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Blood lead–cadmium co-exposure and Chronic Kidney Disease: environmental risk score-based mediation by uric acid and albumin in NHANES 2011–2016

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Abstract. This study was designed to see if co-exposure to blood lead and cadmium is linked to Chronic Kidney Disease (CKD), and whether uric acid, albumin, GGT, and total bilirubin act as mediators in this relationship. Drawing on National Health and Nutrition Examination Survey (NHANES) 2011–2016 data (n = 10,000; 1,740 CKD cases), the research utilized an XGBoost-SHAP model to pinpoint key metals. Logistic regression was then used to assess connections across the whole group and by age/sex, alongside an Environmental Risk Score (ERS) that combined lead, cadmium, and their interaction. Additionally, Bootstrap mediation analysis was conducted to test how these four mediators act on eGFR. The findings revealed that the XGBoost model predicted CKD with a solid AUC of 0.8308, with SHAP analysis highlighting lead and cadmium as the top contributors. Logistic regression showed that both lead (OR = 1.12) and cadmium (OR = 1.13) were significantly tied to CKD. Interestingly, while both older men and women showed significant links, younger men were only sensitive to lead, and younger women showed no significant associations at all. The mediation analysis pointed out that uric acid (32.4%) and albumin (6.1%) served as significant mediators, whereas GGT had a negative effect (−15.4%) and total bilirubin showed no significance. Looking at specific demographic differences, uric acid (33%) and albumin (7.6%) mediated the effects in older women, while uric acid mediated 23% of the effect in older men; no such mediation effects were observed among younger adults. Overall, co-exposure to lead and cadmium is linked to CKD, with uric acid and albumin standing out as key mediators—especially in older women. Ultimately, this ERS-based mediation framework offers a highly practical way to assess risks from mixed exposures.

Keywords: chronic kidney disease, heavy metals, environmental risk score, mediation analysis

1. Introduction

Chronic Kidney Disease (CKD) has become a major public health problem worldwide. About 8%–16% of the global population is affected, and in 2017 the total number of patients was around 843 million [1]. In China,

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the weighted prevalence of CKD among adults is 8.2%, meaning that about 120 million people are living with the disease [2]. CKD not only increases the risk of end-stage kidney disease, but also significantly raises cardiovascular and all-cause mortality. Therefore, identifying modifiable risk factors is crucial for early prevention.

Environmental exposure to heavy metals is an important risk factor for CKD. Metals such as lead and cadmium accumulate in the body, and the kidney is a major target organ. Studies show that higher blood cadmium levels are linked to increased CKD risk [3], and blood lead and cadmium are also associated with lower eGFR and higher urinary albumin-to-creatinine ratio [4]. In Pakistan, Chronic Kidney Disease of unknown etiology (CKDu) is a recognized form of renal failure, and heavy metals such as cadmium and lead have been proposed as possible causes [5]. In reality, people are often exposed to multiple metals at the same time, and traditional regression models struggle with collinearity, nonlinearity, and interactions [6]. XGBoost, a machine learning method, can automatically capture complex associations and is useful for screening key exposures from many metals. However, machine learning is good at prediction and screening; to quantify effects and mechanisms, it still needs to be combined with traditional statistical methods.

Oxidative stress is a key pathway through which heavy metals damage the kidney, and blood markers such as uric acid, albumin, GGT, and total bilirubin can reflect this process. Higher uric acid is associated with declining kidney function [7], and low albumin also indicates poor prognosis in CKD patients [8]. As a marker of oxidative stress, GGT's relationship with CKD remains controversial [9]. Previous studies have mostly focused on a single metal or a single marker, and rarely assess the mediating role of multiple markers under mixed exposure at the same time. The Environmental Risk Score (ERS) can compress multiple exposures into one composite score, and when combined with mediation analysis, it can estimate the total indirect effect of mixed exposure through a certain pathway [10, 11]. This offers a new way to examine the causal chain of "mixed exposure → biomarkers → kidney damage".

Based on this, the present study used NHANES 2011–2016 data. This study first applied XGBoost-SHAP to screen key exposures from blood metals, then used logistic regression to assess their associations with CKD and differences by age and sex. Finally, this paper used ERS to combine lead, cadmium, and their interaction, and conducted Bootstrap mediation analysis to test the mediating roles of uric acid, albumin, GGT, and total bilirubin between lead–cadmium mixed exposure and kidney function.

2. Methodology

2.1. Data source

The data analysed in this study came from the U.S. NHANES. NHANES is a nationally representative, random-sampling research program run by the National Center for Health Statistics (NCHS) under the Centers for Disease Control and Prevention (CDC). Its goal is to understand the health and nutritional status of Americans through a series of activities. Using household interviews, standardized physical examinations, and related laboratory tests carried out at Mobile Examination Centers (MECs), it gathers a broad range of information, including demographic, dietary, health questionnaire, anthropometric, and laboratory biomarker data [12]. NHANES has been conducted every two years since 1999, and its public data serve as an important resource for epidemiological and public health research [13].The study was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB), and written informed consent was obtained from all participants.

2.2. Definition of chronic kidney disease

CKD was defined based on estimated Glomerular Filtration Rate (eGFR) and proteinuria, that is, eGFR < 60 ml/min/1.73 m² or proteinuria (urinary albumin-to-creatinine ratio ≥ 30 mg/g). eGFR was calculated using the CKD-EPI equation, which includes serum creatinine, age, and a sex coefficient [14].

2.3. Covariates and mediating variables

Participant information was obtained from standardized NHANES questionnaires. Demographic characteristics included age, sex, race, education level, and poverty income ratio; lifestyle factors included smoking, alcohol consumption, and physical activity; hypertension and diabetes status were also included as covariates. BMI was calculated as weight (kg) divided by height (m) squared. Smoking status was grouped into smokers (≥ 100 cigarettes) and nonsmokers (< 100 cigarettes); alcohol consumption was grouped into drinkers (> 12 drinks/year) and nondrinkers (< 12 drinks/year). Diabetes was defined as any of the following: a history of diabetes with corresponding treatment, fasting blood glucose ≥ 7.0 mmol/L, or HbA1c ≥ 5.7% [15]. Hypertension was defined as a history of hypertension with current antihypertensive medication, or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥ 90 mmHg [16]. In this study, uric acid, albumin, total bilirubin, and Gamma-Glutamyl Transferase (GGT) were used as mediating variables.

2.4. Study variables and inclusion/exclusion criteria

The research combined information about three cycles (2011-2012, 2013-2014, 2015-2016) and included a total of 29,902 subjects initially. The exclusion criteria were: (1) absence of blood lead, blood manganese, blood cadmium, blood mercury or blood selenium data; (2) absence of blood chronic kidney disease outcome; (3) absence of uric acid, albumin, total bilirubin or gamma-glutamyl transferase data; (4) under age 20 years or pregnant. Following application of multiple imputation to replace missing covariates, a final sample of 10,000 participants were achieved, of which 1,740 had been diagnosed with chronic kidney disease.

2.5. XGBoost model

XGBoost is an ensemble learning algorithm based on gradient boosted decision trees. It can automatically capture nonlinear relationships and interaction effects between variables and outcomes, which gives it an edge when handling environmental mixed-exposure data. It does not require pre-specifying the functional form of the exposure–response relationship, and it can also handle collinearity among pollutants effectively [6].

2.6. SHAP interpretability tool

SHapley Additive exPlanations (SHAP) was proposed by Lundberg and Lee in 2017. It is an additive feature attribution method based on the Shapley value from cooperative game theory. It breaks a single prediction from a complex model into a baseline value plus the contributions of individual features. It satisfies local accuracy, missingness, and consistency, and therefore has a unique solution [17].

2.7. Statistical analysis

All analyses were performed using R 4.3.1 and Python 3.12.1. A two-sided $p < 0.05$ was considered statistically significant. Because continuous variables were non-normally distributed, they were expressed as medians and interquartile ranges, while categorical variables were expressed as frequencies and weighted percentages; between-group comparisons used the Mann-Whitney U test and Rao-Scott chi-square test.

XGBoost-SHAP analysis: five blood metals (log-transformed lead, cadmium, selenium, manganese, and mercury) were used as input variables, and CKD was the outcome. An XGBoost model was built, and SHAP values were used to identify the key metals that contributed most to CKD prediction.

Logistic regression: CKD (yes/no) was the dependent variable, and five blood metals (LogCd, LogPb, LogSe, LogMn, LogHg) were independent variables. Covariates included age, sex, race, education level, marital status, poverty income ratio, smoking, alcohol consumption, BMI, physical activity, hypertension, diabetes, albumin, GGT, uric acid, and total bilirubin. All exposure variables were natural log-transformed. Continuous variables were reported as Odds Ratios (ORs) and 95% confidence intervals (95% CIs) per 1-unit increase in log value. Stratified analyses were performed by age (20–60 years and > 60 years) and sex (male/female), dividing participants into four groups: older men, older women, younger men, and younger women.

ERS construction and mediation analysis: the adaptive elastic-net method proposed by Park et al. was used to build an ERS [10]. Blood lead, blood cadmium, and their interaction term were the key exposure factors, and eGFR was the dependent variable. Five-fold cross-validation was used to select the optimal penalty factor, yielding a penalized regression model. The regression coefficients of the exposure factors and their interaction were used as weights, and ERS = β_1 × blood lead + β_2 × blood cadmium + β_3 × (blood lead × blood cadmium). Then, following the ERS-MA framework proposed by Aung et al. [11], ERS was used as the sole exposure variable, uric acid, albumin, GGT, and total bilirubin were potential mediators, and continuous eGFR was the outcome in a classical mediation model. Analyses were stratified by age (20–60 years and > 60 years) and sex. All continuous variables except the outcome were standardized. The Bootstrap method (500 resampling times) was used to estimate the Average Causal Mediation Effect (ACME), Average Direct Effect (ADE), total effect, and proportion mediated, with 95% confidence intervals obtained by percentiles.

3. Results

3.1. Baseline characteristics of participants

The study included 10,000 participants, of whom 1,740 (17.4%) had CKD and 8,260 (82.6%) did not. Table 1 summarizes their baseline characteristics. In general, CKD patients were older (median 65 vs. 45 years), had higher uric acid (6.00 vs. 5.20 mg/dL), higher GGT (21.00 vs. 19.00 U/L), and higher blood cadmium (0.41 vs. 0.30 μg/L). They also had lower albumin (4.20 vs. 4.30 g/dL) and lower blood manganese, selenium, and mercury levels. Not surprisingly, CKD patients also had a higher BMI (29.00 vs. 27.70 kg/m²) and much higher rates of hypertension (65.5% vs. 30.9%) and diabetes (38.9% vs. 13.2%). Differences in other demographic and lifestyle factors, such as race, education, marital status, income, smoking, and alcohol use, are detailed in Table 1.

Table 1. Characteristics of the study population from the NHANES 2011–2016

Characteristics	Non-CKD (*N* = 8,260)	CKD (*N* = 1,740)	*p* value
Age (years)	45.00 (32.00, 60.00)	65.00 (51.00, 77.00)	< 0.001
Gender, *n* (%)			0.412
male	4,113 (49.8)	847 (48.7)	
female	4,147 (50.2)	893 (51.3)	

Table 1. Continued

Race, *n* (%)			< 0.001
Mexican American	1,085 (13.1)	202 (11.6)	
Other Hispanic	920 (11.1)	154 (8.9)	
Non-Hispanic White	3,128 (37.9)	692 (39.8)	
Non-Hispanic Black	1,739 (21.1)	504 (29.0)	
Other race	1,388 (16.8)	188 (10.8)	
Education group,n(%)			< 0.001
Less than 9th grade	742 (9.0)	263 (15.1)	
9th–11th grade	965 (11.7)	304 (17.5)	
High School Grad/GED	1,762 (21.3)	410 (23.6)	
College Preparatory	2,543 (30.8)	449 (25.8)	
College or above	2,248 (27.2)	314 (18.0)	
Marital status(%)			< 0.001
Married	4,201 (50.9)	817 (47.0)	
Widowed	431 (5.2)	311 (17.9)	
divorced	846 (10.2)	227 (13.0)	
separated	259 (3.1)	74 (4.3)	
Never married	1,785 (21.6)	215 (12.4)	
living with partner	738 (8.9)	96 (5.5)	
PIR group	2.08 (1.05, 4.16)	1.65 (0.94, 3.12)	< 0.001
Smoking (%)	3,410 (41.3)	872 (50.1)	< 0.001
Alcohol consumption (%)	5,993 (72.6)	1,185 (68.1)	< 0.001
Physical activity level (days)	3.00 (2.00, 5.00)	3.00 (2.00, 5.00)	< 0.001
BMI(kg/m²)	27.70 (24.10, 32.30)	29.00 (24.90, 33.80)	< 0.001
Hypertension(%)	2,550 (30.9)	1,139 (65.5)	< 0.001
Diabetes(%)	1,087 (13.2)	677 (38.9)	< 0.001
Uric acid(mg/dL)	5.20 (4.40, 6.20)	6.00 (4.90, 7.10)	< 0.001
Total bilirubin(mg/dL)	0.60 (0.50, 0.80)	0.60 (0.50, 0.70)	0.002
Albumin(g/dL)	4.30 (4.10, 4.50)	4.20 (4.00, 4.40)	< 0.001
Gamma-glutamyl transferase(U/L)	19.00 (14.00, 29.00)	21.00 (14.00, 32.00)	< 0.001
Blood zinc(ug/dL)	1.00 (0.64, 1.58)	1.39 (0.89, 2.25)	< 0.001
Blood manganese(ug/L)	9.33 (7.51, 11.77)	8.75 (6.88, 11.27)	< 0.001
Blood selenium(ug/L)	193.06 (178.70, 208.57)	190.94 (175.72, 206.44)	< 0.001
Blood cadmium(ug/L)	0.30 (0.19, 0.56)	0.41 (0.24, 0.69)	< 0.001
Blood mercury(ug/L)	0.82 (0.43, 1.76)	0.77 (0.41, 1.64)	0.043

3.2. Key metal screening based on SHAP

Figure 1(a) shows the ranking of mean SHAP values for the five blood metals. Blood lead had the highest mean SHAP value, at 0.1106; blood cadmium was second, at 0.0762; this was followed by blood mercury

(0.0375), blood manganese (0.0304), and blood selenium (0.0246). The mean SHAP values of blood lead and blood cadmium were markedly higher than those of the other three metals, suggesting that these two are the key exposure variables contributing most to CKD prediction, with blood lead contributing the most and blood cadmium the second most.

The SHAP summary plot in Figure 1(b) further displays the directional relationships between the exposure concentrations of each metal and their SHAP values. The high-concentration points (red/purple) for blood lead and blood cadmium were mainly distributed on the side with SHAP values greater than 0, while the low-concentration points (blue) were mainly distributed on the side with SHAP values less than 0, suggesting that higher blood lead and blood cadmium levels are associated with increased predicted CKD risk. Blood mercury, blood manganese, and blood selenium showed the opposite trend, with their high-concentration points mostly located on the side with SHAP values less than 0 and their low-concentration points mostly located on the side with SHAP values greater than 0, suggesting that higher blood mercury, blood manganese, and blood selenium levels may correspond to lower predicted CKD risk.

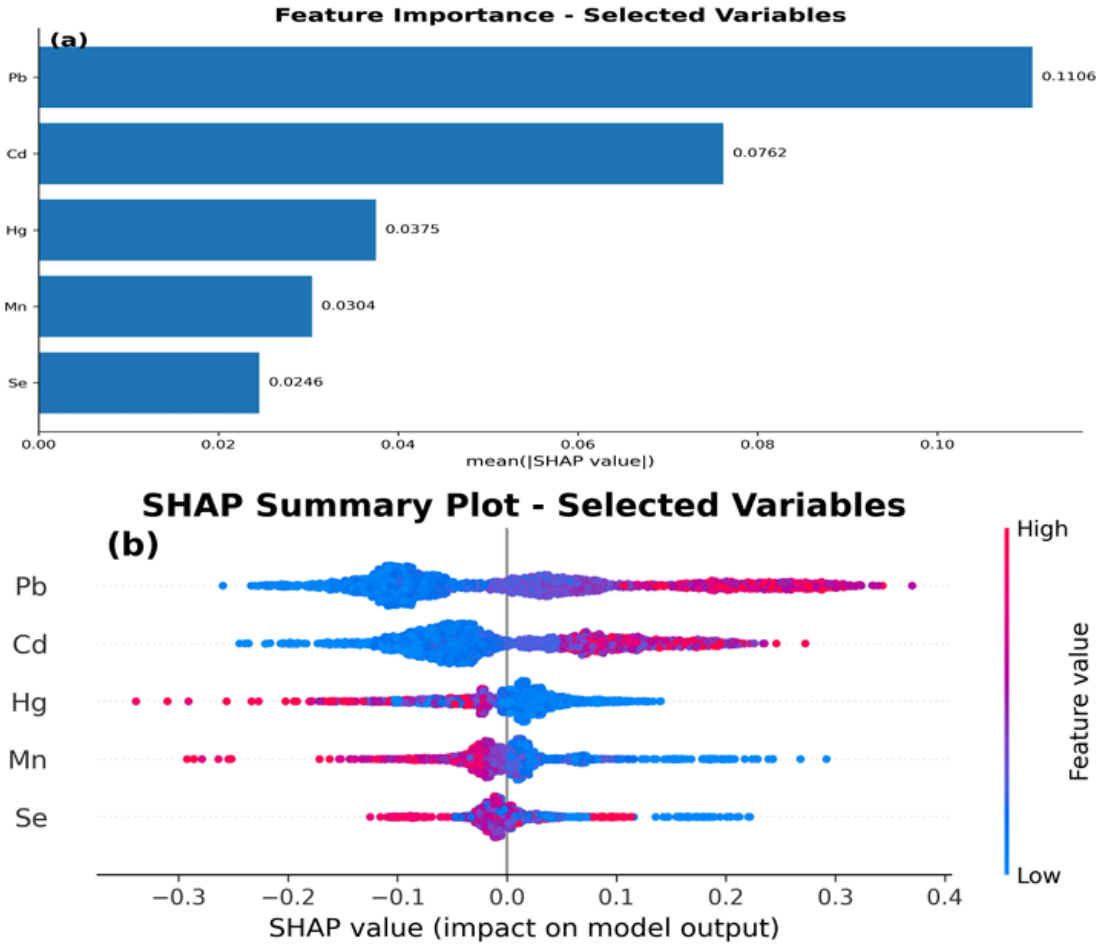


Figure 1. The hierarchy of importance of five blood metals in the NHANES 2011-2016 database. (a) SHAP score plot, (b) SHAP summary plot

3.3. Association analysis of the entire population and subgroups based on a logistic regression model

A multivariable logistic regression analysis showed that, after accounting for age, sex, race, education level, marital status, smoking and alcohol consumption, BMI, annual household income, and various biochemical indicators, the risk effects of blood lead (Pb) and blood cadmium (Cd) on CKD differed across populations. Overall, both blood Pb and blood Cd were closely associated with CKD occurrence (Pb: OR = 1.12, p = 0.002; Cd: OR = 1.13, p = 0.002); put simply, the risk signals for both were fairly clear. In older men, both were also significantly associated with CKD (Pb: OR = 1.16, p = 0.023; Cd: OR = 1.25, p = 0.002). Older women showed a similar pattern (Pb: OR = 1.19, p = 0.011; Cd: OR = 1.25, p = 0.003). What stood out was that, in younger men, only blood Pb was significantly associated with CKD (OR = 1.29, p = 0.001), while blood Cd was not statistically significant (OR = 1.16, p = 0.081). In younger women, neither blood Pb nor blood Cd was significantly associated with CKD (Pb: OR = 1.06, p = 0.361; Cd: OR = 1.03, p = 0.666), as shown in Figure 2.

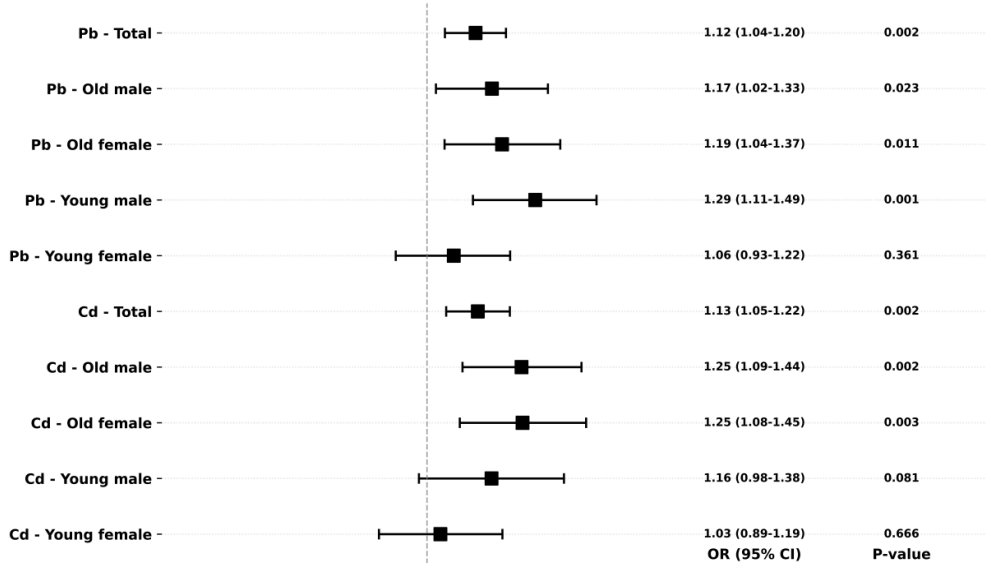


Figure 2. Results of logistic regression analysis in the overall and subgroup populations

3.4. Mediation analysis

In order to examine whether blood lead and cadmium are associated with chronic kidney disease via its effect on eGFR, this paper has utilized the adaptive elastic net to develop an ERS where eGFR is the outcome variable and blood lead, blood cadmium, and their interaction term are included. The estimated coefficients were -0.139441, -0.05205, and 0.011913, respectively, and the ERS calculation equation is given by: ERS = -0.139441 × blood lead + (-0.05205) × blood cadmium + (0.011913) × (blood lead x blood cadmium). The mediation analysis using this ERS as a combined exposure index revealed that, in the whole population, albumin (effect = 0.061, 95% CI: 0.019-0.197), gamma-glutamyl transferase (effect = -0.154, 95% CI: -0.642-0.047), and uric acid (effect = 0.324, 95% CI: 0.159-0.666) all had significant mediating effects (confidence intervals do not contain zero). After the stratification by age and sex into four subgroups, only uric acid acted as a mediator in older men (effect = 0.230, 95% CI: 0.104-0.431); in older women, albumin (effect = 0.076, 95% CI: 0.004-0.246) and uric acid (effect = 0.330, 95% CI: 0.116-0.737) acted as mediators; in older men, albumin, gamma-glutamyl transferase, and total bilirubin, and in older women, gamma-glutamyl transferase

and total bilirubin, do not have significant mediating effects. At the same time, no mediating effects were significant in younger males and females. The mediation analysis results, including the significant indirect effects, are presented in Figure 3.

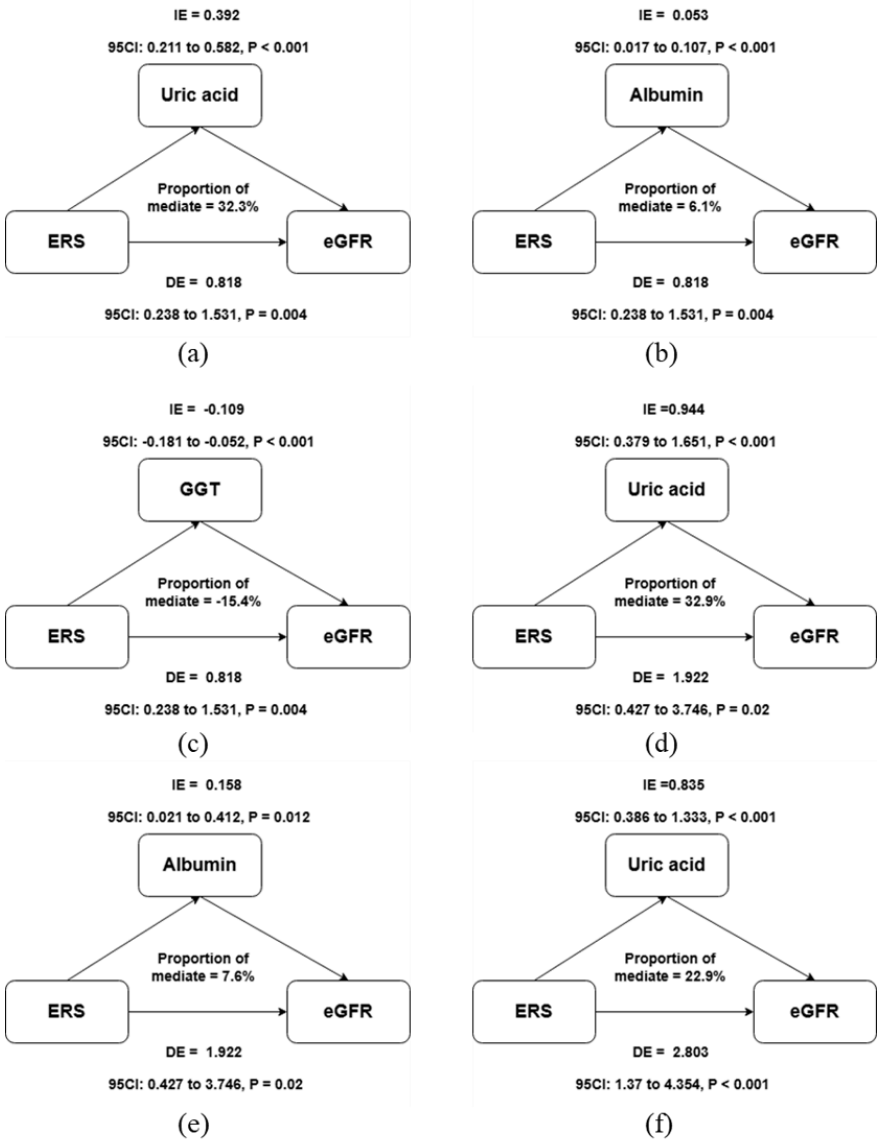


Figure 3. The mediation effect of four mediating variables, namely albumin, GGT, total bilirubin, and uric acid, on the effect of the last environmental risk score of blood lead and cadmium on chronic kidney disease are shown in the figure below (only those with significant mediation effects are presented). The Indirect Effect (IE) and Direct Effect (DE) were calculated. (a-c) denotes that the significant mediation analysis results are obtained based on the overall population, (d-e) based on the older female, and (f) based on the older male

4. Discussion

This study used NHANES 2011–2016 data. First, XGBoost-SHAP was applied to screen key exposures from five blood metals, followed by logistic regression to assess the associations between lead, cadmium, and CKD, and finally built an ERS combining lead, cadmium, and their interaction. Bootstrap mediation analysis was

then used to test the roles of uric acid, albumin, GGT, and total bilirubin. SHAP results showed that blood lead and blood cadmium were the two most important metals for predicting CKD, contributing much more than mercury, manganese, and selenium. Logistic regression further confirmed that lead and cadmium were associated with higher CKD risk, and this association was more obvious in older adults but not significant in younger women. In the ERS mediation analysis, uric acid and albumin were significant mediators in the overall population, GGT showed a negative mediation effect, and total bilirubin had no mediation effect. After stratification, older women had both uric acid and albumin mediation, older men had only uric acid mediation, and no significant mediation was found in younger people.

These findings are broadly consistent with previous NHANES-based studies. In a cross-sectional study of 250 adults in rural Pakistan, lead exposure was strongly associated with CKD (AOR: 2.85), followed by cadmium (AOR: 2.40) [18]. Although the effect sizes are larger than those observed in the present study, the direction is consistent and highlights that lead–cadmium co-exposure is a concern beyond the U.S. population. Higher blood lead and cadmium levels have been linked to increased CKD risk, while selenium and manganese may have some protective effect [19]. In this study, the effect sizes for lead and cadmium were OR = 1.12 and OR = 1.13, respectively, which are close to those reported in some metabolic syndrome populations. Age and sex differences also deserve attention. Older adults have lower renal functional reserve, and eGFR declines with age. Together with long-term metal accumulation and weaker antioxidant capacity, this makes them more vulnerable to the kidney toxicity of lead and cadmium [20]. In women, the protective effect of estrogen weakens after menopause. Lower iron stores and higher intake of plant-based foods may also increase cadmium accumulation and nephrotoxicity, which may help explain why albumin mediation was more obvious in older women [20].

As for mediation mechanisms, uric acid had the largest mediation proportion and was stable in both the overall population and older subgroups. Uric acid is mainly a metabolic waste product retained when glomerular filtration rate falls. Its mediating role looks more like "a result of impaired kidney function" than "a cause of the damage", but this does not reduce its value as an early warning marker [21]. Albumin mediation was significant in the overall population and older women. This may be related to metal–albumin complexes being taken up by proximal tubular cells via the megalin/cubilin receptor, as well as oxidized albumin inducing tubular injury [22]. GGT showed a negative mediation effect in the overall population, which is somewhat counterintuitive and should be interpreted with caution. GGT has long been viewed as a marker of oxidative stress and liver damage. However, under low-level environmental exposure, a mild increase in GGT may reflect an adaptive antioxidant response rather than a pure kidney injury signal [23]. Although total bilirubin has antioxidant capacity in theory, it showed no mediation effect in this ERS model. One possible reason is that lead and cadmium mainly damage the kidney through tubular toxicity and abnormal uric acid metabolism, and these pathways do not rely on bilirubin's antioxidant effect.

Several limitations of this study should be acknowledged when interpreting the present findings. First, given the cross-sectional nature of the NHANES data, it can only observe associations at a single point in time. This limitation means that a definitive causal pathway cannot be established—whether heavy metal exposure actually drives the decline in kidney function, or if impaired kidneys simply retain more metals (reverse causality), remains an open question. Additionally, exposure was assessed via a single blood sample. Given that heavy metals accumulate over a lifetime, a one-time measurement might not fully capture the long-term toxic burden. Another unavoidable limitation is residual confounding. Of course, the authors tried the best to adjust for a wide array of demographic and lifestyle factors, but let face it, NHANES does not capture everything. Unmeasured variables, such as specific dietary habits (like seafood intake), genetic susceptibility, or co-exposure to unrecorded environmental pollutants, might still be lurking in the background. Finally, since

the study cohort is restricted to the U.S. population, generalising these findings directly to other ethnic groups —such as the Chinese population—should be done with caution.

Overall, lead and cadmium are key blood metals affecting CKD, and combined lead–cadmium exposure is associated with higher CKD risk. ERS mediation analysis suggests that uric acid and albumin are the main mediators, GGT shows a negative mediation effect, and total bilirubin has no mediation effect. Older women appear more sensitive to lead and cadmium exposure. ERS provides a quantifiable tool for risk assessment of environmental mixed exposure. Future prospective studies and multi-omics data are needed to further validate these mechanisms.

5. Conclusion

Overall, blood lead and cadmium are key metals associated with CKD. Uric acid and albumin mediate this association, particularly in older women, while GGT shows a negative mediation effect and total bilirubin no effect. ERS offers a quantifiable tool for mixed-exposure risk assessment, but prospective studies are needed.

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Ethics approval and consent to participate

The NHANES 2011–2016 survey protocols were approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB). Written informed consent was obtained from all participants.

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