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Associations of metal exposure with chest pain incidence and mortality in nonpregnant adults

Based on NHANES data

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Abstract

Heavy metals are widespread environmental contaminants that have attracted considerable attention because of the potential human health risks. Heavy metals can lead to cardiovascular disease and chest pain is the most common precursor symptom. The study aimed to investigate the association between metal exposure and chest pain. This cross-sectional study used data obtained from the 2003 to 2012 National Health and Nutrition Examination Survey. Three metals: lead (Pb), cadmium (Cd), mercury (Hg) in the blood and ten metals: barium (Ba), Cd, cobalt (Co), cesium (Cs), molybdenum (Mo), Pb, antimony (Sb), thallium (Tl), tungsten (Tu), uranium (Ur) in the urine were studied. Using weighted logistic regression models, the relationship between the metal exposure and chest pain was investigated. The hazard ratios (HR) and 95% confidence intervals (95% CI) for all-cause mortality were calculated by weighted Cox proportional hazards models. By applying restricted cubic spline (RCS) analysis, we confirmed linear or nonlinear relationships between metal exposure and all-cause mortality. After adjusting for potential confounding factors, our study found a significant positive association between urinary Sb concentration and chest pain (quartile 4 vs quartile 1, odds ratio [OR] 1.55, 95% CI: 1.02–2.35, $P = .042$). Additionally, each 1-unit increase in blood Cd concentration was associated with a 22% increased risk of all-cause mortality (HR: 1.22, 95% CI: 1.01–1.48). Additionally, RCS analysis showed a nonlinear relationship between the urine Sb concentration and chest pain (P for nonlinear = .0009). A linear relationship was revealed between the urine Cd concentration and all-cause mortality in participants without chest pain (P for nonlinear = .0858). We observed higher odds of chest pain in participants with elevated urinary Sb concentrations, with those in the highest quartile of Sb concentration showing 55% increased odds of chest pain compared to the lowest quartile (OR: 1.55, 95% CI: 1.02–2.35, $P = .042$). Besides, urinary Sb concentration levels were significantly associated with chest pain. Cd concentration levels in the blood and urine were associated with all-cause mortality. This study explored the associations between metal exposure and chest pain incidence, as well as all-cause mortality. However, due to the cross-sectional design, causality cannot be established.

Abbreviations: As = arsenic, Ba = barium, BMI = body mass index, Cd = cadmium, CHD = coronary heart disease, CI = confidence intervals, Co = cobalt, Cs = cesium, Hg = mercury, HR = hazard ratios, ICP-DRC-MS = inductively coupled-plasma dynamic reaction cell-mass spectrometry, Mo = molybdenum, NHANES = National Health and Nutrition Examination Survey, OR = odds ratio, Pb = lead, RCS = restricted cubic spline, Sb = antimony, Tl = thallium, Tu = tungsten, Ur = uranium.

Keywords: blood metals, chest pain, mortality, NHANES, urine metal

1. Introduction

Chest pain is a common symptom of emergency department visits after injury in the United States. Chest pain also leads to about 4 million outpatient visits each year.[1–3] Because of the complex diagnostic and treatment challenges, many patients with chest pain are hospitalized for next assessment and therapy.[4] Chest pain can have many causes, ranging from mild to

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The data for this study was obtained from NHANES. All data is accessible online (https://wwwn.cdc.gov/nchs/nhanes/default.aspx).

The subjects provided consent, and the study protocol was approved by NCHS Research Ethics Review Board. NHANES 2011 to 2012 Protocol #2011-17; NHANES 2009 to 2010 Continuation of Protocol #2005-06; NHANES 2007 to 2008 Continuation of Protocol #2005-06; NHANES 2005 to 2006 Protocol #2005-06; NHANES 1999 to 2004 Protocol #98-12.

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potentially life-threatening.[5–7] Chest pain can be caused by most cardiovascular diseases, such as hypertension, Coronary heart disease (CHD), and heart failure.[8] Many people in life occasionally have chest pain. Because the duration is short and the symptoms of pain are mild, people tend not to care too much. Although there are many causes of chest pain, not all of them are fatal. Yet, it could also be a warning sign of a dangerous disease. The following causes need special attention, such as acute myocardial infarction, aortic dissection and pulmonary embolism. Reflux esophagitis and gastritis can also lead to chest pain.[9] In addition, patients after chest surgery also have the symptom of chest pain. However, a significant proportion of patients still experience unexplained chest pain.[10,11] Unexplained chest pain can also be life threatening. Therefore, it is important to identify the contributing factors associated with chest pain.

Heavy metals are widespread in the environment, including air, water, soil, food, and industrial products.[12] The human body is usually exposed to a variety of heavy metals at the same time. Metal elements enter the human body through various routes and can cause significant harm to health.[13] Different types and concentration levels of heavy metals may produce complex interaction after the absorption and metabolism in the human body. A large number of studies have reported that heavy metals pose a serious threat to multiple organ function, such as cardiovascular system,[14,15] pulmonary function,[16,17] kidney function,[18] and hepatic function,[19] resulting in a severe medical burden. Metal exposure is closely linked to the cardiovascular system. And, chest pain is the most common accompanying symptom of cardiovascular disease, which has not been reported in any studies with a specific link to metal exposure. As a result, we aimed to explore the association of metal exposure with chest pain incidence and mortality in adults. The metals selected for this study (lead, cadmium, mercury, barium, cobalt, cesium, molybdenum, antimony, thallium, tungsten, uranium, and others) were chosen based on their widespread environmental presence, potential human health risks, and established associations with cardiovascular disease. These metals are commonly found in various environmental media such as air, water, food, and industrial products, and their exposure has been linked to various health issues, including cardiovascular disease.[20]

While previous studies have explored the effects of metal exposure on cardiovascular health, few have specifically investigated the relationship between metal exposure and chest pain, a common precursor to cardiovascular disease.[21] This study advances the field by being the first to use National Health and Nutrition Examination Survey (NHANES) data to assess this relationship in nonpregnant adults, thereby providing novel insights into the potential role of environmental metals in cardiovascular disease risk. Additionally, many studies have failed to account for the complex interactions between multiple metals and their combined effects on health. This study overcomes these limitations by examining the relationship between metal exposure and chest pain in a large, representative cohort of nonpregnant adults, using advanced statistical methods to control for potential confounders.

The primary objective of this study is to investigate the association between urinary and blood metal concentrations and the incidence of chest pain in nonpregnant adults. Additionally, the study aims to assess the relationship between metal exposure and all-cause mortality, with a focus on metals such as Pb, Cd, and Sb. The research subjects were obtained from the NHANES during the period 2003–2012. Subgroup analysis was performed for subjects with or without chest pain. We used weighted logistic regression, weighted Cox proportional risk models and restricted cubic spline (RCS) linear analyses to explore the relationship between chest pain and metal exposure making this study reasonable. This exploratory study aims to analyze the associations between metal exposure, chest pain incidence, and all-cause mortality. Due to the cross-sectional design, this study cannot infer causal relationships between metal exposure and health outcomes. Consequently, we hypothesize that higher concentrations of certain metals, particularly Cd and Sb, are associated with an increased risk of chest pain and higher all-cause mortality in nonpregnant adults.

2. Materials and methods

2.1. Study design and subjects

The program of NHANES uses a complex sampling method to select typical samples of the American population every 2 years. Its primary goal is to assess people's health and nutritional status in the America since 1960. In addition, all individuals selected for the study provided informed written consent prior in the program. NHANES collects extensive data, including demographics, dietary intake, clinical examinations, laboratory results, and questionnaire responses. Specific study design, method, or data are accessible online at https://www.cdc.gov/nchs/nhanes/ index.htm. Due to the cross-sectional nature of this study, the observed associations between metal exposure, chest pain, and all-cause mortality should not be interpreted as causal. Longitudinal studies are necessary to establish causality.

A total of 5 cycles of NHANES information from 2003 to 2012, including 2003 to 2004, 2005 to 2006, 2007 to 2008, 2009 to 2010, and 2011 to 2012, were used in the current study. Of the total 50,912 participants, 26,982 were nonpregnant individuals older than 20 years and 23,446 were excluded due to lack of urine and blood metal data. Then, 1224 participants were excluded due to lack of data on chest pain. In addition, 35 participants with missing covariate data and missing follow-up data were excluded. Finally, 2277 participants were included in the present analysis from NHANES. All participants provided consent in the NHANES studies. In summary, the exclusion criteria for our study was following: under 20 years of age; pregnant individuals; missing blood and urine metal concentrations; missing chest pain variables; missing covariates, and missing follow-up information.

2.2. Exposure and outcome variables

In this study, the main exposure variables were blood and urine metal concentrations. Between 2003 and 2012, 10 urine metallic elements and 3 blood metals were included in NHANES routine tests and measured at each cycle (L06BMT, L06HM, PBCD, UHM). Samples were processed, saved and transmitted for analysis. Heavy metals concentrations were analyzed with inductively coupled-plasma dynamic reaction cell-mass spectrometry (ICP-DRC-MS). Further details of the dates can be obtained online.

Chest pain status and mortality were the core outcomes. Chest pain was confirmed if participants responded "yes" to the question "Have you ever had pain or discomfort in chest?" (CDQ). To explore whether metal exposure was closely tied with the risk of death in subjects, we conducted survival analyses in different groups. The outcome information of participants can be seen online (https://www.cdc.gov/nchs/data-linkage/mortality.htm). The state of death was determined by the "MORTSTAT" variable, and the follow-up time was determined by the "PERMTH_EXM" variable. The mean follow-up time was 100.8 ± 22.5 months for patients with chest pain. It was 102.9 ± 22.1 months for participants without chest pain.

2.3. Covariate

The details of all participants were provided about age, gender, race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, or other race), education level (less than high school or equivalent, and higher than high school), and

smoking status (smoker and nonsmoker) through the questionnaires. Smoking is an important source of cadmium and lead exposure, and we included it as a covariate in our models.[22] Current smokers were characterized as participants who reported smoking occasionally or daily now, or over 100 cigarettes in life.[23] Body mass index (BMI) was calculated by weight (kg)/height (m^2). BMI was categorized as obese (equal to or exceed 30), overweight (equal to or exceed 25 and <30), normal (equal to or exceed 18.5 and <25), and underweight (<18.5).[24] For the drinking group, current heavy drinking was identified as: equal to or exceed 3 drinks per day for women, equal to or exceed 4 drinks per day for men, or binge drinking (equal to or exceed 4 drinks per occasion for women, equal to or exceed 5 drinks per occasion for men) on 5 or more days per month; Current moderate drinking was identified as: equal to or exceed 2 drinks per day for women, equal to or exceed 3 drinks per day for men, or binge drinking on 2 or more days per month; The other cases were mild.[25] When participants arrived at the mobile examination center, serum specimens were collected, stored under appropriate frozen conditions, and then transported to a reference laboratory for further testing. Then, they were transported to the higher authority for further testing. Chest pain was closely related to cardiovascular system, for this reason, cardiovascular system related diseases were important covariates in this paper, such as CHD, heart failure, heart attack, angina and stroke. Congestive heart failure was identified when the subjects replied "yes" to the question: "Have you ever been told by a doctor or other health professional that you had congestive heart failure?." CHD was identified when the subjects replied "yes" to following question: "Have you ever been told by a doctor or other health professional that you had CHD?." Heart attack was identified according to following question: "Have you ever been told by a doctor or other health professional that you had a heart attack or myocardial infarction?." Angina was identified based on following question: "Have you ever been told by a doctor or other health professional that you had angina?." Stroke was confirmed when the subjects replied "yes" to following question: "Have you ever been told by a doctor or other health professional that you had a stroke?." Hypertension was identified based on one of the criteria: the participants had a mean systolic blood pressure ≥ 140 mm Hg or a mean diastolic blood pressure ≥ 90 mm Hg; the participants replied "yes" to the question: "Have you ever been told by a doctor or other health professional that you had hypertension?," or the participants were presently taking antihypertensive drugs.[26] Participants were diagnosed with diabetes by one of the following criteria: hemoglobin A1C concentration reached 6.5%, fasting blood glucose level reached 126 mg/dL, self-reported use of insulin now, or did a doctor tell you have diabetes.[27]

2.4. Statistical analysis

In our study, the sample weighting code "WTSA2YR" for the 2003 to 2012 was used as the weighting variable. Detailed

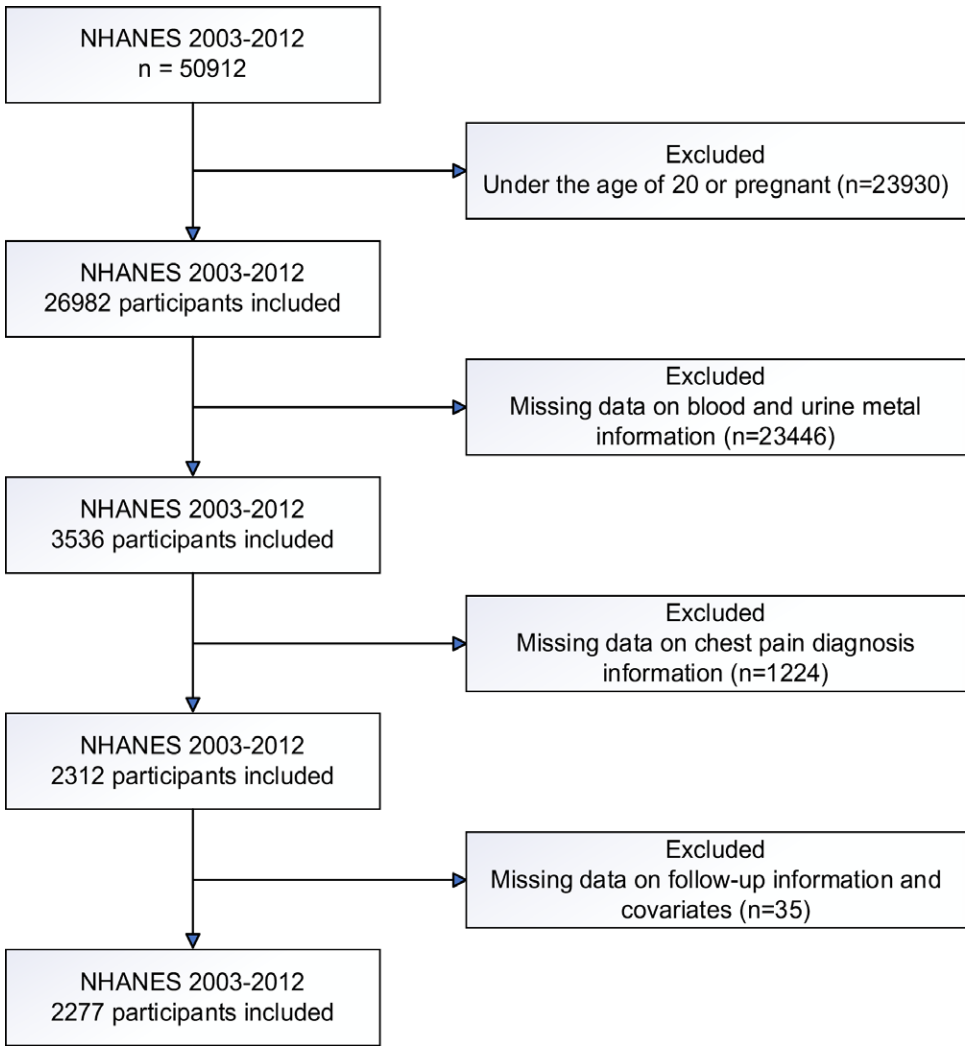

Figure 1. Flow chart of the study participants.

Table 1

All continuous variables are expressed as mean ± SD or categorical variables are expressed as weighted proportion.

Characteristic		Total	Chest pain		*P*-value
			No	Yes	
Age					
	<60	61.18 (58.45–63.84)	61.48 (58.37–64.5)	60.15 (54.38–65.66)	.588
	≥60	38.82 (36.16–41.55)	38.52 (35.5–41.63)	39.85 (34.34–45.62)	
Gender					
	Male	46.97 (44.11–49.85)	45.4 (42.17–48.67)	52.41 (46.43–58.31)	.005
	Female	53.03 (50.15–55.89)	54.6 (51.33–57.83)	47.59 (41.69–53.57)	
Race					
	Mexican American	5.59 (4.86–6.42)	5.46 (4.66–6.39)	6.03 (4.48–8.06)	.951
	Other Hispanic	4.98 (4.26–5.81)	5.05 (4.24–6.01)	4.71 (3.33–6.61)	
	Non-Hispanic White	72.79 (70.72–74.76)	72.71 (70.35–74.95)	73.07 (68.64–77.09)	
	Non-Hispanic Black	10.18 (9.17–11.29)	10.14 (9–11.41)	10.32 (8.32–12.74)	
	Other	6.46 (5.37–7.75)	6.63 (5.41–8.11)	5.87 (3.82–8.93)	
Education					
	≤high school	41.18 (38.45–43.96)	39.93 (36.87–43.06)	45.5 (39.65–51.47)	.024
	>high school	58.82 (56.04–61.55)	60.07 (56.94–63.13)	54.5 (48.53–60.35)	
BMI					
	Underweight	1.84 (1.18–2.88)	1.78 (1.08–2.93)	2.05 (0.75–5.45)	.156
	Normal	25.75 (23.29–28.38)	26.3 (23.49–29.31)	23.86 (19.02–29.48)	
	Overweight	35.4 (32.69–38.2)	36.11 (33.02–39.32)	32.94 (27.54–38.84)	
	Obese	37.01 (34.29–39.81)	35.81 (32.74–39.01)	41.15 (35.46–47.09)	
Diabetes mellitus					
	No	81.88 (79.75–83.84)	83.68 (81.29–85.82)	75.67 (70.71–80.02)	<.001
	Yes	18.12 (16.16–20.25)	16.32 (14.18–18.71)	24.33 (19.98–29.29)	
Hypertension					
	No	51.47 (48.59–54.33)	54.34 (51.08–57.57)	41.5 (35.6–47.65)	<.001
	Yes	48.53 (45.67–51.41)	45.66 (42.43–48.92)	58.5 (52.35–64.4)	
Alcohol consumption					
	Mild	68.59 (65.78–71.26)	68.85 (65.66–71.86)	67.69 (61.61–73.23)	.703
	Moderate	20.67 (18.34–23.21)	20.71 (18.08–23.61)	20.56 (15.89–26.17)	
	Heavy	10.74 (9.05–12.7)	10.45 (8.59–12.66)	11.75 (8.26–16.45)	
Smoking status					
	Nonsmoker	50.8 (47.92–53.67)	53.73 (50.45–56.99)	40.63 (34.98–46.54)	<.001
	Smoker	49.2 (46.33–52.08)	46.27 (43.01–49.55)	59.37 (53.46–65.02)	
Heart failure					
	No	96.96 (96.05–97.67)	98.27 (97.48–98.82)	92.45 (89.23–94.76)	<.001
	Yes	3.04 (2.33–3.95)	1.73 (1.18–2.52)	7.55 (5.24–10.77)	
CHD					
	No	95.47 (94.15–96.5)	98.11 (97.16–98.74)	86.33 (81.53–90.04)	<.001
	Yes	4.53 (3.5–5.85)	1.89 (1.26–2.84)	13.67 (9.96–18.47)	
Angina					
	No	97.30 (96.18–98.1)	99.43 (98.77–99.73)	89.94 (85.51–93.12)	<.001
	Yes	2.7 (1.9–3.82)	0.57 (0.27–1.23)	10.06 (6.88–14.49)	
Heart attack					
	No	95.51 (94.27–96.5)	98.15 (97.23–98.77)	86.39 (81.85–89.93)	<.001
	Yes	4.49 (3.5–5.73)	1.85 (1.23–2.77)	13.61 (10.07–18.15)	
Stroke					
	No	96.84 (96–97.51)	97.6 (96.71–98.26)	94.22 (91.78–95.96)	<.001
	Yes	3.16 (2.49–4)	2.4 (1.74–3.29)	5.78 (4.04–8.22)	
Blood metal concentrations					
Cd(μg/L)		0.545 ± 0.575	0.529 ± 0.550	0.603 ± 0.651	.010
	Q1: 0.11 to 0.24	28.41 (25.78–31.2)	28.65 (25.65–31.85)	27.58 (22.37–33.48)	.161
	Q2: 0.24 to 0.39	26.2 (23.73–28.83)	26.75 (23.93–29.76)	24.31 (19.47–29.91)	
	Q3: 0.39 to 0.66	21.96 (19.8–24.28)	22.24 (19.77–24.92)	20.99 (16.8–25.9)	
	Q4: 0.66 to 8.67	23.43 (21.11–25.92)	22.36 (19.79–25.16)	27.12 (22.15–32.72)	
Urine metal concentrations					
Cd(μg/L)		0.426 ± 0.539	0.507 ± 1.086	0.658 ± 2.707	.062
	Q1: 0.030–0.165	28.6 (25.99–31.36)	29.63 (26.64–32.81)	25.05 (20.04–30.83)	.026
	Q2: 0.165–0.310	28.05 (25.46–30.79)	27.77 (24.86–30.89)	29 (23.65–35.01)	
	Q3: 0.310–0.575	22.05 (19.88–24.38)	20.83 (18.44–23.44)	26.26 (21.52–31.62)	
	Q4: 0.575–6.940	21.3 (19.14–23.64)	21.77 (19.27–24.49)	19.69 (15.67–24.43)	
Mo(μg/L)		50.305 ± 48.341	51.108 ± 49.759	47.524 ± 42.960	.140
	Q1: 1.39–22.20	27.79 (25.21–30.54)	28.54 (25.57–31.7)	25.22 (20.28–30.9)	.030
	Q2: 22.20–39.90	25.62 (23.17–28.23)	25.12 (22.35–28.11)	27.35 (22.36–32.99)	
	Q3: 39.90–67.20	23.29 (20.99–25.76)	22.19 (19.67–24.93)	27.11 (22.01–32.9)	
	Q4: 67.20–541.00	23.29 (21.02–25.73)	24.16 (21.53–26.99)	20.31 (16.14–25.24)	
Sb(μg/L)		0.073 ± 0.130	0.074 ± 0.143	0.071 ± 0.072	.621
	Q1: 0.023–0.029	15.85 (14.02–17.86)	16.83 (14.68–19.22)	12.46 (9.46–16.24)	.001

(*Continued*)

Table 1
(Continued)

Characteristic		Total	Chest pain		*P*-value
			No	Yes	
	Q2: 0.029–0.046	35.43 (32.65–38.32)	36.6 (33.4–39.92)	31.39 (25.98–37.37)	
	Q3: 0.046–0.077	24.1 (21.73–26.63)	23.45 (20.81–26.32)	26.33 (21.37–31.97)	
	Q4: 0.077–4.050	24.62 (22.27–27.14)	23.12 (20.54–25.92)	29.82 (24.6–35.62)	
Tu(μg/L)		0.103 ± 0.177	0.177 ± 0.128	0.167 ± 0.113	.118
	Q1: 0.015 to 0.031	24.34 (21.93–26.92)	24.92 (22.17–27.89)	22.32 (17.7–27.74)	.019
	Q2: 0.031 to 0.062	26.3 (23.81–28.96)	27.05 (24.2–30.11)	23.71 (18.87–29.34)	
	Q3: 0.062 to 0.119	25.14 (22.74–27.71)	23.64 (20.99–26.51)	30.33 (25.05–36.18)	
	Q4: 0.119 to 3.856	24.22 (21.89–26.71)	24.38 (21.72–27.27)	23.64 (19.14–28.83)	

CHD = coronary heart disease; BMI = body mass index.

information on the survey sample design and weight calculation method can be found online.

The baseline features were divided into 2 groups based on whether participants experienced chest pain. Metal concentrations were categorized into quartiles to allow for an intuitive assessment of risk across different exposure levels and to mitigate the influence of extreme values. Moreover, we conducted supplementary analyses treating metal concentrations as continuous variables. Continuous variables were compared using the T-test or Wilcoxon rank-sum test appropriately. Categorical variables were compared by the Pearson Chi-square test.

Using weighted univariate and multivariate logistic regression analyses, the associations between blood and urine metal concentrations and chest pain were analyzed, expressed as odds ratio with 95% CI. The mortality of different metal exposure groups was expressed by Kaplan–Meier curve and compared by log-rank test. Using weighted univariate and multivariate Cox proportional hazard models, the association between metal exposure groups and mortality among participants was estimated for hazard ratios (HR) with 95% CI. Based on multivariate logistic regression and Cox proportional hazard models, the potential nonlinear relationship between metal concentration and chest pain and all-cause mortality was further evaluated by the RCS curve. We employed RCS to explore the potential nonlinear relationships between metal concentrations and outcomes. RCS offers the advantage of flexibly modeling the data without assuming a priori a linear relationship, thereby providing a more detailed understanding of how metal exposure impacts chest pain and all-cause mortality across the range of exposure levels. To control for confounding factors, we used 3 types of weighted logistic regression and weighted Cox regression models respectively: Model 1, unadjusted; Model 2, adjusted for age, gender, race, education and BMI; and Model 3, adjusted for age, gender, race, education, BMI, diabetes, hypertension, alcoholic drink, smoking status, heart failure, CHD, angina, heart attack, stroke.

The covariates in our model are carefully selected variables according to known associations with outcomes and supported by existing literature.[28] Bilateral $P < .05$ was considered statistically significant. All analyses were performed using R version 4.3.3.

3. Results

3.1. Baseline characteristics

A total of 2277 subjects were eligible for the analysis. The details are shown in Figure 1.

In the study, 2277 subjects (1132 men and 1145 women) were included. Table 1 shows the baseline characteristics of subjects. In the study, chest pain symptom appeared in approximately 23% (529) of subjects. Among the participants with chest pain, most were young, male, Non-Hispanic White, higher BMI, current smokers and people with high blood pressure. Additionally, based on the quartile classification of metal concentrations, we found that patients with chest pain had higher concentrations of multiple metals in their blood and urine than those without chest pain (Cd, Mo, Sb, Tu). Complete metal concentration data was presented in additional file: Table S1, Supplemental Digital Content, https://links.lww.com/MD/O905.

3.2. Associations between the metal concentration levels and chest pain

In all subjects, a significant positive association can be found between the urine Sb concentration and chest pain. Subjects in the fourth quartile of the urine Sb concentration (95% CI: 1.02–2.35) had an approximately 55% increased risk of chest pain compared to the reference group (quartile 1) (Table 2), after adjusting for age, sex, race, education, BMI, high blood pressure, diabetes, alcohol consumption, smoking, heart failure, CHD, angina, heart attack and stroke. Figure 2 shows a RCS of the nonlinear relationship between urine Sb concentration and chest pain (nonlinear $P = .0009$).

3.3. Correlation between the metal concentration levels and all-cause mortality

Of all the participants, 366 participants (16.07%) died. The Kaplan–Meier survival curve showed that higher blood and urine Cd concentrations were associated with higher all-cause mortality for all participants with chest pain or not(all log-rank P values < .05, as shown in Figure 3A–F). Multivariate Cox regression model showed that for every 1 unit increase in blood Cd concentration, the mortality adjusted HR was 1.22 (95% CI: 1.01–1.48) for total participants, 1.17 (95% CI: 0.92–1.48) for those without chest pain, and 1.35 (95% CI: 0.95–1.91) for those with chest pain. In participants without chest pain, participants in the fourth quartile of the blood or urine Cd concentrations had increased risk of death compared to the reference group (Table 3). The association between Cd concentration and all-cause mortality was further evaluated by RCS curves (Fig. 4). RCS analysis showed that blood Cd concentration, as a continuous variable, was not significantly linearly related to an increased risk of all-cause mortality correction for all participants (nonlinear $P = .0001$), irrespective of whether they had the symptom of chest pain (chest pain: nonlinear $P = .0003$; no pain: nonlinear $P = .0109$). We also found that there was a linear relationship between urine Cd concentration and all-cause mortality in participants without chest pain ($P = .0858$).

4. Discussion

Metal pollution originates from diverse sources and readily accumulates in various environmental media. Metal pollution

Table 2

The association between the urine Sb concentration and chest pain.

	Model 1			Model 2			Model 3		
Characteristic	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Urine Sb concentrations									
Q1	–	–		–	–		–	–	
Q2	1.159	0.774 to 1.735	.474	1.144	0.762 to 1.719	.516	1.085	0.715 to 1.647	.7
Q3	1.517	1.001 to 2.298	.049	1.478	0.973 to 2.244	.067	1.362	0.882 to 2.103	.163
Q4	1.742	1.16 to 2.618	.008	1.659	1.097 to 2.508	.016	1.546	1.015 to 2.353	.042
P for trend			.074			.069			.053

Model 1: Unadjusted. Model 2: Adjusted for age, gender, race, education and BMI. Model 3: Adjusted for age, gender, race, education, BMI, diabetes, hypertension, alcohol consumption, smoking status, heart failure, coronary heart disease, angina, heart attack, stroke.
OR = odds ratio, CI = confidence interval.

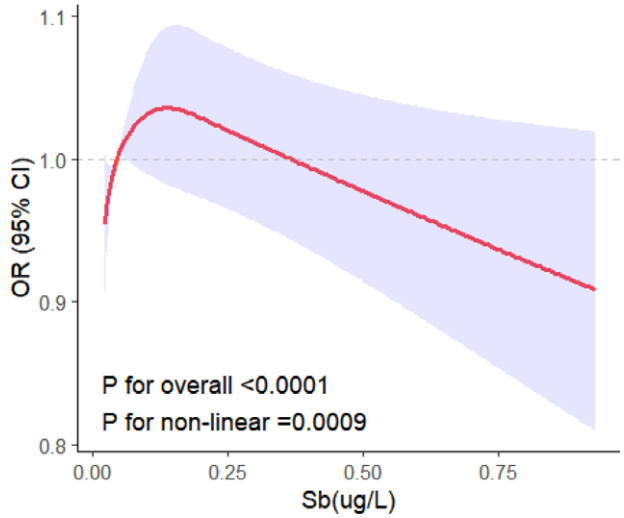

Figure 2. Restricted cubic spline curve for the association between the urine Sb levels and the risk of chest pain. Red lines represent odds ratios, and blue areas represent 95% confidence intervals. The model was adjusted for age, gender, race, education, BMI, diabetes, hypertension, alcohol consumption, smoking status, heart failure, CHD, angina, heart attack, stroke. BMI = body mass index, CHD = coronary heart disease.

has the characteristics of difficult degradation, easy accumulation and potential harm. It has become an environmental problem of global concern and has been widely studied by scholars in various countries. Metals in environmental media can enter the human body through multiple ways and cause serious harm to health. In particular, the cardiovascular system is more susceptible to heavy metals. Chest pain is the most common precursor symptom of the cardiovascular disease. We aimed to explore the association of metal exposure with chest pain incidence and mortality in nonpregnant adults. It should be noted that subgroup analyses, especially those stratified by the presence of chest pain, may suffer from limited statistical power due to smaller sample sizes. Consequently, these findings should be interpreted with caution, and future studies with larger sample sizes are necessary to validate these subgroup-specific associations.

This study used NHANES data from 2003 to 2012 to reveal the association between metal exposure and chest pain symptoms, as well as the relationship between metal exposure and all-cause mortality in subjects of the study. We found that urine Sb concentration levels were related to chest pain, and participants with elevated metal Sb concentrations were at greater risk for chest pain. However, this correlation is not simply linear. Furthermore, we found that blood and urine Cd concentration levels affect mortality. However, this effect was not significant after controlling for all covariates. While arsenic (As) is a well-known toxic metal, it was not included in this study due to limitations in the available data within the NHANES dataset for the period under investigation. Fewer participants had complete chest pain information and arsenic metal data. The focus of this study was on metals that were regularly measured in NHANES during the 2003 to 2012 period, and future research should consider metals not included in this study, including arsenic, to better understand their potential health effects.[29]

While the metal biomarkers used in NHANES are standardized and highly accurate, their results may still be influenced by short-term fluctuations in exposure. Therefore, caution should be exercised when interpreting the findings as representative of long-term exposure, and further studies are needed to assess the reliability of these biomarkers for long-term exposure evaluation.[30]

Numerous studies have demonstrated a strong association between metal exposure (e.g., Pb, Cd, and Hg) and the incidence of cardiovascular disease and all-cause mortality.[31–33] In a previous study, the authors confirmed a clear positive correlation between Cd levels in hair and blood and high blood pressure. This effect may be related to impaired kidney function. Nevertheless, the study was not adjusted for major confounding variables such as age, race and smoking habits.[34] It has also been reported that Pb exposure has a multifaceted effect on heart failure. Elevated Pb levels can lead to increased cardiac pressure overload and peripheral resistance. Altering the electrical conduction of the heart, Pb impairs heart function caused by disturbing the physiological interrelation between myocardial performance and heart rate.[35] Smoking is a well-documented risk factor for cardiovascular disease and a major source of exposure to Cd and Pb. Therefore, smoking is the variable that this study focuses on. Studies have shown a robust correlation between Cd concentration levels and stroke and heart failure in adults, especially in the blood.[36] Smoking, which is a significant source of cadmium and lead exposure, was included as a covariate in this study. However, its direct role in the observed associations requires further exploration. Given the potential for smoking to confound the relationship between metal exposure and health outcomes, future studies should examine the combined effects of smoking and metal exposure more closely.

Chest pain is the typical symptom of cardiovascular disease, but few studies have explored the association between metal exposure and chest pain. Our study showed that urine metal Sb concentration was significantly related with the incidence of chest pain. After full adjustment for age, sex, race, education, BMI, high blood pressure, diabetes, alcohol consumption, smoking, heart failure, CHD, heart attack, angina and stroke, the association remained. Through RCS analysis, we found that the correlation was not linear, but an inverted U-shape. Studies on metal Sb were not commonly found in previous literature studies. One study showed that urine Sb levels were positively related to all-cause heart disease mortality, congestive heart failure prevalence, and heart attack events in the US population. By reason of the insufficient research data on metal Sb, the exact

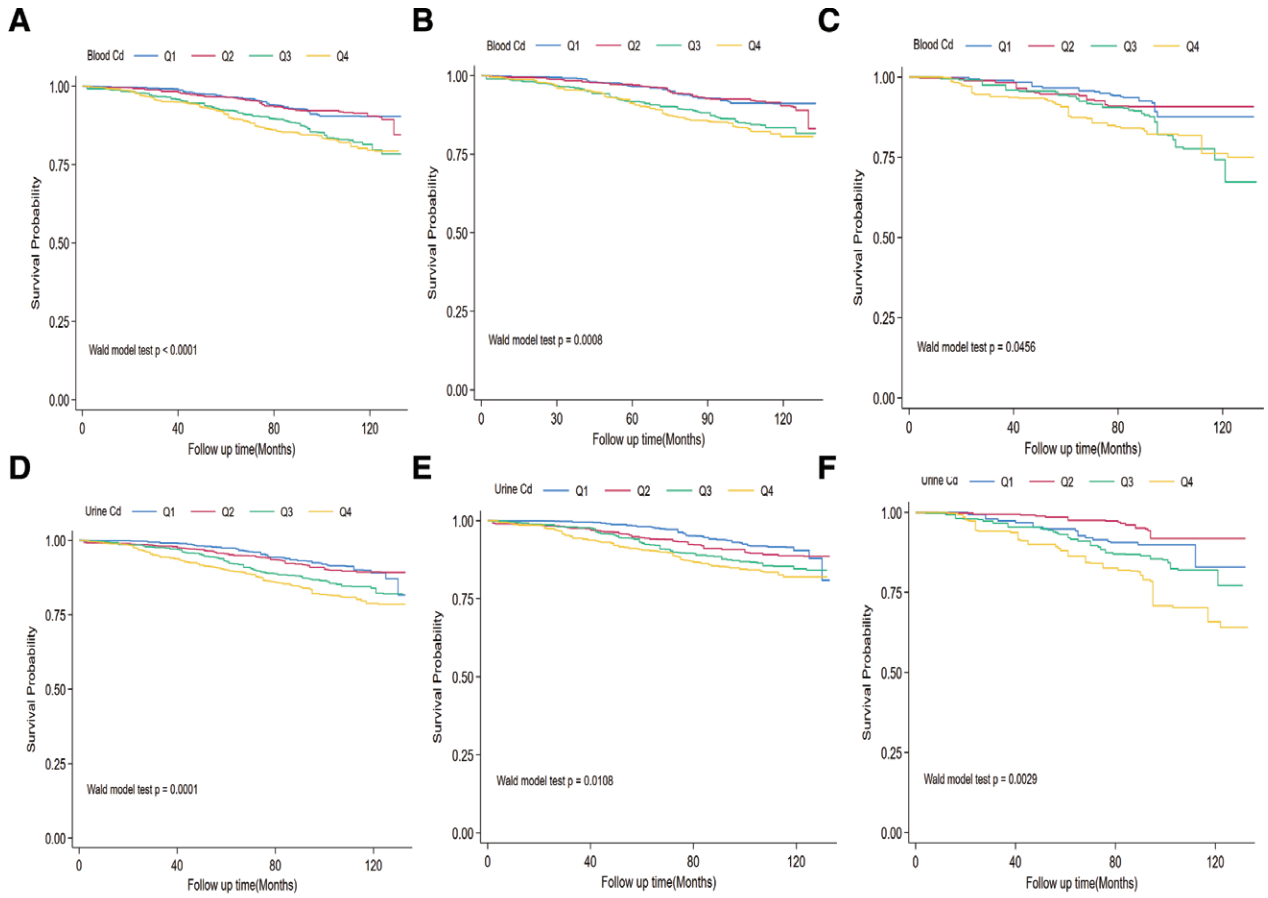

Figure 3. Kaplan–Meier analysis of all-cause mortality (A) blood Cd in total participants, (B) blood Cd in participants without chest pain, (C) blood Cd in participants with chest pain, (D) urine Cd in total participants, (E) urine Cd in participants without chest pain, (F) urine Cd in participants with chest pain.

mechanism was unknown.[37] We were also the first to find the association between the concentration of metal Sb and chest pain. Based on the small number of references, the association should be explained with carefulness. The nonlinear, inverted U-shaped association between urinary Sb and chest pain suggests that at lower concentrations, Sb may induce protective or compensatory mechanisms, whereas at higher concentrations, its toxic effects become more dominant. Such a threshold effect has been observed in other environmental exposures and may explain the observed nonlinearity.[38] However, given the limited literature on Sb, these hypotheses remain speculative and require further research.

Our study found that urine and blood Cd concentrations were related to all-cause mortality in patients with chest pain. Urine Cd is the most meaningful biomarker for long-term Cd exposure, and blood Cd can indicate more short-term exposure because the half-life of Cd in blood differs from urine.[39] Prior to this, a large number of studies have demonstrated that metal Cd exposure is closely associated with all-cause mortality in patients with cardiovascular disease. The observed association between Cd exposure and increased all-cause mortality may be explained by Cd-induced oxidative stress, endothelial dysfunction, and inflammatory responses, which are known contributors to cardiovascular disease.[40] Similarly, the nonlinear association observed between urinary Sb and chest pain could reflect complex dose-dependent effects where lower levels of exposure might trigger compensatory mechanisms, while higher levels result in toxicity. These biological pathways warrant further investigation.[40] In Japan, a prospective cohort study lasting nearly 20 years showed that urinary Cd levels were significantly associated with increased mortality, adversely affecting life outcomes in the population.[41] For all-cause mortality, a study from Sweden observed a statistically significant dose-related correlation with urine Cd exposure (HR: 1.38, 95% CI: 1.10–1.74).[42] Our study also found a significant association between high Cd exposure levels and all-cause mortality (blood Cd: Q4 vs Q1, HR: 2.10, 95% CI: 1.40–3.14, $P < .001$; urine Cd: Q4 vs Q1, HR: 2.16, 95% CI: 1.47–3.19, $P < .001$). After controlling for age, sex, race, education, BMI, high blood pressure, diabetes, alcohol consumption, smoking, heart failure, CHD, angina, heart attack and stroke, this relationship persisted (blood Cd: Q4 vs Q1, HR: 1.78, 95% CI: 1.17–2.71, $P = .008$; urine Cd: Q4 vs Q1, HR: 1.62, 95% CI: 1.06–2.47, $P = .026$). In addition, in participants without chest pain, we found a linear relationship between urine Cd concentration and all-cause mortality (P for nonlinear = .0858). However, we found a complex nonlinear relationship between metal Cd exposure and all-cause mortality in participants with chest pain.

This study relies on blood and urine samples to represent metal exposure; however, due to potential fluctuations in metal concentrations within individuals, this method may not accurately reflect long-term cumulative exposure. Future studies should consider using repeated measurements to more accurately assess long-term exposure. There are still many shortcomings in our research. First, although several confounders were analyzed and adjusted, some confounders of chest pain were not added in our statistical model because of the complexity of these factors. Although we adjusted for several important confounders, other factors, such as dietary habits, occupational exposures, and environmental pollution sources, were not considered in this study. These unmeasured factors may contribute to the observed associations and should be explored in future studies.

Table 3

The correlation between certain metal concentration levels and all-cause mortality.

	Model 1			Model 2			Model 3		
Characteristic	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
All participants									
Blood Cd(μg/L)	1.276	1.109 to 1.468	.001	1.372	1.156 to 1.629	<.001	1.224	1.01 to 1.484	.039
Q1	–	–		–	–		–	–	
Q2	0.977	0.62 to 1.54	.921	0.733	0.463 to 1.161	.185	0.745	0.471 to 1.179	.209
Q3	1.948	1.296 to 2.929	.001	1.294	0.837 to 1.998	.246	1.181	0.774 to 1.803	.441
Q4	2.096	1.399 to 3.141	<.001	1.946	1.282 to 2.956	.002	1.778	1.165 to 2.714	.008
P for trend			<.001			<.001			<.001
Urine Cd(μg/L)	1.273	1.102 to 1.469	.001	1.303	1.096 to 1.549	.003	1.183	0.977 to 1.432	.085
Q1	–	–					–	–	
Q2	1.06	0.684 to 1.641	.794	0.996	0.636 to 1.558	.985	1.078	0.695 to 1.672	.737
Q3	1.662	1.112 to 2.486	.013	1.359	0.909 to 2.03	.134	1.376	0.932 to 2.032	.108
Q4	2.164	1.469 to 3.188	<.001	1.861	1.248 to 2.774	.002	1.618	1.06 to 2.47	.026
P for trend			<.001			.005			.031
No pain									
Blood Cd(μg/L)	1.26	1.057 to 1.503	.01	1.307	1.054 to 1.621	.015	1.166	0.919 to 1.479	.205
Q1	–	–		–	–		–	–	
Q2	1.044	0.614 to 1.775	.873	0.864	0.508 to 1.47	.59	0.835	0.488 to 1.43	.512
Q3	1.91	1.177 to 3.098	.009	1.305	0.764 to 2.23	.33	1.259	0.743 to 2.135	.392
Q4	2.159	1.337 to 3.487	.002	1.99	1.187 to 3.338	.009	1.754	1.034 to 2.975	.037
P for trend			<.001			.004			.005
Urine Cd(μg/L)	1.238	1.048 to 1.462	.012	1.33	1.095 to 1.616	.004	1.214	0.977 to 1.509	.08
Q1	–	–		–	–		–	–	
Q2	1.231	0.748 to 2.026	.413	1.184	0.715 to 1.961	.511	1.23	0.742 to 2.038	.423
Q3	1.68	1.038 to 2.717	.035	1.381	0.865 to 2.206	.176	1.367	0.857 to 2.181	.189
Q4	2.018	1.288 to 3.163	.002	1.858	1.174 to 2.939	.008	1.641	1.009 to 2.669	.046
P for trend			<.001			.012			.061
Pain									
Blood Cd(μg/L)	1.268	1.007 to 1.596	.043	1.552	1.244 to 1.935	<.001	1.345	0.946 to 1.913	.099
Q1	–	–		–	–		–	–	
Q2	0.803	0.332 to 1.943	.626	0.367	0.146 to 0.924	.033	0.396	0.157 to 0.999	.05
Q3	2.027	0.964 to 4.26	.062	1.065	0.531 to 2.134	.859	0.85	0.375 to 1.929	.698
Q4	1.868	0.884 to 3.946	.102	1.817	0.936 to 3.527	.078	1.889	0.871 to 4.099	.107
P for trend			.024			<.001			.009
Urine Cd(μg/L)	1.429	1.145 to 1.783	.002	1.136	0.658 to 1.959	.647	1.218	0.813 to 1.825	.34
Q1	–	–		–	–		–	–	
Q2	0.601	0.24 to 1.505	.277	0.52	0.191 to 1.415	.2	0.696	0.266 to 1.817	.459
Q3	1.442	0.687 to 3.028	.334	1.25	0.529 to 2.953	.611	1.47	0.639 to 3.38	.365
Q4	2.551	1.215 to 5.356	.013	1.682	0.744 to 3.804	.211	1.65	0.645 to 4.218	.296
P for trend			.003			.072			.061

Model 1: unadjusted; Model 2: adjusted for age, gender, race, education and BMI; Model 3: adjusted for age, gender, race, education, BMI, diabetes, hypertension, alcohol consumption, smoking status, heart failure, coronary heart disease, angina, heart attack, stroke.

HR = hazard ratio, CI = confidence interval.

Additionally, the NHANES dataset did not provide detailed information on potential confounders such as occupation and other environmental pollutants. The omission of these factors may lead to residual confounding, and future studies should aim to include these variables to more comprehensively assess the impact of metal exposure on chest pain and mortality. Second, NHANES used random blood and urine samples to measure metal concentrations. The accuracy of metal concentration measurements requires further improvement. Due to limitations in the available NHANES dataset – particularly the limited variability and missing data for some key variables such as occupation, diet, and other environmental pollutants. It is challenging to conduct a comprehensive sensitivity analysis under the current conditions. Third, we adopted a cross-sectional design, so the causality could not be further assessed. The current analysis could only conclude that certain metals in blood and urine were intimately related to chest pain and all-cause mortality. As this study is a cross-sectional analysis, although significant associations between metal exposure and chest pain and mortality were observed, these associations should not be interpreted as causal. Future longitudinal studies could better reveal causal relationships between metal exposure and health outcomes.

5. Conclusion

The study is the first to investigate the association between metal exposure (three metals in the blood; ten metals in the urine) and chest pain and all-cause mortality, using NHANES data from 2003 to 2012. Our findings suggest that higher levels of specific metals in blood and urine are associated with an increased risk of chest pain and all-cause mortality among nonpregnant adults. The results showed that Sb in urine was associated with chest pain, and Cd in blood and urine was related to all-cause mortality. It is important to note that, due to the observational design and potential residual confounding, these findings should be interpreted with caution. Future studies with longitudinal designs and more comprehensive data collection are needed to further validate these associations.

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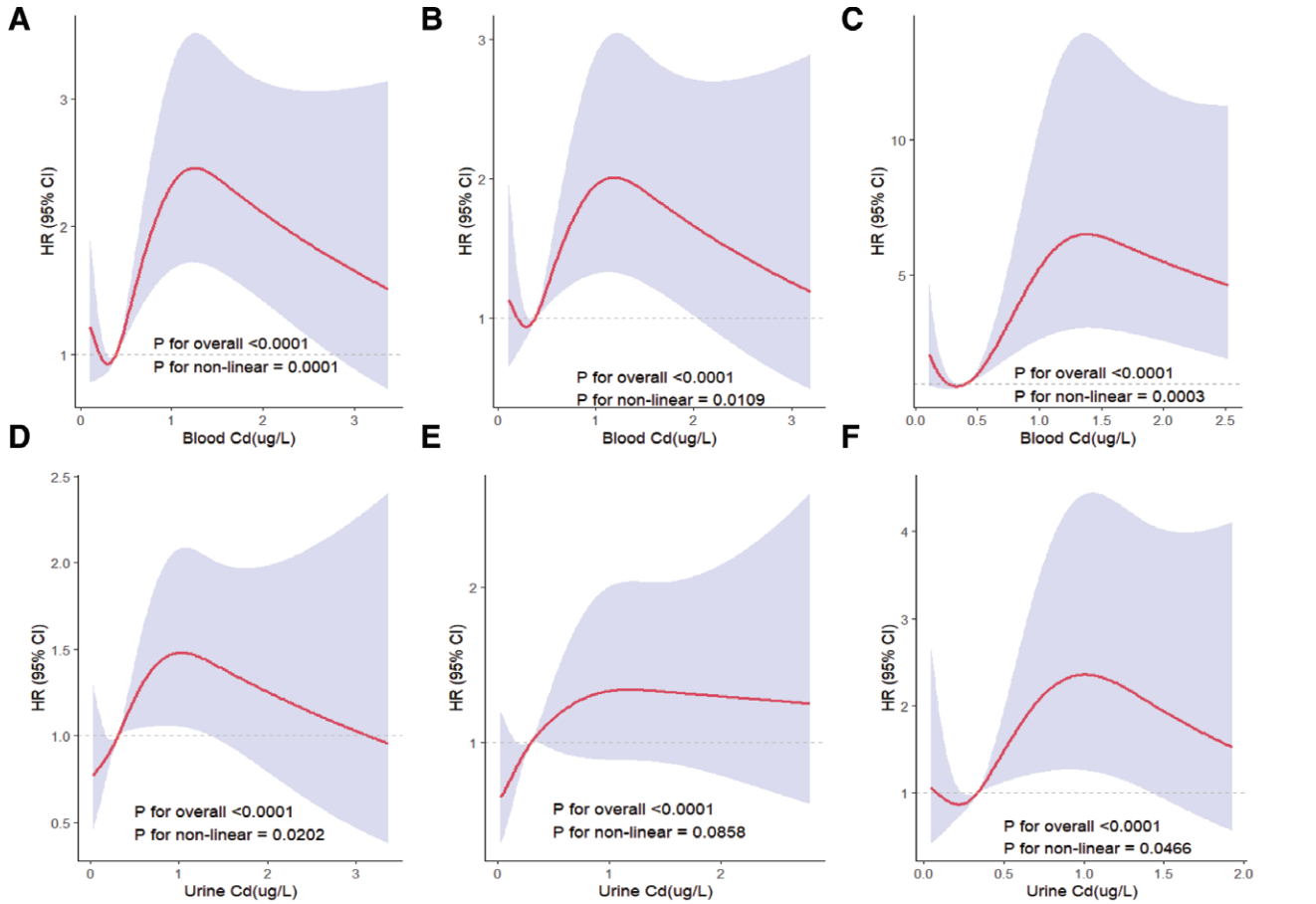

Figure 4. Restricted cubic spline curves for the association between the blood and urine Cd levels and all-cause mortality. (A) blood Cd in total participants, (B) blood Cd in participants without chest pain, (C) blood Cd in participants with chest pain, (D) urine Cd in total participants, (E) urine Cd in participants without chest pain, (F) urine Cd in participants with chest pain. Red lines represent references for hazard ratios, and blue areas represent 95% confidence intervals. The model was adjusted for age, gender, race, education, BMI, diabetes, hypertension, alcohol consumption, smoking status, heart failure, CHD, angina, heart attack, stroke. BMI = body mass index, CHD = coronary heart disease.

Author contributions

Conceptualization: Hanlin Wang, Renquan Zhang.
Data curation: Yuan Hong.
Formal analysis: Long Yao, Yuan Hong.
Funding acquisition: Renquan Zhang.
Writing – original draft: Hanlin Wang.
Writing – review & editing: Hanlin Wang.

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