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A U-shape dose-response relationship between whole blood manganese level and the risk of hyperuricemia: evidence from a cross-sectional study based on retired Workers

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Abstract

The present work was designed to examine the relationship between whole-blood metal levels and hyperuricemia along with their dose-response pattern, which can support evidence-based prevention and management of health risks from occupational metal exposure-induced hyperuricemia. Based on manganese-exposed workers healthy cohort-retired workers sub-cohort, general demographic information and lifestyle data were collected via questionnaire surveys. Metal levels in whole blood were assessed with a coupled plasma mass spectrometer, and uric acid was measured using an automated biochemical analyzer. The Least Absolute Shrinkage and Selection Operator (LASSO) model, Bayesian Kernel Machine Regression (BKMR) and Restricted Cubic Splines (RCS) were employed to analyze the association between metals and hyperuricemia. This study included 583 retired workers, of whom 57 (9.8%) had hyperuricemia. Both LASSO and BKMR analysis indicated that strontium, rubidium, manganese, calcium, and magnesium were the primary driving factors, with strontium and rubidium showing positive correlations with hyperuricemia. RCS analysis showed that a significant linear relationship between whole-blood magnesium and hyperuricemia ($P_{overall}$ = 0.0090, $P_{nonlinear}$ > 0.05), while a positive linear correlation was found between whole-blood strontium and hyperuricemia showed ($P_{overall}$ = 0.0007, $P_{nonlinear}$ > 0.05) and U-shaped dose-response relationship were found between whole-blood calcium, manganese and hyperuricemia ($P_{overall}$ < 0.05, $P_{nonlinear}$ < 0.05).. This study found that metal mixture exposure was associated with the risk of hyperuricemia among retired workers, with strontium, rubidium, manganese, calcium, and magnesium being the primary contributing metals. These findings provide population-based evidence for the health risk assessment of metal exposure and the establishment of exposure limits; however, they still require validation through large-scale cohort studies and experimental research to clarify the underlying mechanisms.

1. Introduction

Uric acid (UA) constitutes the terminal metabolite derived from both dietary and endogenous purine metabolism. Primarily produced in the liver, UA continuously excreted via the kidneys (approximately 75%) and intestines to maintain homeostasis and prevent toxic accumulation(Fathallah-Shaykh and Cramer 2014). As the final metabolite of purine metabolism, increased UA production or reduced excretion can lead to hyperuricemia(Sun et al. 2017). According to a 2024 report by China's National Health Commission(Fang et al. 2024), t hyperuricemia prevalence in Chinese adults has reached 14%. Evidence indicates that hyperuricemia is closely associated with the development of hypertension(Kuwabara 2015), type 2 diabetes(Mortada 2017), cardiovascular disease(Borghi et al. 2015), and chronic kidney disease(Ruilope and Pontremoli 2013). Therefore, investigating the etiology of hyperuricemia holds significant public health implications.

With the acceleration of industrialization, environmental metal exposure, particularly occupational metal exposure, has become a significant risk factor threatening public health. Guangxi, China is rich in metal mineral resources, ranking first nationally in manganese ore reserves (Yi 2022). A substantial number of workers in Guangxi are engaged in manganese-related occupations. From 2019 to 2022, the maximum

manganese exposure levels among these workers exceeded the occupational exposure limit for airborne manganese (0.15 mg/m³) by 3.89 to 21.37 times (Shao et al. 2024). Manganese gains access to the human body via ingestion, inhalation and dermal absorption, causing harm (Pan Chen et al. 2018). Excess manganese readily accumulates within the liver, pancreas, skeletal tissues, kidneys and brain (Chen et al. 2018), exhibiting neurotoxicity and cardiovascular toxicity (O'Neal and Zheng 2015), and impairing vital organ functions such as the lungs, liver, and kidneys (Gandhi et al. 2022). When kidney function is impaired, its ability to excrete UA, leading to its accumulation in the body and resulting in hyperuricemia. One cross-sectional investigation (n = 1039) identified an inverse association between blood manganese and serum uric acid (SUA) [β=-18.50] (Wang et al. 2023), consistent with findings from another cross-sectional analysis (n = 3926) based on National Health and Nutrition Examination Survey (NHANES) datasets, which indicated a negative relationship exists between urinary manganese and SUA concentration [β=-5.53] (Ma et al. 2022). In contrast, evidence from the 2015 Guangdong, China Chronic Disease and Nutrition Surveillance Survey showed a positive association between serum manganese levels and the risk of hyperuricemia in men [OR = 1.68, 95% CI: (1.68, 2.39)] (Wu et al. 2023). A cross-sectional analysis of American adults revealed a U-shaped connection between whole blood manganese and hyperuricemia (Tan et al. 2023), suggesting a potential nonlinear association. Consequently, the relationship between manganese and hyperuricemia remains controversial, with its underlying mechanisms unclear.

In the real world, workers in manganese mining are exposed to a combination of various metals, not just one (Yang et al. 2021), such as Sr, Rb, Ca, and Mg. Previous investigations have mainly concentrated on the relationship between metal exposure levels among the general populace and hyperuricemia. For example, in a study assessing middle-aged and older people at one specific time (n = 3,379), binary logistic regression results indicated that plasma magnesium levels in the third quantile were inversely associated with hyperuricemia risk [OR (95% CI) = 0.634 (0.476, 0.867)], while the quartile levels of plasma iron, nickel, strontium, molybdenum, and tin were positively associated with the risk of hyperuricemia (OR values: 1.432, 1.544, 1.928, 1.395, and 1.372, respectively; all $P < 0.05$) (Guan et al. 2025); A study in Hunan, China, with participants aged 40 and above (n = 6,337) found a positive dose-response link between serum calcium levels and hyperuricemia risk (Liu et al. 2019). Nonetheless, there are limited studies on the link between metal exposure and hyperuricemia among workers. A prospective cohort study was carried out in Kailuan, China (n = 3,706), a WQS regression model revealed a positive association between metal mixtures and the likelihood of hyperuricemia, primarily influenced by iron, magnesium, lead, and zinc (Wang et al. 2024). A study examining Chinese coke oven workers (n = 1,379) found that higher levels of rubidium and strontium in urine were significantly associated with a lower risk of hyperuricemia ($P_{trend} < 0.05$)(Guo et al. 2023). Given inconsistent findings in previous studies, tmaking it essential to study the connection between mixed metal exposure and hyperuricemia, as well as the dose-response relationship in occupational populations.

Owing to the buildup of toxic metals within the organism and their rather extended half-lives, current blood metal concentrations in retired workers better reflect their cumulative exposure throughout their entire careers. Furthermore, a "healthy worker effect" may exist among active workers-that is, those in

poor health may have been transferred to other positions, leaving only healthy individuals in their original roles-which could lead to an underestimation of the hazards of occupational exposure. Therefore, based on a cohort of retired workers with a history of occupational metal exposure, this study examined the link between serum levels and hyperuricemia and evaluated the influence of a past of chronic industrial metal involvement on the likelihood of hyperuricemia.

2. Materials and methods

2.1 Study Participants

The subjects for this research were selected from the manganese-exposed employees health cohort-Retired Personnel Sub-cohort. The study adopted the following inclusion criteria: (1) workers employed at a manganese-iron alloy smelter in Guangxi prior to retirement; (2) six months or longer local residence after retirement; (3) voluntary participation in health examinations and questionnaire surveys. A total of 623 individuals were enrolled. The following exclusion criteria were applied: (1) missing whole blood manganese data (n = 13), (2) missing ethnicity or education level data (n = 3), (3) missing glomerular filtration rate data (n = 1), (4) pre-existing kidney disease prior to study initiation (n = 18), and (5) medication use affecting UA levels (n = 5) Ultimately, 583 participants were included in this study All survey content and relevant testing procedures were explained in detail to the study participants prior to the study's commencement, and informed consent forms were voluntarily signed by the participants

2.2 Epidemiological Data Collection

Trained investigators administered a questionnaire designed specifically for this study on-site, guiding participants face-to-face as they filled out basic information, including demographic characteristics (name, gender, height, weight, age, marital status, etc.), daily habits (smoking and drinking habits, educational background, etc.), medical history, medication history, allergy history, and occupational history.

2.3 Physical Examination

Health examinations for retired workers were conducted by licensed physicians. The test involved measuring height, weight, blood pressure etc. The examination should measure the height and weight of the examinee with his/her feet bare. They measured the outcomes to one decimal place (0.1kg or 0.1cm) and determined body mass index (BMI). BMI was recorded as kg/m^2.

2.4 Whole Blood Metal Concentration Determination

The blood samples are kept in an ultra-low temperature freezer at -80℃. Prior to use, they should be heated gradually and eventually at room temperature. Then, 0.1mL of blood sample is aspirated and diluted with diluent, i.e., 0.1 percent nitric acid, 0.1 percent Triton, and 1 percent n-butanol, up to a final volume of 2 mL. The solution is put into an inductively coupled plasma mass spectrometer (ICP-MS) to quantify the levels of 21 elements in whole blood, which include magnesium, calcium, titanium,

vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, arsenic, selenium, rubidium, strontium, molybdenum, cadmium, tin, antimony, barium and lead. The detection limits (LOD) of 21 metals were in the range of 0.001-2.020ug/L. To calculate concentrations of metals below LOD, the square root of 2 was divided by the LOD values.

2.5 Blood Sample Collection and Serum UA Level Testing

Licensed nurses from the hospital collected four tubes of 5ml fasting peripheral venous blood from study subjects between 7:00 AM and 10:00 AM. Two tubes contained EDTA (Ethylenediaminetetraacetic Acid) anticoagulant, and two tubes contained clotting agent. Blood testing was performed using the hospital laboratory's fully automated biochemical analyzer.

2.6 Definition of Terms

Hyperuricemia diagnostic parameters are derived in accordance with the Chinese Guidelines on the Diagnosis and Treatment of Hyperuricemia and Gout (2019). Hyperuricemia had been defined as SUA level greater than 420 mol/L (Endocrinology 2020).

The category of smoking may be categorized into three types such as: current smoker, ex-smoker, and non-smoker. Current smoker is a person who has been taking at least one cigarette daily within the last 6 months or more. The ex-smoker is a person who stopped smoking 6 months or more. Those who have not ever smoked are called never smokers.

The category of drinking may be categorized into three types such as: current drinker refers to consuming at least 5 milliliters per drinking occasion for more than 3 months. former drinker refers to abstaining from alcohol for over 2 weeks. Never drinker refers to having no history of alcohol consumption (Li 2018).

The diagnostic criteria of hypertension are based on the Chinese Hypertension Prevention and Treatment Guidelines, i.e., blood pressure of at least 140 mmHg (systolic) and/or 90 mmHg (diastolic) without antihypertensive treatment. Alternatively, retired workers who report a prior diagnosis of hypertension and are currently taking antihypertensive medication may also be diagnosed with hypertension.

Diabetes: The study participant self-reports a history of diagnosed diabetes or was currently taking hypoglycemic medication for treatment.

The estimated value of glomerular filtration rate (eGFR):

$$\begin{aligned} \mathrm{eGFR}\left(\frac{\mathrm{ml}}{\mathrm{min}}\mathrm{m}^2\right) &= 175\times(\mathrm{Scr})^{-1.154}\times\mathrm{age}^{-0.203} \\ &\quad \times 0.742(\mathrm{if\ female})\times 1.212(\mathrm{if\ black}), \end{aligned}$$

Among these, Scr is expressed in mg/dL, and age is expressed in years(Levey et al. 2006). According to the KDIGO CKD Clinical Practice Guidelines for Evaluation and Management (2024 Edition)(Stevens et al. 2024) eGFR is categorized as follows: ≥90mL•min-1•m-2 is considered normal or high; 60-89.9mL•min-1•m-2 indicates mild decline; and < 60mL•min-1•m-2 signifies mild to moderate decline.

2.7 Statistical Methods

The data given above were statistically analyzed using SPSS 27.0 and R 4.4.3, all analyses employed two-tailed tests, with statistically significant differences were achieved at a level of $P < 0.05$. In descriptive analysis, categorical variables were expressed in number (%). Continuous variables underwent Shapiro-Wilk normality testing. Those that fulfilled the normality assumption were expressed as (mean standard deviation) but others that did not fulfill the normality assumption were expressed as median (25th percentile, 75th percentile). The classification of the subjects into the groups based upon their hyperuricemia state was non-hyperuricemic group (n = 526) and hyperuricemic group (n = 57). To examine the differences among the groups, chi-square tests (when the data are categorical) and Mann-Whitney U test or Kruskal-Wallis H test (when the data are continuous) were performed. Because the distributions of whole blood metals were skewed, the subsequent analyses included whole blood metals in the model after log10 transformation.

To address the multicollinearity issue in the metal mixture, we selected the LASSO regression with ten-fold cross-validation (using the "glmnet" package). After determining the key metals that are connected to hyperuricemia, the best penalty parameter (= lambda) which minimized the mean square error (MSE) was obtained through optimization. Then, a Bayesian kernel machine regression (BKMR) was employed to investigate how the combined effect of the key metals, the exposure-response relationship, and the metal-metal interactions affected the outcome. The posterior inclusion probability (PIP) was used as a measure of quantifying the importance of the metals. Meanwhile, the dose-response relationship curves of the metals chosen by LASSO and hyperuricemia were calculated using restricted cubic splines, investigating the dose-response relationships.

3. Results

3.1 Basic demographic characteristics and UA levels of the study participants

Table 1 gives the demographics and the uric acid levels of study participants. Finally, every one of the 583 retirees who participated in this research was assigned to non-hyperuricemia group (n = 526) or hyperuricemia group (n = 57) depending on the presence of hyperuricemia. The group with hyperuricemia had significantly higher uric acid levels than the non-hyperuricemia group (median, 451.0 μmol/L vs. 287.0 μmol/L). The mean ages of the non-hyperuricemic and hyperuricemic participants were 72.0 and 75.0 years respectively, and there was a tendency of longer service length among the hyperuricemic participants, and their BMI was higher with median 28.0 years and 34.0 years and 23.4 kg/m^2 and 25.2

kg/m^2 respectively ($P < 0.05$). The median glomerular filtration rate of the non-hyperuricemia group was 70.0 mL•min^{-1}•m^{-2} whereas it was 53.3 mL•min^{-1}•m^{-2} in the hyperuricemia group respectively. ($P < 0.05$).

The hyperuricemia group contained more men, current and ex-smokers, current and ex-drinkers as compared to the non-hyperuricemia group (all $P < 0.001$). The results of the comparison of both groups showed that there were no statistically significant differences regarding the ethnicity ($P = 0.404$), marital status ($P = 0.218$), education level ($P = 0.753$) and the prevalence of diabetes ($P = 0.066$).

3.2 Metal Levels in Whole Blood of Study Participants

The levels of metals in whole blood of the study subjects are shown in Table 2. The content of calcium, titanium, manganese and copper in whole blood showed a significant reduction in hyperuricemia group over non-hyperuricemia group (all $P < 0.05$) and the content of iron, zinc, arsenic, rubidium, strontium, molybdenum, and lead in whole blood was significantly increased in hyperuricemia group over non-hyperuricemia group (all $P < 0.05$). Other metals did not show any statistically significant difference in their concentrations in whole blood across both groups (all $P > 0.05$).

3.3 Screening for Key Metals Associated with Hyperuricemia Using the LASSO Model

Using a LASSO model combined with 10-fold cross-validation, we performed variable selection on 21 log-transformed whole-blood metal markers and determined the optimal regularization parameter (λ.min) based on the minimum mean squared error (MSE). The LASSO coefficient path plot shows that as Log (λ) increases, the regression coefficients of the metal variables are gradually compressed to 0. Ultimately, 10 key metals associated with hyperuricemia were identified: Mg, Ca, Ti, Mn, Co, Se, Rb, Sr, Mo, and Ba (as shown in Fig. 1).

3.4 BKMR Analysis of the Association Between Mixed-Metal Exposure and Hyperuricemia

The 10 critical metals found in the LASSO were included in a Bayesian Kernel Machine Regression model (BKMR) to determine the total effect of the metal mixture, the significance of each metal individually, the exposure-response relationship, and metal interactions (as shown in Fig. 2). Among ten metals, Sr (PIP = 0.95), Rb (PIP = 0.82), Mn (PIP = 0.81), Ca (PIP = 0.71), and Mg (PIP = 0.62) were the primary drivers. The specifics of how univariate exposure-responses are related are described in Fig. 2a. The analysis of single-metal effect estimates revealed a significant positive correlation between Sr and Rb and hyperuricemia (Fig. 2b). When other metals were held constant at the 75th and 25th percentiles, respectively, the effect estimates for each metal did not change significantly, and no interaction between metals and hyperuricemia was observed (Fig. 2c). The BKMR results showed that, compared with the 50th percentile level, ten metal mixture revealed a positive overall effect on hyperuricemia risk (Fig. 2d).

3.5 Dose-Response Associations of Whole-Blood Metal Concentrations With Hyperuricemia

The findings of the restricted cubic spline regression of whole-blood metal concentration and hyperuricemia are depicted in Fig. 3. The results of the analysis of whole-blood metal concentrations after they were transformed to the log10 scale and included in the restricted cubic spline model showed that the association between whole-blood magnesium and hyperuricemia was significantly linear ($P_{overall}$=0.0090, $P_{nonlinear}$>0.05), whole-blood calcium and hyperuricemia had a U-shaped dose-response curve ($P_{overall}$=0.0245, $P_{nonlinear}$=0.0214), and whole-blood manganese and hyperuricemia also had a U-shaped dose-response correlation($P_{overall}$<0.001, $P_{nonlinear}$=0.0003), whole-blood strontium and hyperuricemia had positive and linear relationships ($P_{overall}$=0.0007, $P_{nonlinear}$>0.05), and the dose-response correlations between hyperuricemia and other metals were all statistically nonsignificant ($P_{overall}$>0.05, $P_{nonlinear}$>0.05).

4. Discussion

Based on a cross-sectional design, we investigated the association and dose-response relationship between whole-blood metal concentrations and the risk of hyperuricemia. Our data indicated that combined metal exposure burden was correlated with elevated risk of hyperuricemia, with Sr (PIP = 0.95), Rb (PIP = 0.82), Mn (PIP = 0.81), Ca (PIP = 0.71), and Mg (PIP = 0.62). Results from restricted cubic spline analysis showed a significantly linear and negative correlation between Mg in relation to hyperuricemia, a U-shaped dose-response pattern for Ca, Mn with respect to hyperuricemia, together with a positive and linear correlation between Sr and hyperuricemia.

Magnesium functions as an indispensable trace element and co-factor for various biocatalysts and participates in uric acid metabolism through multiple mechanisms, including improving insulin resistance, reducing inflammatory responses, and regulating urate reabsorption within kidney tubules (Kunze et al. 2015). Current research findings regarding the links between magnesium as related to hyperuricemia are inconsistent. Results from a Chinese Kailuan cohort study (n = 3,706) showed that serum magnesium concentrations in the hyperuricemia group (median: 44.85μg/mL) displayed markedly higher values compared with participants without hyperuricemia (median: 40.03μg/mL), and increased magnesium levels were linked to higher odds of hyperuricemia among Chinese adults (Wang et al. 2024); however, several investigations have shown an inverse correlation between plasma and serum magnesium levels with regard to hyperuricemia risk (Cao et al. 2020; Wang et al. 2018; Zeng et al. 2015). The differences between tour present findings and earlier published outcomes may stem from several factors. First, the biomarkers used differ: most studies employ serum or plasma magnesium, which reflect transient extracellular concentrations; this study measured whole-blood magnesium, which incorporates intracellular storage pools and better represents long-term systemic magnesium status. Second, the range of exposure differs: the whole-blood Mg concentrations among non-hyperuricemia group and the hyperuricemia group within our present investigation (median values of 41.3μg/mL and

42.9μg/mL, respectively) showed no statistically meaningful gap between the two groups ($P > 0.05$). Compared with data from the Kailuan cohort, the difference in the range of whole-blood Mg concentrations was not significant.

Calcium, as the most plentiful mineral inside the human organism, is vital for maintaining normal physiological functions. This study showed a U-shaped dose-response pattern for whole-blood calcium in relation to hyperuricemia. This differs from the findings of most studies, which showa positive correlation linking serum calcium to hyperuricemia risk (Gu et al. 2022; Liu et al. 2019; Wang et al. 2024); however, certain investigations have reported non-linear associations. For example, a U.S. study involving adults aged 18 years and older (n = 20,028) found a non-linear positive correlation between total calcium and hyperuricemia (Pnonlinearity = 0.024) (Hong Lei and Guan). This discrepancy may be attributed to the wider range of calcium exposure among the occupational population, which includes both individuals with lower and higher calcium levels. The risk at the low-calcium end may be associated with endocrine and metabolic disorders; secondary hyperparathyroidism is a well-established consequence of hypocalcemia. Studies have shown that elevated parathyroid hormone can downregulate the expression of renal and intestinal urate transporters (such as ABCG2), thus lowering urate elimination (Lin et al. 2019). Furthermore, hypocalcemic status is linked to the pathogenesis of insulin resistance. Hyperinsulinemia, a marker of insulin resistance, can enhance renal tubular reabsorption of uric acid by upregulating transporters such as URAT1 (Toyoki et al. 2017), leading to uric acid accumulation. In contrast, risks associated with the high-calcium end may be mediated by renal calcium deposition and renal dysfunction (Coe et al. 2016). Chronic hypercalcemia can lead to renal calcium deposition and tubular damage, impairing glomerular filtration and tubular secretory functions, resulting in impaired uric acid excretion and elevated uric acid concentrations (Gu et al. 2022). Furthermore, intracellular calcium overload can induce mitochondrial dysfunction and oxidative stress(Cole et al. 2022), exacerbating renal interstitial fibrosis and vascular sclerosis, and promoting increased uric acid levels. Overall, further research-particularly prospective studies-is needed to confirm our findings.

Manganese, an indispensable trace element required by human organisms, maintains uric acid homeostasis through various mechanisms within physiologically appropriate concentration ranges. Here we observed a U-shaped dose-response pattern for Mn in relation to hyperuricemia, which agreed well with that among the general adults from the United States (Cao et al. 2020; Munusamy and MacMillan-Crow 2009). A cross-sectional survey (n = 3,926) conducted at Wuhan University in China to assess the correlation between a mixture of metals and serum urate concentrations and hyperuricemia status found that, through analysis based on generalized linear regression model, urinary manganese exhibited negatively correlated with hyperuricemia risk (Zeng et al. 2015). Results from another cohort study (n = 6,886) based on the 1997–2009 China Health and Nutrition Survey showed that dietary manganese consumption was negatively correlated against hyperuricemia (Chen et al. 2024). The inconsistency among the above study results may stem from the following mechanisms: When manganese is deficient, organismal MnSOD levels decrease, which could induce mitochondrial dysfunction, thereby promoting excessive accumulation of ROS and aggravating oxidative-stress-mediated injury (Munusamy and

MacMillan-Crow 2009). On the one hand, increased oxidative stress elevates XO activity, promoting uric acid production (Chen et al. 2023); on the other hand, excessive ROS production causes sustained injury to proximal renal tubule cells, bringing about reduced eGFR and preventing the adequate reabsorption of uric acid, which ultimately results in hyperuricemia (Chen et al. 2023). When manganese is present in excess, the body's MnSOD levels may decrease or its function may be impaired, leading to mitochondrial dysfunction. This, in turn, results in insufficient clearance of superoxide anions (O_2^-), while dysfunction of the electron transport chain (ETC) causes further electron leakage, increasing ROS levels, exacerbating oxidative stress damage, and raising uric acid levels.

Strontium represents a trace element that readily accumulates within human skeletal tissues, but its mechanisms underlying biological effects remain unclear. Previous studies have suggested that strontium has a protective association with the development of hyperuricemia (Guo et al. 2023) and may mitigate damage caused by oxidative stress. The results of one cross-sectional investigation conducted among residents of Hunan, China (n = 2021) showed that serum strontium had a negative effect on hyperuricemia risk, with strontium (− 43.6%) acting as the major contributing factor (Dai et al. 2026). However, other investigations have yielded divergent findings. One prospective cohort analysis (n = 3,957) indicated that elevated plasma Sr concentrations were linked to higher odds of hyperuricemia (Xu et al. 2023); another cross-sectional survey in rural Guangxi (n = 3,379) joint exposure to a blend of various metals displayed positive correlations with the risk of hyperuricemia, with Sr together with Fe being major risk determinants (Guan et al. 2025). These findings aalign with our current experimental outcomes, prompting further consideration of the mechanisms by which strontium affects the human body. Existing researches demonstrate that serum strontium levels in patients suffering from uremia are significantly higher than in those with normal renal function (Cabrera et al. 1999). In another cohort study of pregnant women, serum strontium was found to be negatively correlated with total antioxidant activity (TAA) (r = − 0.40) (Barneo-Caragol et al. 2018). These findings may suggest that strontium is excreted via the kidneys; elevated strontium levels may induce oxidative stress, leading to DNA damage (Lu et al. 2016), which in turn affects uric acid metabolism and results in hyperuricemia. Therefore, this apparent contradiction likely stems from differences in the study populations and biomarkers; future research should focus on elucidating the mechanisms underlying the biological roles of strontium in blood and urine across different populations.

This study has the following strengths: Using BKMR, RCS, and logistic regression models, it revealed dose-response relationships between whole-blood metal levels of Sr, Rb, Mn, Ca, and Mg and hyperuricemia in a cohort of retired occupational workers after adjusting for potential confounding factors, and plotted dose-response curves. Second, compared with single-metal analysis, the mixed-exposure model provides a more accurate reflection of actual occupational exposure. This study has the following limitations: First, all study participants were drawn from the retired worker sub-cohort of a health cohort of occupationally exposed workers; therefore, tour findings cannot be generalized toward the general public. Second, the sample size is relatively limited and the sample distribution was uneven, so the findings require further validation. Third, as a cross-sectional study, this research could only

conduct an association analysis and cannot draw any conclusions regarding causality; prospective cohort researches are required to further verify these observations.

5. Conclusion

The present investigation found that occupational mixed metal exposure is correlated with elevated odds of hyperuricemia among retired workers, with strontium, rubidium, manganese, calcium, and magnesium being the primary contributing metals. Manganese and calcium exhibited a U-shaped dose-response relationship with hyperuricemia susceptibility, while magnesium demonstrated a significant linear association with hyperuricemia. Strontium exhibited a positive linear correlation, and elevated blood rubidium concentrations were significantly linked to higher risk of this condition. These findings provide population-based support for health-related risk evaluation and establishment regarding exposure limits for metals; however, they still require further validated through big-sample cohort investigations and lab-based experimental research to elucidate the underlying mechanisms.

Declarations

Competing interest

The authors have no relevant financial or non-financial interests to disclose.

Ethical Approval

The study was approved by the medical ethics committee at Guangxi Medical University (ID:2018077).

Consent to participate

Written informed consent was obtained from all individual participants included in the study.

Consent for publish

All participants agreed to the publication.

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Author Contribution

Jianxun Chen: Writing - original draft, Writing - review & editing; Hainqin Liu: Writing - review & editing; Pengfei Duan: Writing - original draft, data analysis; Zhirui Xie: data analysis; Siqi Huo: data analysis; Mingli Zhang: Investigation, Data curation; Junxiu He: Investigation, Data curation; Ying Yang: Investigation, Data curation. Sencai Lin: Investigation, Data curation. Xiaoting Ge: Supervision, Project administration; Xiaobo Yang: Supervision.

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Data Availability

Data will be made available on reasonable request.

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Tables

Tables 1 and 2 are available in the Supplementary Files section.

Figures

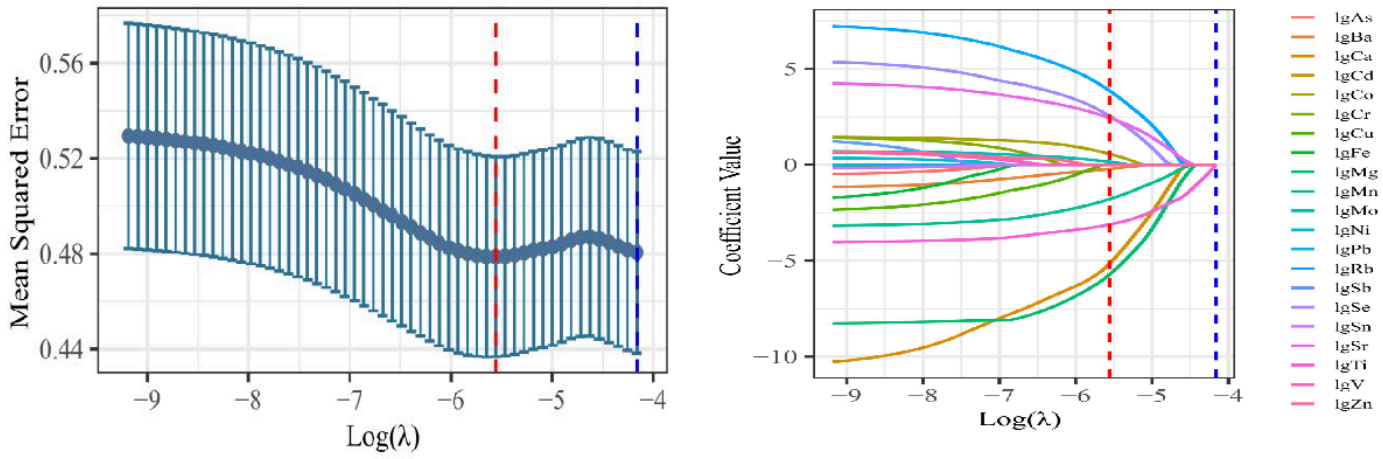


Figure 1

The LASSO penalized regression analysis for the associations between whole blood metals and hyperuricemia.

Prediction mean square error (left) and the path of estimated coefficient (right) of metals in the LASSO model. We predicated an optimal model using tenfold cross-validation, according to λ, where the mean square error (MSE) was the minimum (vertical red dashed line). Models were adjusted for age, seniority, gender, ethnicity, marital status, education, smoking status, drinking status, BMI, hypertension, diabetes, and eGFR but not shows in graph.

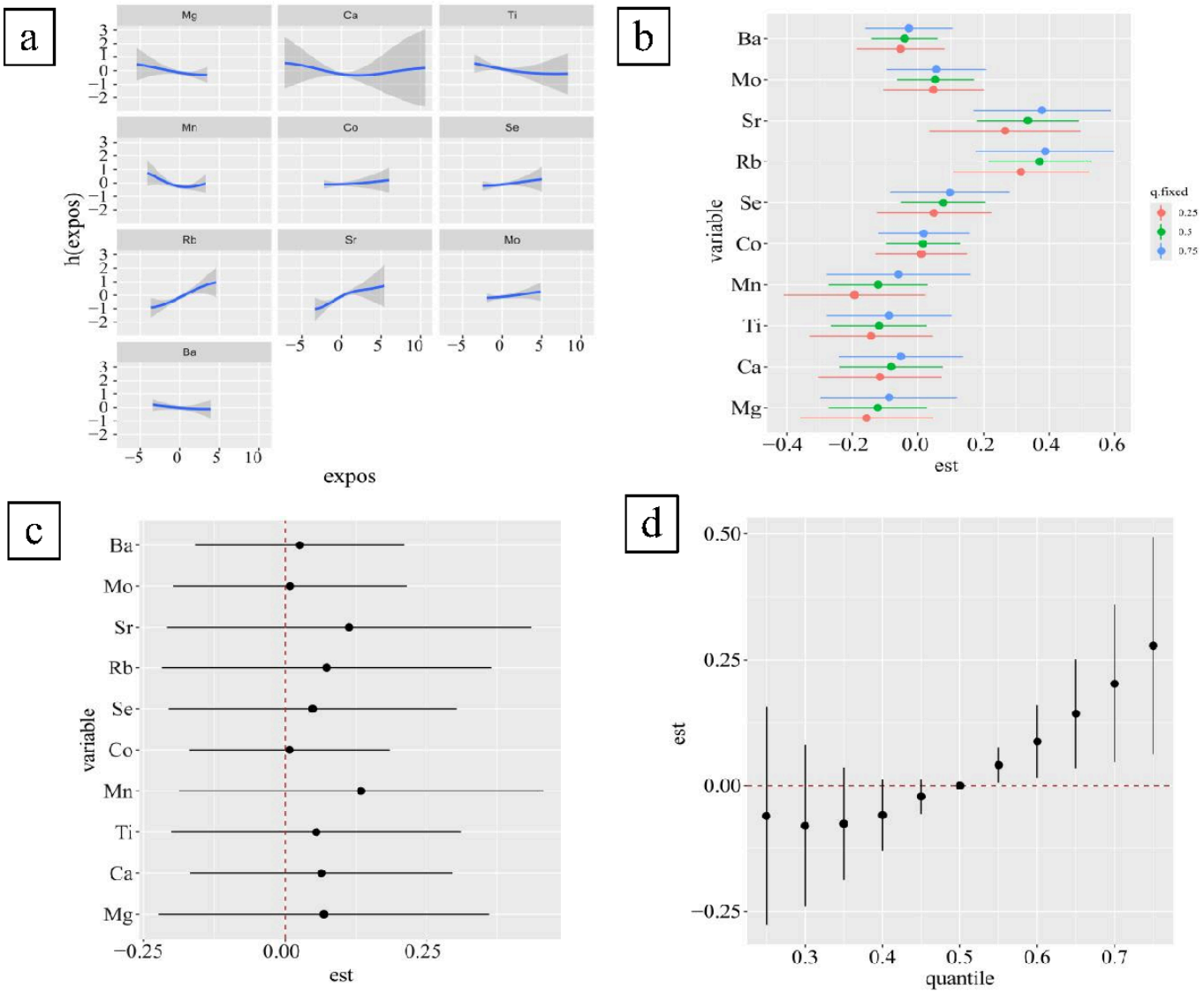


Figure 2

Associations between whole blood metals and hyperuricemia estimated by BKMR models.

Figure a: Univariate exposure–response functions and 95% confidence bands for each metal with the other metals fixed at the median. Figure b: Single metal association (estimates and 95% confidence intervals). This plot compares the probit of hyperuricemia when a single metal is at the 75th vs. 25th percentile, when all the other exposures are fixed at either the 25th, 50th, and 75th percentile. Figure c: Interaction plot. Compare the single-exposure health risks when all the other exposures are fixed to their 75th percentile to when all the other exposures are fixed to their 25th percentile. Figure d: Overall association between the whole blood metals (estimates and 95% confidence intervals) and hyperuricemia. This figure plots the estimated difference in the probit of hyperuricemia when exposures are at a particular percentile (x-axis) in comparison with when exposure are all at the 50th percentile.

Models were adjusted for age, seniority, gender, ethnicity, marital status, education, smoking status, drinking status, BMI, hypertension, diabetes, and eGFR.

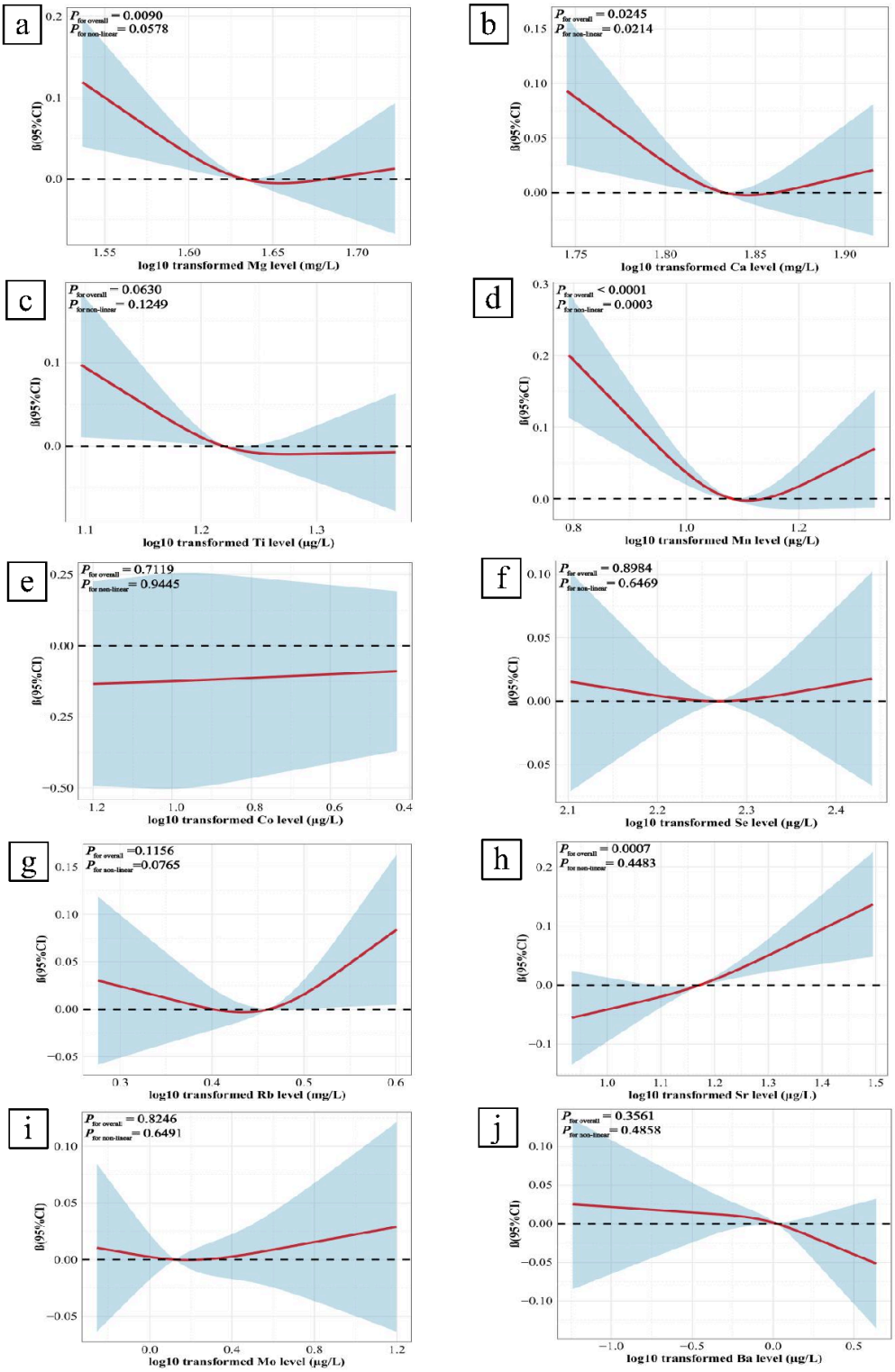


Figure 3

Restricted cubic spline analysis of whole blood metals and hyperuricemia

Figure a: Mg; Figure b: Ca; Figure c: Ti; Figure d: Mn; Figure e: Co; Figure f: Se; Figure g: Rb; Figure h: Sr; Figure i: Mo; Figure j: Ba. The red curve represents the dose-response relationship between whole blood Mn, Pb, As, Cu, Fe, and hyperuricemia. The blue area denotes the 95% confidence interval (CI). Restricted cubic spline analysis included log10-transformed whole blood levels of metals and hyperuricemia, adjusted for age, seniority, gender, ethnicity, marital status, education, smoking status, drinking status, BMI, hypertension, diabetes, and eGFR.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table12.xlsx