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The association between blood and urine heavy metal levels and the risk of rheumatoid arthritis in U.S. adults: A cross-sectional study of NHANES 2011-2020

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ABSTRACT

Objective: To examine the association between blood and urine heavy metal concentrations and the risk of rheumatoid arthritis (RA) in U.S. adults using data from the National Health and Nutrition Examination Survey (NHANES) 2011-2020. **Methods:** We analyzed data from 5,530 participants aged ⩾20 years. Heavy metal levels were measured via mass spectrometry, and RA was diagnosed based on self-reported physician diagnosis. Multivariate logistic regression models were used to assess the relationship between heavy metals and RA risk, adjusting for potential confounders including age, gender, BMI (body mass index), race, education level, marital status, smoking history, diabetes history, hypertension history, coronary heart disease history, and serum albumin levels. Subgroup analyses and interaction tests were also conducted. **Results:** Elevated blood cadmium levels (OR = 1.23, 95% CI: 1.05-1.44) and urine lead levels (OR = 1.31, 95% CI: 1.09-1.57) were positively associated with RA risk, while higher blood mercury levels were inversely associated (OR = 0.78, 95% CI: 0.67-0.91), though this finding may reflect residual confounding rather than a true protective effect. Dose-response relationships were observed for these metals. The negative correlation between blood mercury and RA was stronger among non-smokers and individuals with diabetes (P<.05 for interaction). **Conclusion:** Elevated blood cadmium and urine lead levels are associated with increased RA risk, whereas higher blood mercury levels were inversely associated with RA, although this relationship likely reflects residual confounding rather than a biologically protective effect of mercury. These relationships are influenced by smoking and diabetes status. Further prospective studies are needed to establish causality and explore the underlying mechanisms.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disease primarily affecting joints and periarticular soft tissues [1]. Clinically, RA is characterized by joint pain, stiffness, and swelling [2]. Extra-articular manifestations may include subcutaneous nodules, anemia, fever, weight loss, pulmonary fibrosis, and coronary artery dysfunction [1][3]. In the absence of effective treatment, RA can lead to progressive joint damage, culminating in disability and a significant reduction in the quality of life for patients [4]. The precise etiology of RA remains elusive; however, it is widely accepted that immune dysregulation, inflammatory pathways, genetic predispositions, environmental exposures, and metabolic disturbances all contribute to its pathogenesis [5]. In recent years, environmental pathogenic factors have garnered considerable research attention. Heavy metals encompass toxic elements such as arsenic, cadmium, lead, mercury, as well as essential trace elements including chromium, cobalt, copper, magnesium, manganese, molybdenum, nickel, selenium, tungsten, vanadium, iron, and zinc. These metals are recognized as detrimental environmental pollutants due to their ubiquitous presence in air, water, soil, food, and industrial products [6]. Exposure to heavy metals can induce a spectrum of lesions across various organs and tissues, encompassing neurological dysfunction, cardiovascular diseases, reproductive impairments, renal disorders, respiratory illnesses, and acute poisoning symptoms [7]. Currently, the role of heavy metal exposure in the induction of autoimmune diseases is garnering increasing attention. For

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instance, elevated levels of lithium and lead in blood have been shown to significantly influence the incidence of systemic lupus erythematosus [8]. Furthermore, urinary levels of barium, cesium, antimony, uranium, and cadmium have been positively associated with the risk of psoriasis [9]. Serum albumin, the most abundant protein in the human body, plays a pivotal role in the transport, absorption, metabolism, distribution, and excretion of drugs [10]. It also serves as a crucial carrier for the transport of various metal ions, modulating their aggregation and playing a significant role in the pathogenic processes involving heavy metal ions [11][12]. However, the capacity of serum albumin to bind heavy metal ions and its impact on the risk of RA remains unclear. Consequently, in light of the current research landscape, this study aims to further investigate the potential association between heavy metal levels in blood and urine and the risk of RA. Additionally, through mediating effect analysis, this study seeks to preliminarily explore the role of serum albumin in this relationship.

2. Materials and Methods

2.1. Database Selection and Inclusion/Exclusion Criteria for Study Population

The National Health and Nutrition Examination Survey (NHANES) is a comprehensive cross-sectional survey conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention in the United States. It assesses the health and nutritional status of the U.S. population through a combination of interviews, physical examinations, and laboratory tests. In this study, we included a total of 45,462 subjects from NHANES 2011-2020. Among them, 24,968 participants were excluded due to being under 20 years of age, 60 participants were excluded due to lack of RA history information, 14,432 participants were excluded due to lack of heavy metal data, and 472 participants were excluded due to lack of covariate data. Finally, 5,530 participants who met all the criteria were included in this study. The detailed screening process is shown in Fig 1. The data were accessed for research purposes on January 10, 2026. The Ethics Review Board of the National Center for Health Statistics approved all NHANES protocols. Specifically, the NHANES protocols for the years 2007-2008 and 2009-2010 were approved under Protocol 2005-06; the protocols for 2011-2012, 2013-2014, and 2015-2016 were approved under Protocol 2011-17; and the protocols for 2017-2018 and 2019-2020 were approved under Protocol #2018-01. The study utilized data from NHANES, a publicly available dataset. All methodologies were conducted in compliance with pertinent guidelines and regulations, including the Declaration of Helsinki. Prior to study participation, all individuals provided written consent. The datasets utilized in the present study can be accessed from the NHANES database at https://wwwn.cdc.gov/nchs/nhanes/.

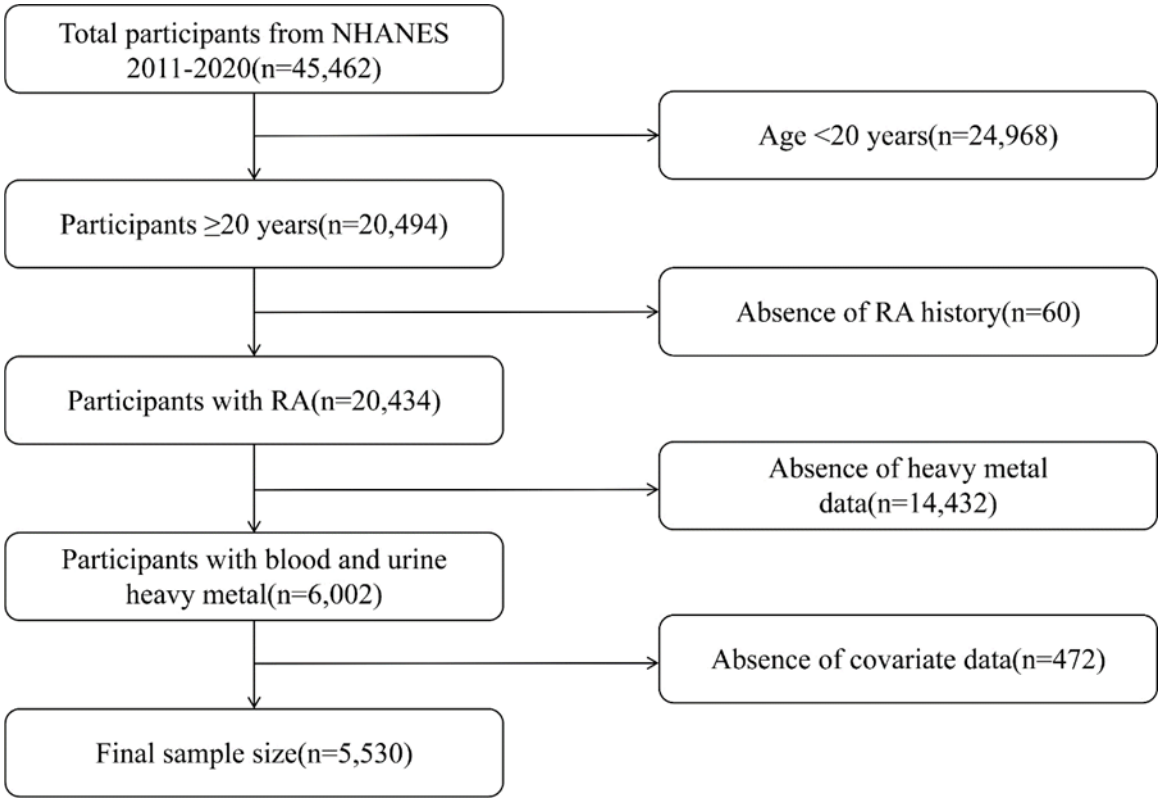

Fig. 1 - Flow chart of study population inclusion and screening. Abbreviations: NHANES, National Health and Nutrition Examination Survey; RA, rheumatoid arthritis.

2.2. Measurement of Heavy Metal Levels

Blood and urine heavy metal samples were collected at the mobile examination center. Non-fasting blood samples were collected through venipuncture, and 24-hour urine samples were collected. The collected blood and urine samples were transported to the National Center for Environmental Health of the Centers for Disease Control and Prevention in Atlanta, Georgia, at a frozen temperature of -30°C. Heavy metal

concentrations in the blood and urine samples were measured by mass spectrometry. Detailed laboratory testing methods can be obtained from the NHANES website (https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx).

2.3 Diagnosis of RA

The history of RA was collected through questionnaires. Participants were asked, "Have you ever been told by a doctor that you have arthritis?" and "What type of arthritis do you have?" If the participant answered "I have had arthritis" and the type was "rheumatoid arthritis," they were considered to have RA. Those who answered "I have never had arthritis" were considered not to have RA.

2.4 Covariates

The covariates in this study included age, gender, BMI, race, education level, marital status, history of hypertension, diabetes, coronary heart disease, smoking history, and serum albumin levels. Age and BMI were entered as continuous variables in all regression models. For subgroup interaction tests only, age was divided into 20-40, 41-60 and 61-80 years, and BMI was categorised according to WHO criteria: ⩽25, 25-30, and >30. We retained coronary heart disease history in the model because chronic lead exposure has been repeatedly associated with atherosclerosis and coronary heart disease, while the systemic inflammatory milieu that characterises RA also accelerates coronary atherogenesis [13][14]. Consequently, coronary heart disease history may act as a shared pathway and potential confounder in the association between heavy metal exposure and RA, and its inclusion helps to mitigate residual confounding attributable to pre-existing cardiovascular disease. Race was categorized as Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other races. Education level was divided into high school or below and greater than high school. Marital status was categorized as married/living with partner, widowed/divorced/separated, and never married.

2.5 Statistical Methods

Continuous data were described using the median (interquartile range), and group comparisons were made using the weighted Mann-Whitney U nonparametric test. Categorical data were expressed as frequency (percentage), and group comparisons were made using the weighted chi-square test to observe the differences in heavy metal indicators in blood and urine and other covariates between the groups. To assess the association between each heavy metal indicator and the risk of RA, three models were set in univariate and multivariate weighted logistic regression analyses. The crude model did not adjust for any confounding factors; Model 1 included age, race, education level, marital status, and BMI; Model 2 further added smoking history, diabetes history, coronary heart disease history, hypertension history, and serum albumin levels. The results were presented as OR and 95%CI. Subsequently, restricted cubic spline plots were constructed to assess the dose-response relationship between heavy metal levels and the risk of RA. Subgroup analyses and interaction analyses were further conducted to obtain the differences in the expression results of the association between heavy metal indicators and the risk of RA in different subgroups. The analysis process was completed using EmpowerStats 4.1 and R 4.2.0, with P<.05 indicating statistical significance.

3. Results

3.1. Characteristics of Participants

A total of 5,530 subjects were included in this study, with 6.2% (341/5,530) having RA and 93.8% (5,189/5,530) not having RA. The details of each indicator in the RA and non-RA groups are shown in Table 1. There were significant statistical differences in age, BMI, blood lead, blood cadmium, blood mercury, blood selenium, blood manganese, serum albumin, urine cadmium, urine cobalt, urine lead, urine tin, urine thallium, race, education level, marital status, history of hypertension, diabetes, smoking, and coronary heart disease between the two groups (P<.05). The levels of blood lead, blood cadmium, urine cadmium, urine lead, and urine tin were higher in the RA group than in the non-RA group, while the levels of blood mercury, blood selenium, blood manganese, urine cobalt, and urine thallium were lower in the RA group than in the non-RA group.

Table1 - Baseline characteristics of the study population

	Non-rheumatoid arthritis	Rheumatoid arthritis	P
N	5,189	341	
Age (years)	42.00 (31.00-57.00)	62.00 (53.00-71.00)	<.001
BMI (kg/m^2)	27.50 (23.90-32.10)	29.20 (26.30-34.10)	<.001
Blood lead (ug/L)	0.91 (0.58-1.48)	1.21 (0.83-1.86)	<.001
Blood cadmium (ug/L)	0.29 (0.18-0.54)	0.36 (0.22-0.66)	.003
Blood mercury (ug/L)	0.74 (0.39-1.63)	0.64 (0.36-1.34)	.006
Blood selenium (ug/L)	190.26 (175.73-206.50)	187.50 (171.84-202.14)	.041
Blood manganese (ug/L)	9.41 (7.55-11.86)	8.50 (6.75-11.08)	<.001
Serum albumin (g/dL)	4.30 (4.00-4.50)	4.10 (3.90-4.40)	<.001
Urine barium (ug/L)	1.02 (0.49-2.04)	0.92 (0.49-1.82)	.172
Urine cadmium (ug/L)	0.18 (0.09-0.37)	0.32 (0.16-0.61)	<.001
Urine cobalt (ug/L)	0.35 (0.19-0.58)	0.34 (0.19-0.57)	<.001

	Non-rheumatoid arthritis	Rheumatoid arthritis	P
Urine cesium (ug/L)	4.33 (2.57-6.57)	4.46 (2.81-6.19)	.231
Urine molybdenum (ug/L)	37.40 (18.71-64.98)	35.50 (21.20-63.49)	.924
Urine manganese (ug/L)	0.09 (0.09-0.15)	0.09 (0.09-0.16)	.142
Urine lead (ug/L)	0.33 (0.18-0.58)	0.41 (0.24-0.74)	<.001
Urine antimony (ug/L)	0.05 (0.03-0.08)	0.05 (0.03-0.08)	.593
Urine tin (ug/L)	0.41 (0.20-0.91)	0.64 (0.32-1.34)	.020
Urine thallium (ug/L)	0.17 (0.10-0.26)	0.15 (0.09-0.22)	.023
Urine tungsten (ug/L)	0.06 (0.03-0.12)	0.06 (0.03-0.12)	.713
Urine mercury (ug/L)	0.21 (0.09-0.49)	0.20 (0.09-0.45)	.367
Sex (%)			.074
Male	2,709 (52.21%)	161 (47.21%)	
Female	2,480 (47.79%)	180 (52.79%)	
Race (%)			<.001
Mexican American	766 (14.76%)	46 (13.49%)	
Other Hispanic	578 (11.14%)	35 (10.26%)	
Non-Hispanic White	1,719 (33.13%)	124 (36.36%)	
Non-Hispanic Black	1,152 (22.20%)	106 (31.09%)	
Other Race	974 (18.77%)	30 (8.80%)	
Education level (%)			.002
High school or below	2,178 (41.97%)	173 (50.73%)	
Greater than high school	3,011 (58.03%)	168 (49.27%)	
Marital status (%)			<.001
Married/Living with partner	3,152 (60.74%)	192 (56.30%)	
Divorced/Widowed/Separated	825 (15.90%)	125 (36.66%)	
Never married	1,212 (23.36%)	24 (7.04%)	
Smoking history (%)			<.001
Yes	2,047 (39.45%)	179 (52.49%)	
No	3,142 (60.55%)	162 (47.51%)	
Diabetes (%)			<.001
Yes	544 (10.48%)	94 (27.57%)	
No	4,645 (89.52%)	247 (72.43%)	
Coronary heart disease (%)			<.001
Yes	129 (2.49%)	21 (6.16%)	
No	5,060 (97.51%)	320 (93.84%)	
Hypertension (%)			<.001
Yes	1,393 (26.85%)	213 (62.46%)	
No	3,796 (73.15%)	128 (37.54%)	

Value in continuous variables are median (Q1-Q3) and frequency (percentage) for categorical variables. Abbreviation: BMI, body mass index.

3.2. The Relationship between Blood and Urine Heavy Metal Levels and RA

Univariate and multivariate weighted logistic regression analyses were conducted to examine the relationship between blood lead, blood cadmium, blood mercury, blood selenium, blood manganese, urine cadmium, urine cobalt, urine lead, urine tin, urine thallium, and RA, as shown in Table 2. In the univariate weighted logistic regression analysis, blood lead, blood cadmium, urine cadmium, urine cobalt, urine lead, and urine tin levels were positively correlated with RA, while blood mercury, blood selenium, blood manganese, and urine thallium levels were negatively correlated with RA. After multivariate weighted logistic regression analysis with Model 1 and Model 2, a positive correlation between blood cadmium and urine lead levels and RA, as well as a negative correlation between blood mercury levels and RA, were still observed.

Table2 Association between heavy metal levels and rheumatoid arthritis

	Crude model OR (95% CI)	P value	Model 1 OR (95% CI)	P value	Model 2 OR (95% CI)	P value
Blood lead (ug/L)	1.13840 (1.08040-1.19952)	<.001	1.05435 (0.98494-1.12867)	.128	1.05493 (0.98394-1.13105)	.132
Blood cadmium (ug/L)	1.27712 (1.08752-1.49978)	.003	1.35292 (1.12188-1.63153)	.002	1.25704 (1.02195-1.54620)	.030
Blood mercury (ug/L)	0.90128 (0.83930-0.96784)	.004	0.90330 (0.83264-0.97995)	.014	0.90868 (0.83700-0.98650)	.022
Blood selenium (ug/L)	0.99537 (0.99094-0.99981)	.041	0.99671 (0.99229-1.00115)	.146	0.99718 (0.99260-1.00177)	.228
Blood manganese (ug/L)	0.93308 (0.90196-0.96528)	<.001	0.97550 (0.94271-1.00943)	.155	0.97998 (0.94706-1.01404)	.246
Urine cadmium (ug/L)	1.59322 (1.33268-1.90469）	<.001	1.23561(0.99223-1.53868）	.059	1.1493 (0.91285-1.44714）	.236
Urine cobalt (ug/L)	1.09642 (1.03482-1.16168）	.002	1.05473(0.98992-1.12378）	.100	1.0617 (0.99523-1.13269）	.069
Urine lead (ug/L)	1.11583 (1.03789-1.19963）	.003	1.10896(1.01236-1.21478）	.026	1.1198 (1.02374-1.22507）	.013
Urine tin (ug/L)	1.02154 (1.00232-1.04114）	.028	1.00905(0.98519-1.03349）	.460	1.0074 (0.98365-1.03184）	.543
Urine thallium (ug/L)	0.37034 (0.15753-0.87062）	.023	1.06727(0.45679-2.49364）	.880	1.16994(0.50222-2.72545）	.716

Crude model: Univariate weighted logistic regression analysis
Model 1: Corrected for age, race, education level, marital status, BMI
Model 2: Corrected for age, race, education level, marital status, BMI, smoking history, diabetes, coronary heart disease, hypertension, serum albumin
Abbreviations: BMI, body mass index.

3.3. Restricted Cubic Spline Plots between Blood Cadmium, Blood Mercury, Urine Lead and RA

Based on the univariate and multivariate weighted logistic regression analysis, restricted cubic spline plots were further constructed to display the relationship between the odds ratios in the logistic regression model and the variables, as shown in Fig 2 (a-c). There was a significant dose-response relationship between blood cadmium, blood mercury, urine lead levels and the risk of RA. An increase in blood cadmium and urine lead levels was associated with an increased risk of RA, while an increase in blood mercury levels was associated with a decreased risk of RA.

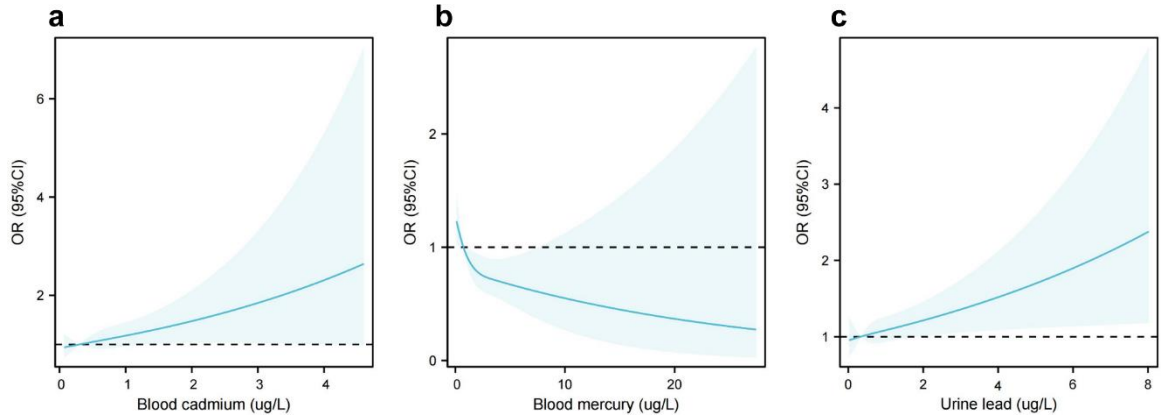

Fig.2 - The restricted cubic plots between blood cadmium, blood mercury, urine lead and RA (a-c).

(a) blood cadmium; (b) blood mercury; (c) urine lead. The horizontal axis represents the levels of blood cadmium, blood mercury and urinary calcium respectively, the vertical axis represents the logical regression OR of the model, the solid line represents the restricted cubic spline curve, and the shaded part represents the 95%CI. Adjusted for age, race, education level, marital status, BMI, smoking history, diabetes history, coronary heart disease history, hypertension history, and serum albumin. Abbreviations: RA, rheumatoid arthritis; BMI, body mass index.

3.4. Subgroup Analysis and Interaction Test

To further analyze whether the correlation between heavy metal exposure and RA is affected by confounding factors, subgroups were set for blood cadmium, blood mercury, and urine lead, respectively, including age, gender, BMI, race, education level, marital status, history of hypertension, diabetes, coronary heart disease, and smoking. The interaction was observed to examine the differences in the results of multivariate weighted

logistic regression analysis in Model 2 in different subgroups. Age was divided into 20-40 years; 41-60 years; 61-80 years, and BMI was divided into ⩽25; 25-30; >30. The detailed results are shown in Fig 3-5. In the subgroup analysis of blood cadmium and urine lead, the P values of interaction were all >.05 in all subgroups, indicating that age, gender, BMI, race, education level, marital status, history of hypertension, diabetes, coronary heart disease, and smoking had no significant impact on the relationship between blood cadmium, urine lead and RA. However, in the subgroup analysis of blood mercury, the P values of interaction in the smoking and diabetes subgroups were <.05, indicating that the relationship between blood mercury and RA was significantly different in populations with different smoking and diabetes histories. For non-smokers and individuals with diabetes, this negative correlation was strong and significant, while in smokers and individuals without diabetes, this association was not significant.

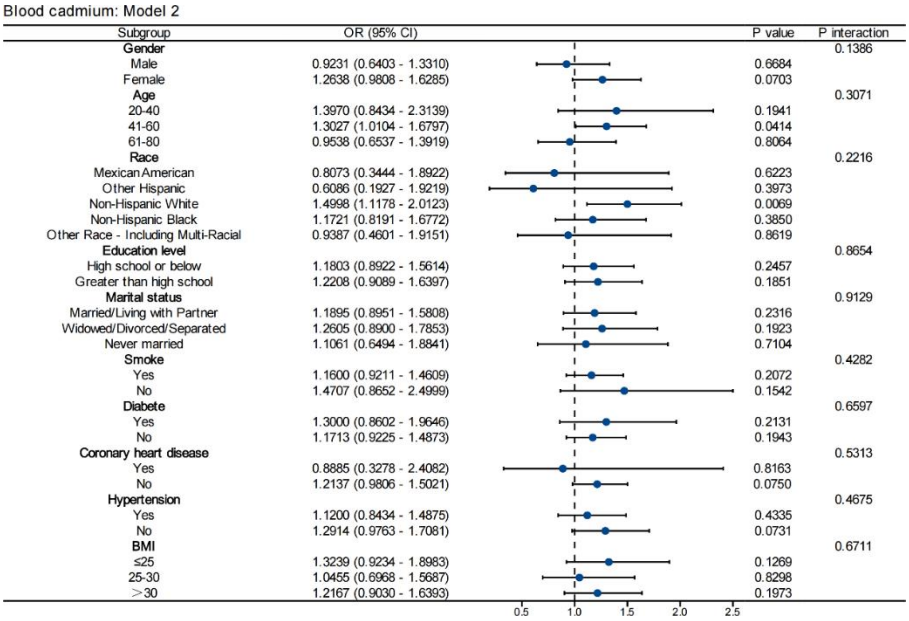

Fig.3 - Subgroup analysis between blood cadmium levels and RA. Abbreviations: RA, rheumatoid arthritis; BMI, body mass index.

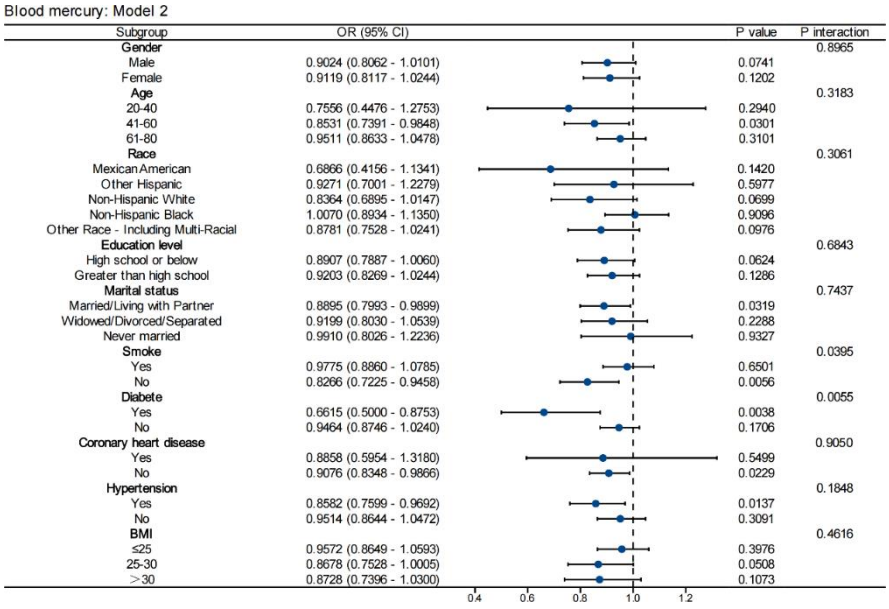

Fig.4 - Subgroup analysis between blood mercury levels and RA. Abbreviations: RA, rheumatoid arthritis; BMI, body mass index.

3.5. 3.5 Supplementary analysis

To evaluate potential selection bias introduced by the exclusion of 14,432 participants with missing heavy-metal data, we compared baseline characteristics between the final analytic cohort (n = 5,530) and those excluded due to absent blood or urine metal measurements, and conducted additional post-weighting and imputation checks.

Among the 45,462 eligible adults aged ⩾20 years identified in NHANES 2011-2020, 14,432 (31.8%) lacked heavy-metal measurements. Table S1 summarizes the baseline characteristics of the 5,530 participants included in the analysis and the 39,932 excluded solely because of missing metal data. Prior to weighting, the prevalence of self-reported RA was virtually identical between groups (6.2% vs. 6.5%, P =.41), and all standardized mean differences for age, gender, race, education level, BMI, smoking history, history of hypertension, diabetes, coronary heart disease were <0.10, indicating negligible imbalance.

After applying the NHANES 2011-2020 ten-cycle examination weights, the marginal distributions of age, gender, race, educational level, and BMI in the final sample differed from the 2020 U.S. Census/American Community Survey benchmarks by ⩽0.4 percentage points (Table S2); all corresponding standardized mean differences were <0.05, confirming national representativeness.

To further assess robustness to the missing-data mechanism, we performed multiple-imputation sensitivity analyses under two extreme scenarios: (A) all missing heavy-metal concentrations were imputed at the 90th percentile of the observed distribution, and (B) all were imputed at the 10th percentile. Twenty multiply-imputed datasets (n = 20,962) were pooled using Rubin's rules. Adjusted OR for RA (Model 2) shifted by ⩽0.02 and remained statistically significant for blood cadmium, blood mercury, and urinary lead (Table S3).

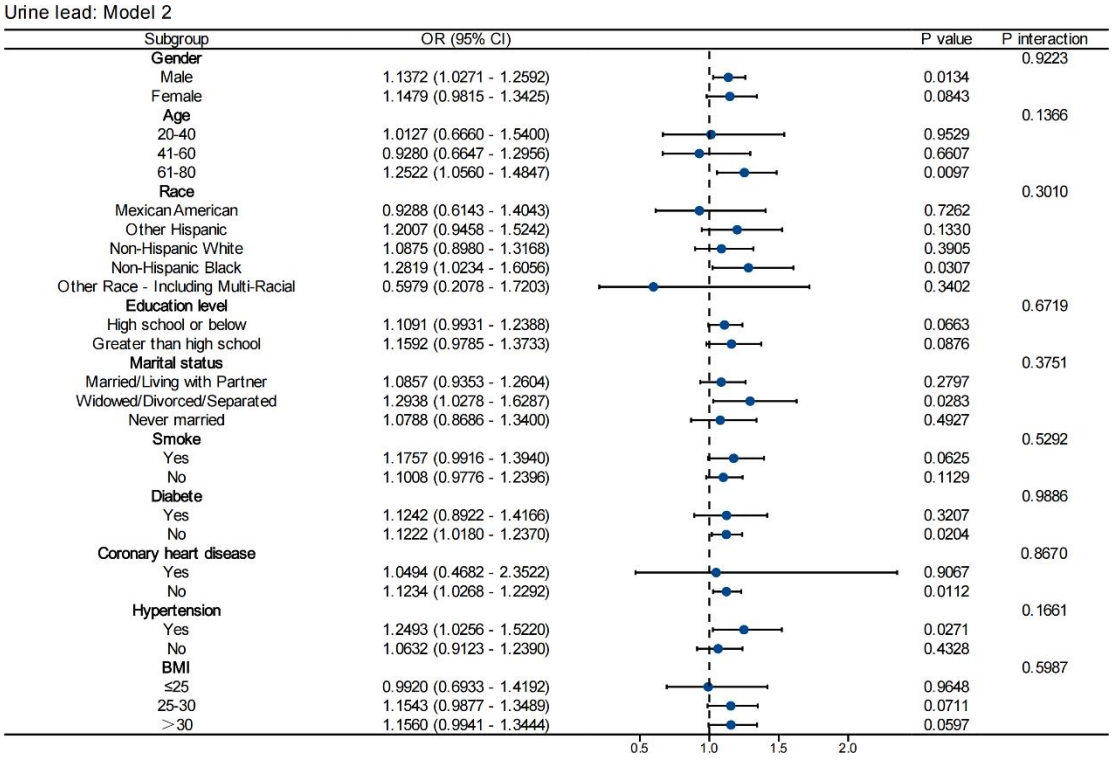

Fig.5 - Subgroup analysis between urine lead levels and RA. Abbreviations: RA, rheumatoid arthritis; BMI, body mass index.

4. Discussion

To the best of our knowledge, lead exposure has been identified as significantly associated with cardiovascular disease, cognitive impairment, chronic kidney disease, and preterm birth [15]. Moreover, the long-term accumulation of cadmium in the body has been shown to be associated with lesions in multiple organ systems, including the kidney, bone, liver, and nervous system [16]. In the present study, a significant positive correlation was observed between blood cadmium and urine lead levels and RA. These findings are consistent with experimental evidence linking these metals to bone-related pathways. For instance, lead exposure has been associated with lower bone mineral density and accelerated bone loss in animal models [17], while both metals have been linked to osteoblast apoptosis through inhibition of Wnt/β-catenin signaling or activation of the mitochondrial p53 pathway, respectively [18][19][20]. Cadmium exposure has also been associated with suppression of BMP-2/4, SMAD4, and p-SMAD1/5/9 complexes, limiting osteogenic differentiation of marrow stromal cells [21], and lead exposure has been linked to decreased osteocalcin and alkaline phosphatase, with potential implications for bone matrix integrity [22]. Because osteoblasts sustain skeletal integrity by synthesizing and mineralizing collagenous matrix [23], and these processes are altered in RA [24], one might speculate that metal-associated osteoblast dysfunction could coincide with the bone-wasting observed in chronic synovitis, though such an interaction remains to be empirically demonstrated. Indeed, persistent synovial inflammation erodes articular cartilage and underlies the progressive joint destruction and osteoporosis characteristic of RA [25][26], while disrupted bone homeostasis produces a net deficit in bone mass [27]. These experimental observations raise the hypothesis that cadmium or lead exposure may be associated with bone perturbations that coincide with, or possibly amplify, inflammation-mediated bone loss observed in RA, a proposition that requires verification in prospective studies.

Mercury has been designated by the WHO as one of the ten chemicals of major public health concern, with documented associations with adverse effects on human neurodevelopmental functions, the cardiovascular system, and the immune system [28]. Interestingly, an inverse relationship between blood mercury levels and the presence of RA was observed in the present study. This inverse trend warrants cautious interpretation, as it may stem

from residual confounding rather than a true biologically protective effect of mercury. For example, blood mercury correlates strongly with fish consumption, a dietary pattern associated with higher intake of anti-inflammatory omega-3 fatty acids that have been inversely linked to RA prevalence [29][30]. Certain studies have reported that mercury can inhibit the activation of the NLRP3 inflammasome and the secretion of IL-1β and IL-18 [31], however, these observations are insufficient to establish an anti-inflammatory role of mercury in human RA. The mean blood mercury concentration in our sample (1.6 μg/L) lies well below the WHO toxicity threshold (>5 μg/L) [32], nevertheless, the possibility that sub-toxic mercury exerts clinically relevant immunomodulation remains speculative. The stronger inverse association noted among non-smokers and participants with diabetes may reflect differential dietary patterns or mercury kinetics rather than a true protective interaction. Smoking has been associated with increased mercury retention [33], whereas diabetes has been inversely correlated with blood mercury levels [34], further complicating the interpretation of this association.

This study has several limitations that should be acknowledged. Firstly, the RA history was ascertained via personal interviews, which may introduce recall bias. Participants' self-reported data on RA diagnosis might not be entirely accurate, potentially affecting the validity of our findings. This self-reported approach, while common in large-scale surveys, lacks the precision of rheumatologist-administered joint examinations or hospital-record verification and may therefore result in misclassification of RA status. Secondly, the cross-sectional nature of the study precludes the determination of definitive causality. Because NHANES captures exposure and outcome simultaneously, we cannot establish whether blood or urine heavy-metal concentrations preceded RA onset, nor can we exclude the possibility that RA itself or the medications used to treat it altered the metabolism or accumulation of these metals. Specifically, although we hypothesize that elevated levels of cadmium and lead may contribute to the development of RA through mechanisms involving bone destruction and oxidative stress, it is also plausible that RA patients, who are often exposed to specific environments such as pesticides and traffic pollution, may have higher levels of heavy metals due to these exposures. Long-term exposure to pesticides and traffic pollution has been shown to increase the levels of heavy metals in the body, and these exposures are associated with an increased risk of developing RA [35][36]. Therefore, the elevated levels of heavy metals observed in our study may be influenced by the presence of RA patients who are exposed to these specific environments. Third, despite adjustment for a wide range of established covariates, we cannot exclude residual confounding by unmeasured or imprecisely measured factors. Examples include occupational heavy-metal exposure, detailed dietary intake, genetic predisposition to RA or metal metabolism, physical activity levels, and small-area socioeconomic characteristics. Given these considerations, future prospective studies should incorporate occupational histories, repeated 24-hour dietary recalls, genetic polymorphisms related to metal detoxification and immune regulation, and area-level deprivation indices, and prioritise longitudinal cohort or intervention designs to establish temporal relationships and further elucidate the causal pathways between heavy metal exposure and RA. Finally, the NHANES study population is comprised solely of U.S. individuals, thereby restricting the generalizability of the findings to other populations. The unique environmental, genetic, and lifestyle factors of the US population might influence the observed associations, and further studies in diverse populations are needed to confirm our results. Despite these limitations, our study provides valuable insights into the potential role of heavy metals in the pathogenesis of RA.

5. conclusion

In summary, our study revealed a significant positive correlation between blood cadmium and urine lead levels with RA, and a significant negative correlation between blood mercury levels and RA. Further research is needed to establish causality and explore the underlying mechanisms.

Acknowledgements

Competing interests

The authors declare that they have no competing interests.

Author's contribution

Tingwei Shu: Conceptualization, Writing - original draft; Jia Lu: Investigation, Methodology; Rui Liu: Data curation, Software; Jianpeng Yu: Writing - review & editing. All the authors approved the final version and its submission for publication.

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