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Multiple metals exposure and estimated pulse wave velocity: a cross-sectional analysis of the US adults

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Background and objectives: Arterial stiffness has been demonstrated to be associated with a range of adverse cardiovascular events. Nevertheless, the epidemiological evidence on the association between metal exposure and arterial stiffness remains inconclusive.

Methods: The data concerning 12 urine metals were derived from the National Health and Nutrition Examination Survey (NHANES) conducted from 2003 to 2016. Multiple linear regression and restricted cubic spline (RCS) analyses were applied to explore the potential linear and nonlinear associations between urine metal and ePWV. A parallel mediation analysis was conducted in order to explore the potential intermediate factors in metal-induced ePWV elevation. Weighted quantile sum (WQS) regression and Quantile g-computation (Qgcomp) were conducted to estimate the individual and combined associations between urine metal and ePWV.

Results: Following adjustment for the relevant covariates, it was found that urine Cd, Pb, Co, and U were found to be significantly correlated to elevated ePWV in both the multiple linear regression and the RCS model. Mediation analysis revealed that high - density lipoprotein (HDL) and total cholesterol (TC) might be partly implicated in the correlation between urine metal and ePWV. WQS regression and Qgcomp analyses consistently indicate a positive correlation between exposure to mixed metals and elevated ePWV, with Cd and Pb identified as the primary contributors to this phenomenon.

Conclusion: The present study indicated a significant association between the presence of a mixture of metals and elevated ePWV, with Cd and Pb identified as the primary risk factors. And HDL and TC might participate in mediating mixed metals exposure induced ePWV changes.

KEYWORDS

multiple metals exposure, ePWV, NHANES, WQS, Qgcomp, mediation analysis

1 Introduction

Arterial stiffness is a phenotype that appears early in the development of many cardiovascular diseases. Therefore, arterial stiffness is accounted as a predict index of several adverse cardiovascular outcomes such as hypertension, atherosclerosis and stroke (1–3). Pulse wave velocity (PWV) has been recommended as a non-invasive means of assessing arterial stiffness. This, in turn, can be used to evaluate organ damage resulting from arterial hypertension (4–7). In 2016, Greve et al. derived estimate pulse wave velocity (ePWV) based on carotid-femoral pulse wave velocity (cfPWV) and demonstrated that ePWV has better predictive value in healthy patients and untreated hypertensive patients (8). And ePWV was gradually recognized for its reliability and low threshold. Vlachopoulos et al. have utilized ePWV as a metric to evaluate the incidence of adverse cardiovascular outcomes, including stroke, coronary heart disease and cardiovascular death, in individuals at risk of cardiovascular disease (CVD) within the SPRINT subgroups (9). Solini et al. also established that in patients diagnosed with type 2 diabetes, elevated level of ePWV indicated a lower survival rates of patients with cardiac and renal complications (10).

Metals are widely used in storage batteries, electroplating industry, chemical raw materials and other industries (11). With the progress of industrialization and urbanization, a mass amount of metals are discharged into the environment in the approach of mining, smelting, exhaust emissions and sewage irrigation, which are contacted and introduced into the human body through drinking water and crops, and then accumulated in the human body (12–14). Metals are generally considered to affect a range of systems and organs, including the nervous system (15–17) and hematopoietic system (18–20). Recent years have seen an increased focus on the association between metal exposure and cardiovascular disease risk. However, there is a paucity of research on the association between metal exposure and arterial stiffness, and the conclusions vary (21, 22). Therefore, the potential role of metal exposure in arterial stiffness remains understudied.

In this study, we extracted data pertaining to urine metal and other sociodemographic characteristics of the population during 2003–2016 cycle, and then calculated ePWV based on age and blood pressure. The relationship between urine metals and ePWV were investigated through several different statistical strategies. In addition, we also investigated which potential factors could mediates the association between urine metal levels and ePWV.

2 Materials and methods

2.1 Study population

The data utilized in this study has been drawn from the NHANES database. The latter is a cross-sectional study conducted on a nationwide scale, overseen by the National Center for Health Statistics. The survey enables researchers to obtain information related to demographics, socioeconomics, diet, health, and physical examination from a sample of the US population that is representative of the whole population. The survey data can then be utilized to appraise the health and nutritional status of the population. In summary, from 2003 to 2016, relevant indicators were collected from approximately

70,000 U.S. residents. All data and indicator sources for the study can be referred to on public access.[1]

Among the 71,058 subjects available for the study, the following conditions were set for data cleaning: (1) lack of data on metal exposure and data required for calculation of the ePWV index; (2) subjects under the age of 20 or pregnant; (3) missing one or more covariates. Eventually, 8,800 samples were included in the analysis to verify the association between metal exposure and ePWV. The detailed flow chart of the included subjects is shown in Figure 1.

2.2 Acquisition of estimated pulse wave velocity (ePWV)

The formula for ePWV is referenced in Greve et al. and is derived from the collaborative reference value for arterial stiffness (8). ePWV $= 9.587 - 0.402 \times \text{age} + 4.560 \times 10^{-3} \times \text{age}^2 - 2.621 \times 10^{-5} \times \text{age}^2 \times \text{MBP} + 3.176 \times 10^{-3} \times \text{age} \times \text{MBP} - 1.832 \times 10^{-2} \times \text{MBP}$. MBP was calculated by the following formula: (DBP) $+ 0.4$ (SBP $-$ DBP). And ePWV was trisected as T1 (<6.88 m/s), T2 (6.88–9.20 m/s), T3 (>9.20 m/s).

2.3 Measurement of metals in urine

Urine metal levels are favored as a noninvasive assay for large follow-up cohorts compared to serum metal levels. According to the guiding manual, the urine samples were pretreated, stored on appropriate medium and transported to the laboratory for analysis. Urine levels of 12 selected metals [including Barium (Ba), Cobalt (Co), Cesium (Cs), Molybdenum (Mo), Antimony (Sb), Tungsten (W), Uranium (U), Thallium (Tl), Lead (Pb), Cadmium (Cd), Mercury (Hg), Arsenic (As)] were measured by inductively coupled plasma mass spectrometry (ICP-MS) analysis (23). Based on these results, we extracted data of urine metal levels in the period 2003 to 2016, and all 12 metals were detected at a rate of more than 60%, and were corrected by creatinine (Supplementary Table S1). The distribution of these metals among the study participants can be seen in Supplementary Table S2.

2.4 Covariates

In accordance with the previous literature, the core covariates selected for this study are outlined below: sociodemographic characteristics, including sex (male/female), age (under 40 years old/40–60 years old/over 60 years old), race (Mexican American/other Hispanic/non-Hispanic White/non-Hispanic Black/other), education level (less than 11th grade/ high school grade/ some college or above), poverty income ratio (PIR); life style and body measurement indicators, including physical activity, body mass index (BMI), TC, HDL, white blood cell counts; alcohol consumption, smoking status, total energy intake and urine creatinine. PIR (%) was divided into categorical variable according to the quartile [Q1 (<1.18), Q2

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1 https://www.cdc.gov/nchs/nhanes/

FIGURE 1
Flow diagram for participant inclusion.
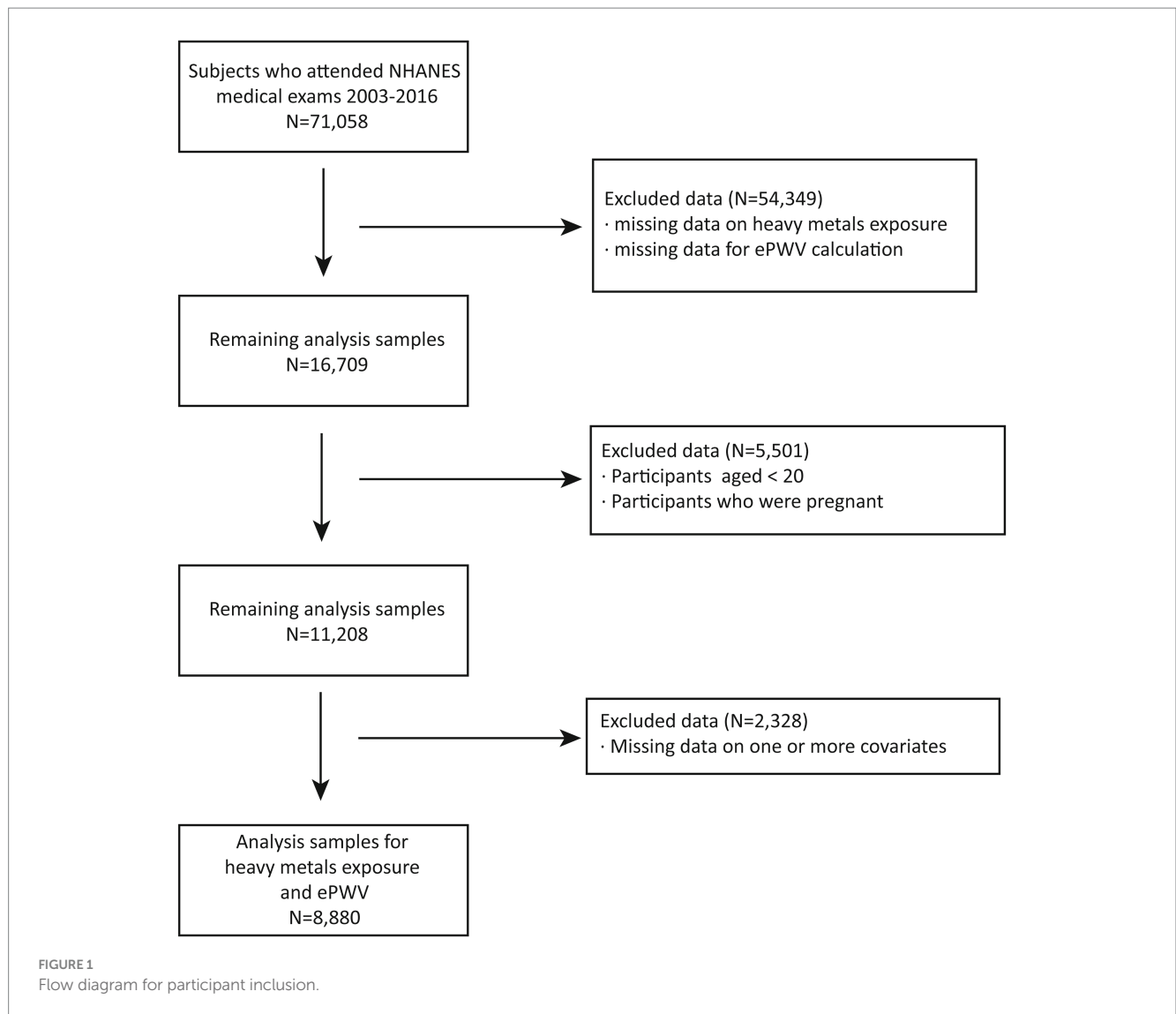
(1.18–2.20), Q3 (2.21–4.10), Q4 (>4.10)]. Physical activity was divided into three categories based on the questionnaire (never/moderate/vigorous). Smoking status was (never/former/current) based on cigarettes consumption (more than 100) and whether smoking currently. Drinking status was based on alcoholic beverage consumption. The conversion of alcohol consumption was in accordance with the previous method. The results were "No" and "Yes." BMI was coded as continuous variables (24). Considering the correlation between arterial stiffness and related disease, we additionally regarded diabetes, hypertension, and CVD as covariates in our analysis (25).

2.5 Statistical analysis

The mean ± standard deviation (SD) was utilized to depict continuous variables conforming to a normal distribution, in order to provide descriptive information on the sociodemographic characteristics. Other variables were defined as categorical variables and are expressed as n (%). In this study, metal concentrations (μg/mg)

were adjusted by urine creatinine to analyze the correlation between urine metal and ePWV. In order to circumvent the potential bias engendered by a skewed distribution, the concentrations of urine metals were transformed through log10 function in order to achieve approximate normal distribution (continuous variable), or categorized into quartiles (Q1, Q2, Q3, and Q4) as categorical variables. The internal relevance between the mixed urine metals was evaluated by Spearman's correlation coefficient.

Multiple linear regression model was utilized to investigate the association between each urine metal and ePWV. Mediation analysis was performed to ascertain the mediating effect of serum lipid levels and white blood cell counts on the associations between urine metals and ePWV. Considering the complexity of real environmental exposure, WQS analysis was employed to investigate the joint effects of mixed metal exposures on ePWV. And the contribution of every single metal to the holistic indices effect can then be assessed through the weight assigned to each variable by the model. Additionally, we introduced the Qgcomp model to confirm the effects of each urine metal on ePWV. This was achieved by allocating positive or negative weights to each factor in the model. Restricted cubic spline (RCS)

regression was employed to estimate the potential nonlinear relationship between each urine metal and ePWV. Spearman's correlation coefficient was employed to examine relationships between urine metals.

All statistical methods have been adjusted for the aforementioned confounding variables. These analyses were executed utilizing the R software platform (R 4.1.1). In the statistical model, significance was affirmed by a two-sided p-value of under 0.05.

3 Results

3.1 Baseline characterization

The basic characteristics of the participants which were involved in study are shown in Table 1. A total of 71,058 participants were collected for this study and the final number included in the analysis was 8,880, including 4,585 male and 4,295 female. Higher level of ePWV was prefer to exist in the subgroup which participants over 60 years old, male, of Non-Hispanic White, have lower level of education, with less exercise, had a history of smoking. Additionally, we observed the higher levels of ePWV were accompanied by a higher prevalence of hypertension, CVD, diabetes.

3.2 Spearman's correlation coefficient for the mutual correlations among the urine metals

In order to investigate mutual correlations among the environmental metal exposures, we calculated Spearman's correlation coefficients to check the correlation between pairwise urine metals. Positive but weak correlations were observed between almost all of the 12 metals in urine (Supplementary Figure S1). The highest levels of correlation were observed between U and Ba ($r = 0.21$, $p < 0.05$), Tl and Cs ($r = 0.2$, $p < 0.05$).

3.3 Associations between urine metals and ePWV

According to the results exhibited in Figure 2, Supplementary Table S3, we found that Cd ($\beta = 0.012$, 95% CI: 0.006, 0.017), Co ($\beta = 0.012$, 95% CI: 0.006, 0.017), Cs ($\beta = 0.008$, 95% CI: 0.001, 0.015), Pb ($\beta = 0.024$, 95% CI: 0.019, 0.029), U ($\beta = 0.031$, 95% CI: 0.012, 0.051) levels were positively correlated with the ePWV. And an inverse correlation has been observed between Sb ($\beta = -0.009$, 95% CI: -0.018, -0.001), Tl ($\beta = -0.015$, 95% CI: -0.024, -0.005), W ($\beta = -0.008$, 95% CI: -0.015, -0.002), Hg ($\beta = -0.005$, 95% CI: -0.009, -0.002) and the levels of ePWV ($p < 0.05$).

3.4 RCS analysis between multiple metals exposure and ePWV

We conducted RCS analysis to visualize the potential nonlinear relationships between urine metals and ePWV. As exhibited in Figure 3, nine of all urine metals were significantly associated with

ePWV (p-overall < 0.05), while U, Pb, Co, Cd showed positive associations with ePWV. The analysis results also revealed that Cs, Mo were positively correlated with the ePWV and in a nonlinear mode (p-non-linear < 0.05).

3.5 WQS analysis of the effects of multiple and individual metal exposure on ePWV

Our findings indicated that the WQS indices exhibited a substantial correlation with ePWV. As shown in Figure 4A, the upper quartile of the WQS indices was significantly related to elevated ePWV ($\beta = 0.022$, 95% CI: 0.017, 0.028), in which U ($\beta = 0.15$), Pb ($\beta = 0.48$), Co ($\beta = 0.15$), and Cd ($\beta = 0.1$) were the dominating contributors to the positive correlation ($p < 0.01$).

3.6 Qgcomp analysis of the effects of multiple and individual metal exposure on ePWV

Unlike other mixed exposure models, Qgcomp analysis does not require all weight indices to be aligned in the same direction. Our findings showed mixed metals exposure were significantly and positively associated with ePWV ($\beta = 0.022$, 95% CI: 0.016, 0.027). For the levels of ePWV, the urine level of Pb ($\beta = 0.4$) showed the strongest positive correlation, followed by Cd ($\beta = 0.18$), Co ($\beta = 0.16$) and Cs ($\beta = 0.10$) (Figure 4B). When it comes to negative relationship between urine metals and ePWV, Tl, Hg, W, Sb exhibited a negative tendency with ePWV.

3.7 Mediation analysis of potential intermediate factors in the association between urine metals and ePWV

To explore potential underlying mechanisms between metal exposure and ePWV, a parallel mediation analysis was conducted to evaluate the mediating effect of serum lipid levels and white blood cell counts on the aforementioned association. Parallel mediation analysis demonstrated that HDL and TC exerted a weak but significant mediation effect on the association between mixed metals WQS indices and ePWV, and the proportion of mediation was 2.14 and 3.70% (Table 2). The mediated proportion of HDL on the associations between Co, Cs, Pb, U, As and ePWV was 1.50, 5.73, 2.29, 5.29 and 18.82% ($p < 0.05$). TC similarly mediated the association between Ba, Cd, Co, Cs, Pb, U and ePWV, and the proportion of mediation was 11.88, 6.44, -6.04%, 5.55, 4.91 and 6.40% (Supplementary Table S4).

4 Discussion

In this study, we observed an association between metal exposure and ePWV based on the NHANES cohort. In the multiple linear regression analysis, higher levels of urine U, Pb, Cd and Co were related to increased ePWV. Mixture analysis models revealed a significant correlation between metal mixture and elevated ePWV, with Pb and Cd as the primary contributors. Furthermore, mediation

TABLE 1 Baseline characteristics of the participants in the analyses.

Characteristics	Total population	ePWV (m/s)		
		T1 (<6.88)	T2 (6.88–9.20)	T3 (>9.20)
Overall	8,880	2,931	2,930	3,019
Age (years, %)				
<40	2,857 (32.2)	2,402 (82.0)	453 (15.5)	2 (0.1)
40–60	2,957 (33.3)	523 (17.8)	2,102 (71.7)	332 (11.0)
>60	3,066 (34.5)	6 (0.2)	375 (12.8)	2,685 (88.9)
Gender (%)				
Male	4,585 (51.6)	1,415 (48.3)	1,565 (53.4)	1,605 (53.2)
Female	4,295 (48.4)	1,516 (51.7)	1,365 (46.6)	1,414 (46.8)
Race (%)				
Mexican American	1,413 (15.9)	565 (19.3)	479 (16.3)	369 (12.2)
Other Hispanic	754 (8.5)	278 (9.5)	250 (8.5)	226 (7.5)
Non-Hispanic White	4,238 (47.7)	1,246 (42.5)	1,361 (46.5)	1,631 (54.0)
Non-Hispanic Black	1785 (20.1)	553 (18.9)	617 (21.1)	615 (20.4)
Other	690 (7.8)	289 (9.9)	223 (7.6)	178 (5.9)
Education level (%)				
Less Than 11th Grade	2,189 (24.7)	592 (20.2)	643 (21.9)	954 (31.6)
High School Grad	2064 (23.2)	655 (22.3)	685 (23.4)	724 (24.0)
Some College or above	4,627 (52.1)	1,684 (57.5)	1,602 (54.7)	1,341 (44.4)
Physical activity (%)				
Inactive	4,760 (53.6)	1,416 (48.3)	1,493 (51.0)	1851 (61.3)
Moderate	2,158 (24.3)	677 (23.1)	706 (24.1)	775 (25.7)
Vigorous	1962 (22.1)	838 (28.6)	731 (24.9)	393 (13.0)
Past-year alcohol drinking (%)				
No	2,466 (27.8)	693 (23.6)	760 (25.9)	1,013 (33.6)
Yes	6,414 (72.2)	2,238 (76.4)	2,170 (74.1)	2006 (66.4)
Smoking status (%)				
Never	4,715 (53.1)	1758 (60.0)	1,545 (52.7)	1,412 (46.8)
Former	2,353 (26.5)	405 (13.8)	709 (24.2)	1,239 (41.0)
Current	1812 (20.4)	768 (26.2)	676 (23.1)	368 (12.2)
Family PIR (%)				
Q1 (<1.18)	2,112 (23.8)	822 (28.0)	630 (21.5)	660 (21.9)
Q2 (1.18–2.20)	2,211 (24.9)	705 (24.1)	624 (21.3)	882 (29.2)
Q3 (2.21–4.10)	2,261 (25.5)	727 (24.8)	742 (25.3)	792 (26.2)
Q4 (>4.10)	2,296 (25.9)	677 (23.1)	934 (31.9)	685 (22.7)
Total energy intake (kcal, %)				
Q1 (<1472.0)	2,124 (23.9)	530 (18.1)	623 (21.3)	971 (32.2)
Q2 (1472.0–1915.0)	2,230 (25.1)	670 (22.9)	676 (23.1)	884 (29.3)
Q3 (1915.1–2502.5)	2,238 (25.2)	757 (25.8)	751 (25.6)	730 (24.2)
Q4 (>2502.5)	2,288 (25.8)	974 (33.2)	880 (30.0)	434 (14.4)
CVD (%)				
No	7,913 (89.1)	2,874 (98.1)	2,717 (92.7)	2,322 (76.9)
Yes	967 (10.9)	57 (1.9)	213 (7.3)	697 (23.1)
Hypertension (%)				

(Continued)

TABLE 1 (Continued)

Characteristics	Total population	ePWV (m/s)		
		T1 (<6.88)	T2 (6.88–9.20)	T3 (>9.20)
No	5,673 (63.9)	2,661 (90.8)	1875 (64.0)	1,137 (37.7)
Yes	3,207 (36.1)	270 (9.2)	1,055 (36.0)	1882 (62.3)
Diabetes (%)				
No	7,608 (85.7)	2,830 (96.6)	2,470 (84.3)	2,308 (76.4)
Yes	1,272 (14.3)	101 (3.4)	460 (15.7)	711 (23.6)
BMI (kg/m^2)	29.04 ± 6.67	27.78 ± 6.68	30.32 ± 6.88	29.01 ± 6.20
HDL (mg/dL)	53.05 ± 16.16	52.54 ± 14.78	51.70 ± 16.44	54.86 ± 16.99
TC (mg/dL)	195.62 ± 42.09	185.94 ± 37.97	202.58 ± 42.85	198.26 ± 43.43

All data originated from NHANES 2003–2016. Data are presented as frequencies (%) for categorial variables, and mean ± geometric standard deviation continuous variables.
ePWV, Estimated Pulse Wave Velocity. T, Tri-sectional quantile. Q, quartile. Family PIR, ratio of family income to poverty. CVD, Cardiovascular diseases. BMI, Body mass index. HDL, High-Density Lipoprotein. TC, Total Cholesterol.
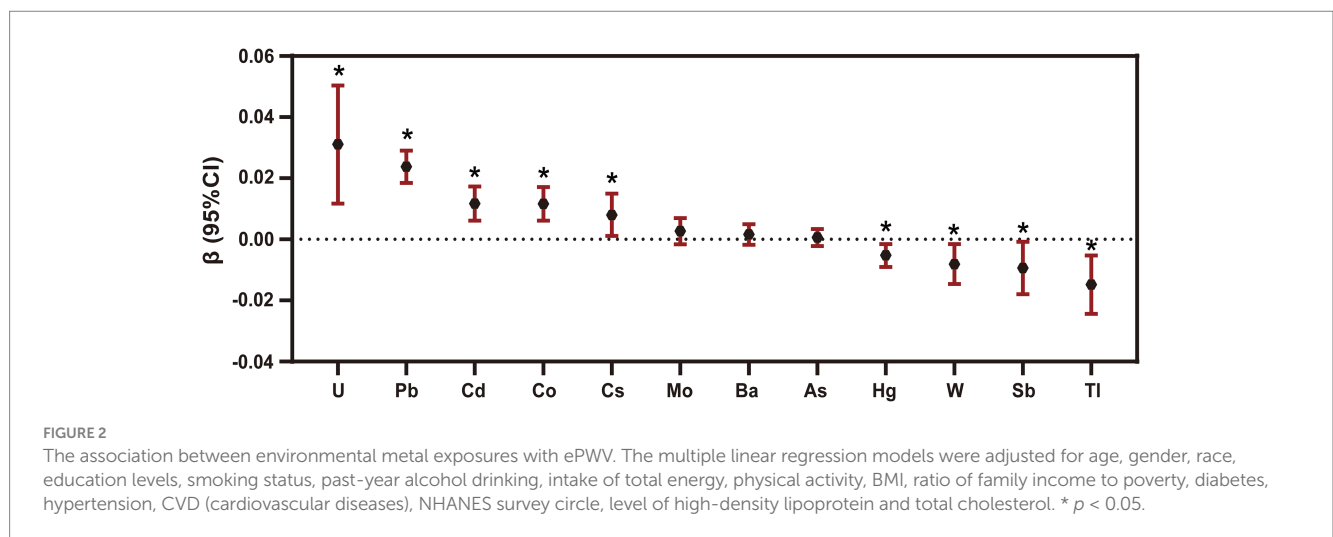

FIGURE 2
The association between environmental metal exposures with ePWV. The multiple linear regression models were adjusted for age, gender, race, education levels, smoking status, past-year alcohol drinking, intake of total energy, physical activity, BMI, ratio of family income to poverty, diabetes, hypertension, CVD (cardiovascular diseases), NHANES survey circle, level of high-density lipoprotein and total cholesterol. * $p < 0.05$.

analysis indicated that HDL and TC accounted for a mediation effect of 2.14 and 3.70% on the association of multiple metals WQS index with ePWV.

Metals are widely used in industrial production and are therefore released into the environment. The general population is mainly exposed to metals through air, food, and drinking water, while occupational exposure exists in mining, smelting, and chemical manufacturing industries (13). Considering the complexity of real-world scenarios, individuals are always exposed to multiple metals. We further used the WQS and Qgcomp models to evaluate the collective effects of multiple metals. Based on the aforementioned models, we found that mixed metal exposure increases the risk of arterial stiffness. This finding is supported by a multicenter study involving multiple ethnic groups, where higher levels of urine metals were linked to the progression of coronary artery stiffness (26). Furthermore, we identified that urine Cd and Pb contributed most to the elevated ePWV through a mixture analysis model. These findings provide a basis for reducing related metals exposure. Additionally, we observed that the WQS regression revealed a significant association between U and increased ePWV, whereas the conclusion of Qgcomp was different. This phenomenon may be attributed to the nature that WQS regression is restricted to gaging risk factors in the same direction (27).

Our mediation analysis indicate that HDL/TC play a promotional role in the association between metal exposure and elevated ePWV. Substantial evidence implicates Pb and Cd could elevate TC level, as well as reduced HDL level (28, 29). HDL and TC were also associated with baPWV/cfPWV (30, 31). Preclinical studies in animal models suggests that metal exposure can disrupt lipid metabolism (32). These evidences indicate that Pb and Cd can disrupt the biological activity of enzymes involved in lipid metabolism, leading to lipid metabolism disorders and promoting arterial stiffness.

However, it should be emphasized that although the mediating effect of HDL and TC was significant, its proportion of total effect was faint in our model. These findings suggest that the mechanism underlying the metal-induced arterial stiffness remains to be elucidated. However, the findings from animal studies may offer some clues. Pb and Cd exposure can reduce NO production by inhibiting eNOS (33, 34), augment the secretion levels of endothelial cell adhesion molecule (35, 36), eventually resulting in endothelial dysfunction and vascular injury. Furthermore, Pb and Cd may also compete with calcium in calcium-dependent processes and interact
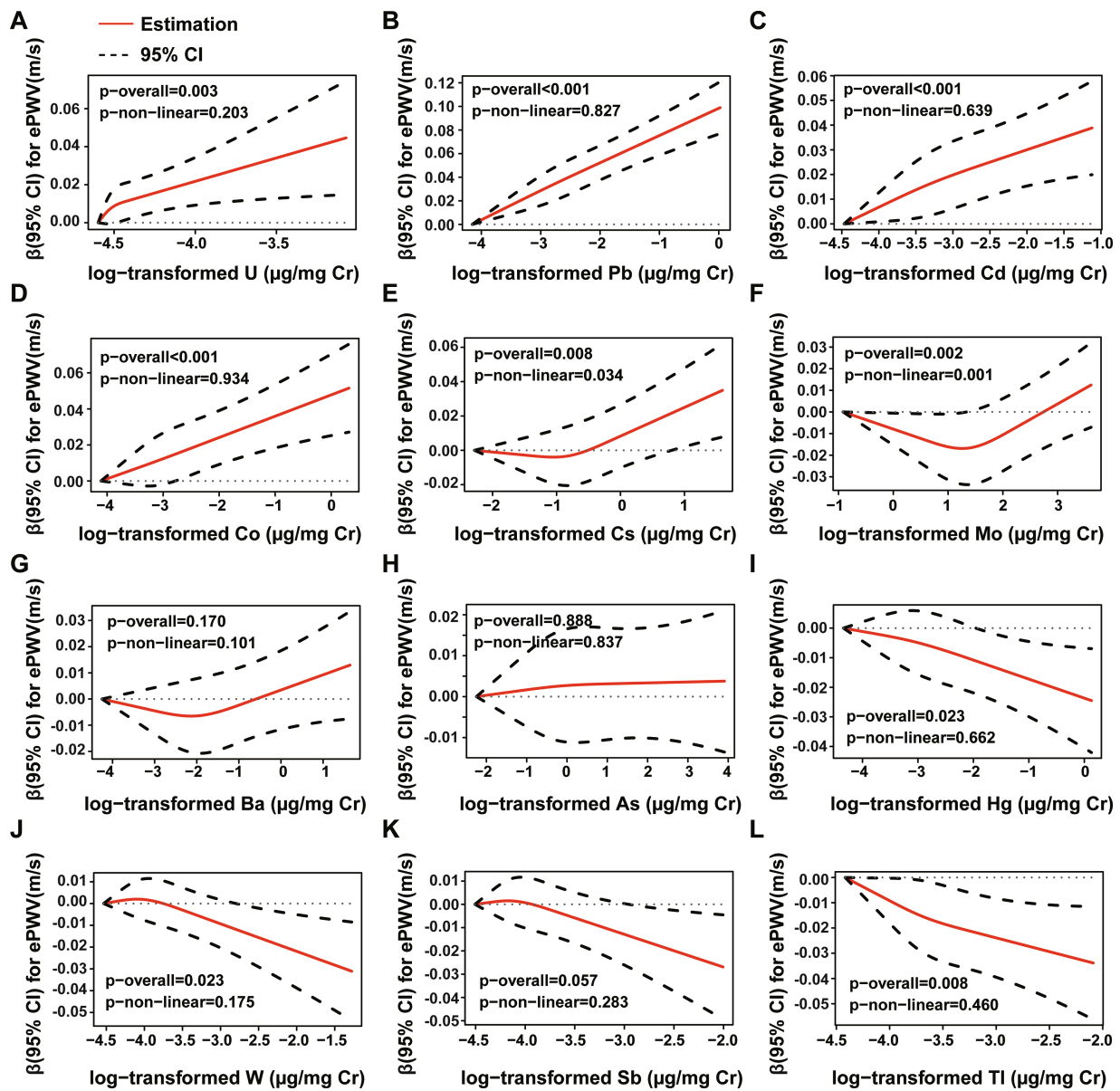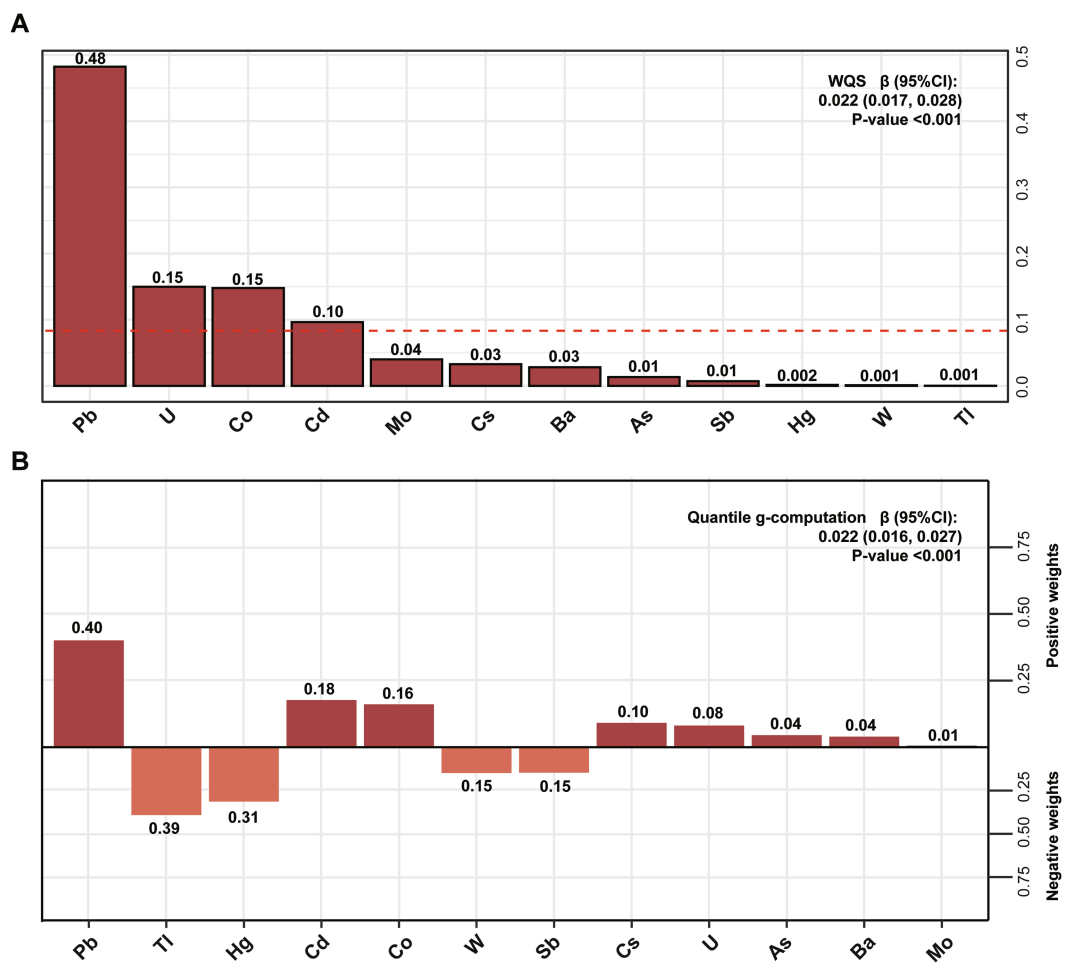
FIGURE 3
RCS regression between individual urine metal and ePWV. **(A)** U, **(B)** Pb, **(C)** Cd, **(D)** Co, **(E)** Cs, **(F)** Mo, **(G)** Ba, **(H)** As, **(I)** Hg, **(J)** W, **(K)** Sb, **(L)** Tl. The model was adjusted for gender, age, race, education levels, smoking status, past-year alcohol drinking, intake of total energy, physical activity, BMI, ratio of family income to poverty, diabetes, hypertension, CVD, NHANES survey circle, level of high-density lipoprotein and total cholesterol.

with calmodulin, thereby disrupting calcium homeostasis and inducing smooth muscle contraction and relaxation dysfunction (37).

This study highlights several notable advantages. First, we conducted a comprehensive population-based analysis to ascertain the role of metal exposure in the progression of arterial stiffness, providing important corroborations with regard to the cardiovascular consequences induced by metal exposure. Second, we employed two mixture analysis models to simulate real-world scenarios and discriminate high-risk metals. Third, we explored potential mechanisms through mediation analysis, suggesting that metal exposure may exacerbate arterial stiffness through perturbations in lipid homeostasis. The findings presented herein provide indispensable epidemiological evidence for identifying the vascular impairment caused by metal exposure. It also indicates that policymakers should

take measures to mitigate and control sources of exposure, which is crucial to reducing metal contamination in air, water, and food, thereby ensuring public health.

A few limitations should be acknowledged. First, the cross-sectional nature of our study design limits the capacity to establish a causal relationship between metal exposure and arterial stiffness. Second, given the disparity in half-life and distribution between metals, urine metal levels may not accurately represent actual exposure *in vivo*. Third, our analyses did not consider sampling weights, which may have impacted the conclusions. In conclusion, it is imperative that the findings pertaining to the association between metal exposure and arterial stiffness are corroborated in forthcoming experimental studies and prospective studies with augmented sample sizes.

FIGURE 4
Both the joint and individual effects of urine metals on ePWV were evaluated by WQS **(A)** and Qgcomp **(B)** model. Models were adjusted for gender, age, race, education levels, smoking status, past-year alcohol drinking, intake of total energy, physical activity, BMI, ratio of family income to poverty, diabetes, hypertension, CVD, NHANES survey circle, level of high-density lipoprotein and total cholesterol.

TABLE 2 Mediation analysis on the association of multiple metals WQS index with ePWV.

Mediators	Indirect effects	Direct effects	Total effects	Mediated proportion (%)	p-value
	β (95% CI)	β (95% CI)	β (95% CI)		
HDL	0.0006 (0.0002, 0.0009)	0.027 (0.023, 0.031)	0.028 (0.023, 0.032)	2.14%	<0.001
TC	0.001 (0.0007, 0.002)	0.026 (0.022, 0.030)	0.027 (0.024, 0.031)	3.70%	<0.001
WBC	0.001 (−0.002, 0.003)	0.026 (0.022, 0.031)	0.026 (0.022, 0.031)	-	0.892
LYM	−0.001 (−0.001, 0.0001)	0.026 (0.022, 0.031)	0.026 (0.022, 0.031)	-	0.732
MON	0.001 (−0.001, 0.001)	0.026 (0.022, 0.031)	0.026 (0.022, 0.031)	-	0.866
NEU	−0.001 (−0.001, 0.001)	0.026 (0.022, 0.031)	0.026 (0.022, 0.031)	-	0.726
EOS	−0.001 (−0.002, 0.001)	0.027 (0.022, 0.031)	0.026 (0.022, 0.031)	-	0.238
BAS	−0.001 (−0.001, 0.001)	0.026 (0.022, 0.031)	0.026 (0.022, 0.031)	-	0.900

Model was adjusted for age, gender, race, education levels, smoking status, past-year alcohol drinking, intake of total energy, physical activity, BMI (body mass index), ratio of family income to poverty, diabetes, hypertension, CVD (cardiovascular diseases), NHANES survey circle, level of high-density lipoprotein and total cholesterol (apart from the analyses of HDL and TC).
ePWV, Estimated Pulse Wave Velocity. WBC, White blood cell count. LYM, Lymphocyte number. MON, Monocyte number. NEU, Segmented neutrophils number. EOS, Eosinophils number. BAS, Basophils number. HDL, high-density lipoprotein. TC, total cholesterol.

5 Conclusion

Our research provides the following findings. First, mixed and single exposure model emphasized that metal exposure increases the risk of high ePWV level, especially Pb and Cd. Furthermore, HDL and TC may act as mediating factors for the associations of metal exposure with elevated ePWV, though this mediating effect is negligible.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://www.cdc.gov/nchs/nhanes/.

Ethics statement

The studies involving humans were approved by National Center for Health Statistics Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

SZ: Writing – original draft, Validation, Methodology, Investigation. ZX: Writing – original draft, Investigation, Formal analysis, Validation. BS: Writing – original draft. ZF: Validation, Methodology, Investigation, Writing – original draft. SW: Methodology, Writing – original draft. WL: Writing – review & editing, Visualization. ZL: Software, Writing – original draft. QL: Supervision, Resources, Writing – review & editing. XG: Supervision, Writing – review & editing. AG: Funding acquisition, Conceptualization, Project administration, Writing – review & editing.

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Conflict of interest

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2025.1606518/full#supplementary-material

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Glossary

ePWV - estimate pulse wave velocity

cfPWV - carotid-femoral pulse wave velocity

NHANES - National Health and Nutrition Examination Survey

WQS - Weighted Quantile Sum regression

Qgcomp - Quantile g-computation

RCS - restricted cubic spline regression

PIR - poverty income ratio

Sb - antimony

As - arsenic

Ba - barium

Cd - cadmium

Cs - cesium

Co - cobalt

Pb - lead

Mo - molybdenum

Hg - mercury

TI - thallium

W - tungsten

U - uranium

HDL - high-density lipoprotein

TC - total cholesterol

MBP - mean blood pressure

SBP - systolic blood pressure

DBP - diastolic blood pressure