycerides and total cholesterol.[33] Vanadium salts were also believed to normalise elevated blood pressure and to regulate blood lipids and glucose levels.[34 35] UA is also a risk factor for CVDs. The relationships of chromium and vanadium with SUA were largely unknown. We found reverse associations of SUA with urinary chromium and vanadium. However, whether chromium and vanadium play a protective role in CVDs by decreasing UA still needs further mechanism studies.

Few previous studies have determined the relationship of tin with UA, gout and CVDs. In the present study, we found that tin were associated with decreased SUA levels. The potential mechanism is unclear.

In this study, we found no significant associations between metals and SUA in workers in the logistics department. It might be partly due to the relatively low concentrations of metals. Further studies are needed to investigate the dose-effect relationship between urinary metals and SUA.

Cigarettes are a source of heavy metal traces.[36] Our stratified analysis showed that chromium, vanadium,

Table 3 The interaction of adjusted regression coefficients and 95% CIs of SUA by metals according to smoking status

	Non-current smokers* (n=102)		Current smokers (n=84)			
Metals	β (95% CI)†§	P value†	β (95% CI)†§	P value†	$P_{for\ interaction}$†	P_{FDR}‡
Vanadium	−3.1 (−27.2 to 21.1)	0.804	−55.6 (−80.9 to −30.3)	<0.001	0.007	0.028
Chromium	−11.1 (−35.6 to 13.4)	0.375	−46.8 (−74.0 to −19.7)	0.001	0.121	0.161
Tin	−5.8 (−15.0 to 3.3)	0.212	−24.3 (−39.2 to −9.4)	0.001	0.085	0.161
Lead	−20.1 (−42.8 to 2.6)	0.083	−14.7 (−27.5 to −2.0)	0.023	0.789	0.789

*Non-current smokers included nine ever smokers and 93 non-smokers.
†Adjusted for age, gender, drinking, physical activity, employment duration, seafood intake, urinary creatinine, BMI, hypertension, diabetes and coronary heart disease.
‡FDR-adjusted for four interaction tests.
§The effect estimate were shown as changes per IQR increase of the metals on SUA.
FDR, false discovery rate ; SUA, serum uric acid.

tin and lead were negatively associated with SUA in current smokers but not in non-current smokers. Most importantly, significant interaction between vanadium and smoking was found in the present study, suggesting that metal exposure and smoking jointly affected SUA. However, the potential mechanisms are still unclear. Previous epidemiology studies found that ROS from oxidative stress induced by smoking might consume antioxidants including UA.[37] In addition, vanadium carries out the toxic effect mainly by inducing the generation of ROS.[38] Thus, it is assumed that oxidative stress mediated by ROS may be the shared biological effect, jointly resulting in the decreased SUA.

To the best of our knowledge, this is the first study to investigate the effects of urinary metal profiles on SUA of traffic policemen in a seriously polluted Chinese city. For each participant SUA and 23 urinary metals were measured, in order to evaluate the internal exposure to metals and possible response of SUA levels. Several limitations should be considered in our study. First, the cross-sectional design might prevent us to identify the causal associations between metal profiles and SUA. Second, urinary metal concentrations were considered as biomarkers for internal exposure to metals, although they did not exactly reflect the occupational exposure as well as exposure to tobacco metals of traffic policemen. Third, a relatively small sample size might reduce statistical power of our study. Future prospective studies with a larger sample size are warranted to validate our findings and to elucidate the air pollution constituents in the external working environment of traffic policemen.

CONCLUSIONS

In summary, this cross-sectional study found negative associations of vanadium, chromium, tin and lead in urine with SUA even after FDR adjustment for multiple testing of traffic policemen. High correlation was observed between chromium and vanadium. Vanadium and cigarette smoking jointly affected SUA levels. Further studies are warranted to explore the potential mechanisms.

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Contributors XD, QD and ZP planned the study. XD, DG, LN and JL collected the data. XD, ZC, LZ, TX and WS analysed the data and drafted the manuscript. YL, LH, CH and GY assisted with the analysis. All authors contributed to the interpretation of the results and assisted in revising the manuscript. All authors have read and approved the final manuscript.

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