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ORIGINAL PAPER

Correlation of heavy metals' exposure with the prevalence of coronary heart disease among US adults: findings of the US NHANES from 2003 to 2018

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Abstract We sought to explore the association between heavy metal exposure and coronary heart disease (CHD) based on data from the US National Health and Nutrition Examination Survey (NHANES, 2003–2018). In the analyses, participants were all aged > 20 and had participated in heavy metal subtests with valid CHD status. The Mann–Kendall test was employed to assess the trends in heavy metals' exposure and the trends in CHD prevalence over 16 years. Spearman's rank correlation coefficient and a logistics regression (LR) model were used to estimate the association between heavy metals and CHD prevalence. 42,749 participants were included in our analyses, 1802 of whom had a CHD diagnosis. Total arsenic, dimethylarsonic acid, monomethylarsonic acid, barium, cadmium, lead, and antimony in urine, and cadmium, lead, and total mercury in blood all showed a substantial decreasing exposure level tendency over the 16 years (all $P_{for\ trend} < 0.05$). CHD prevalence varied from 3.53 to 5.23% between 2003 and 2018. The correlation between 15 heavy metals and CHD ranges from −0.238 to 0.910. There was also a significant positive correlation between total arsenic, monomethylarsonic acid, and thallium in urine and CHD by data release cycles (all $P < 0.05$). The cesium in urine showed a negative correlation with CHD ($P < 0.05$). We found that exposure trends of total arsenic, dimethylarsonic acid, monomethylarsonic acid, barium, cadmium, lead, and antimony in urine and blood decreased. CHD prevalence fluctuated, however. Moreover, total arsenic, monomethylarsonic acid, and thallium in urine all showed positive relationships with CHD, while cesium in urine showed a negative relationship with CHD.

Keywords Coronary heart disease · Heavy metals · Spearman's rank correlation · US NHANES

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Introduction

According to the American Heart Research Association report, there were 874,613 cardiovascular disease-related (CVD) deaths in the US in 2019,

with coronary heart disease (CHD) accounting for 41.3% of them (Agarwala et al., 2020; Heidenreich et al., 2011; Jilani et al., 2021). Nowadays, genetic and environmental factors, or a combination of these factors, play an integral role in CHD (Daniali et al., 2020). Although many studies have been conducted on traditional risk factors such as diabetes, hyperlipidemia, increased blood pressure, tobacco and alcohol use, obesity, genetic mutations, and psychological illnesses (Al-Shaar et al., 2020; Lahm et al., 2021; Lu et al., 2020), there has been limited research on the association of heavy metals and CHD.

The majority of previous studies have reported that cadmium, lead, mercury, and arsenic are related to CHD (Fan et al., 2022; Jia et al., 2021; Wang et al., 2022). Researchers have largely focused on cross-sectional and case–control studies for detecting biological molecules and interactions between heavy metals and diseases; however, there has been a lack of focus on prospective cohort studies or long-term consistency studies that might demonstrate a relationship between heavy metals' exposure and CHDs in populations (Boyd et al., 2022).

Our study examined the 16-year trend of heavy metals' exposure and the prevalence of CHD using data from the National Health and Nutrition Examination Survey (NHANES, 2003–2018). Further, we estimated the association between heavy metals' exposure and the corresponding CHD prevalence in survey participants.

Method

Study participants

The NHANES was an annual cross-sectional study that employed a wide range of collection methods including interviewing participants and conducting clinical examinations of local community population samples from all over the country (NHANES, 2014). Our study data was drawn from the NHANES from 2003 to 2018.

The following criteria were used to determine who was appropriate for inclusion: (1) participants who were older than 20 years; and (2) participants who had participated in the heavy metal sub-test. Exclusion criteria were defined as: (1) Participants without CHD tracking; and (2) Participants having uncertain CHD status. Finally, 42,749 participants were included in our analyses.

Covariates' determination

Participants' demographic characteristics comprised gender, age (years), race/Hispanic, education level, poverty-to-income ratio (PIR), and body mass index (BMI, kg/m^2). All demographic characteristics were described in our previous study (Li et al., 2023). The PIR reflects the economic income level. We divided the PIR into high, medium, and low levels (Krieger et al., 2003). Lifestyle factors included physical exercise (vigorous/moderate/none), smoking (current smoker/ex-smoker/none), and alcohol consumption (heavy drinking/none).

For our analyses, 15 heavy metal samples were collected from urine or blood; detailed information is provided in Table 2. Inductively-coupled plasma dynamic reaction cell-mass spectrometry (ICP-DRC-MS) was used to measure all heavy metal levels while adhering to stringent control procedures (NHANES, 2013).

Outcome ascertainment

In the current study, CHD status was inferred from self-report participant questionnaires prior to December 31, 2015. Subsequently, CHD status was identified by professional doctors who used codes *I00-09, I11, I13, or I20-51* for labeling participants according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, (ICD-10)* (Hirsch et al., 2015; Mou & Ren, 2020).

Statistical analysis

Participants' demographic characteristics were summarized in the data release cycle. Categorical variables were represented as number (%), while continuous variables were calculated as the median (interquartile range). We employed the chi-square test or Wilcoxon two-sample test to compare characteristics throughout the 16-year survey duration. Heavy metals were reported as geometric means and geometric standard deviations every two years. The

Mann–Kendall test was used to assess the trends in heavy metals' exposure or CHD prevalence over the 16 years. We conducted Principal Component Analysis (PCA) on the 15 heavy metals to reduce the dimensionality and visualize the average levels on a 2D plane. Further, to provide a comprehensive analysis, we performed PCA for heavy metals every two years, considering different CHD statuses. Using Wilcoxon's two-sample test, we compared the contents of heavy metals in different CHD statuses. Meanwhile, we used Spearman's rank correlation coefficient to estimate the correlation between heavy metals and the corresponding CHD prevalence.

Additionally, we computed the odds ratio (OR) and 95% confidence interval (CI) using a logistic regression (LR) model to determine the link between heavy metals and CHD. Model 1 was unadjusted; Model 2 was adjusted for gender and age; and Model 3 was adjusted for variables in model 2 plus demographic characteristics and lifestyle factors.

All analyses were executed through Python 3.8.0, with statistically significant difference defined as $P < 0.05$.

Results

Participants' demographic characteristics in the study

The study participants' demographic characteristics from 2003 to 2018 (NHANES) are shown in Table 1. A total of 42,749 participants were included in the analyses, 48.25% of them men, and the average participant age was 49 (interquartile range, 34.0–64.0). At each data release cycle, there were significant differences in participants' age, race, education level, PIR, BMI, physical activity, smoking, and alcohol consumption (all $P < 0.05$). During the 16 years, other races, high education level, and BMI have all shown significant increasing tendencies (all P for trend < 0.05).

Level of heavy metal exposure over 16 years

In Table 2, we describe the level of heavy metals' exposure for each data release cycle. Over 16 years, there was a substantial decreasing exposure tendency for total arsenic (−2.71 μg/L the difference value between years 2003 and 2018), dimethylarsonic acid (−0.97 μg/L the difference value between years 2003 and 2018), monomethylarsonic acid (−0.44 μg/L was the difference value between years 2003 and 2018), barium (−0.35 ng/mL the difference value between years 2003 and 2018), cadmium (−0.07 ng/mL the difference value between years 2003 and 2018), lead (−0.39 ng/mL the difference value between years 2003 and 2018), and antimony (−0.09 ng/mL the difference value between years 2003 and 2018) in urine, and cadmium (−0.09 μg/L the difference value between years 2003 and 2018), lead (−0.79 μg/dL the difference value between years 2003 and 2018), and total mercury (−0.37 μg/L the difference value between years 2003 and 2018) in blood (all $P_{\text{for trend}} < 0.05$), while cobalt, cesium, thallium, tungsten, and uranium in urine followed a constant trend (all $P_{\text{for trend}} > 0.05$).

Prevalence of CHD over the 16 years

Among the 42,749 participants in the 16-year study, 1802 were diagnosed with CHD, the prevalence of CHD being 4.22%. The prevalence over the years is shown in Fig. 1. From 2003 to 2012, the annual prevalence of CHD decreased from 5.23 to 3.53%; however, CHD prevalence increased from 3.53 to 4.63% after 2012 (Fig. 1a). The trend in CHD prevalence fluctuated over the 16 years ($P_{\text{for trend}} = 0.197$). According to the prevalence of CHD, a polynomial dotted curve was fitted ($R^2 = 0.737$). In addition, Fig. 1b shows the CHD prevalence by gender from 2003 to 2018. Men showed a higher CHD prevalence than women every two years ($P < 0.05$). Further, participants who were aged > 60 had the highest CHD prevalence among the different age groups in each data release cycle ($P < 0.05$) in Fig. 1c.

The distribution of heavy metals in relation to CHD

Due to the nature of PCA analysis, it was necessary to have complete data for each sample. As a result, PCA analysis of all the heavy metals was performed on 3,185 participants; the levels of heavy metals are described in Fig. 2a. In addition, we conducted PCA of heavy metals by different CHD statuses in Fig. 2b.

Table 1 Characteristics of the study participants from 2003 to 2018 in NHANES

Characteristics	Cycles of NHANES									*P*	$P_{for\ trend}$
	2003–2004 (n = 4719)	2005–2006 (n = 4749)	2007–2008 (n = 5679)	2009–2010 (n = 6033)	2011–2012 (n = 5300)	2013–2014 (n = 5570)	2015–2016 (n = 5450)	2017–2018 (n = 5249)	Total (n = 42,749)		
Men	2264 (47.98)	2270 (47.80)	2777 (48.90)	2913 (48.28)	2610 (49.25)	2657 (47.70)	2605 (47.80)	2532 (48.24)	20,628 (48.25)	0.603	0.902
Age, years	49.00 (33.00–67.00)	46.00 (31.00–63.00)	50.00 (36.00–65.00)	49.00 (34.00–64.00)	48.00 (33.00–63.00)	48.00 (34.00–63.00)	49.00 (34.00–64.00)	53.00 (36.00–65.00)	49.00 (34.00–64.00)	< 0.001	0.521
Race/Hispanic										< 0.001	
Mexican American	943 (19.98)	955 (20.11)	977 (17.20)	1090 (18.07)	518 (9.77)	746 (13.39)	945 (17.34)	696 (13.26)	6870 (16.07)		0.536
Other Hispanic	142 (3.01)	147 (3.10)	634 (11.16)	612 (10.14)	535 (10.09)	491 (8.82)	720 (13.21)	495 (9.43)	3776 (8.83)		0.386
Non-Hispanic White	2502 (53.02)	2372 (49.95)	2656 (46.77)	2901 (48.09)	1941 (36.62)	2388 (42.87)	1781 (32.68)	1800 (34.29)	18,341 (42.90)		0.174
Non-Hispanic Black	931 (19.73)	1084 (22.83)	1182 (20.81)	1093 (18.12)	1404 (26.49)	1143 (20.52)	1158 (21.25)	1238 (23.59)	9233 (21.60)		0.063
Other Race	201 (4.26)	191 (4.02)	230 (4.05)	337 (5.59)	902 (17.02)	802 (14.40)	846 (15.52)	1020 (19.43)	4529 (10.59)		0.009
Education level										< 0.001	
College or above	3320 (70.35)	3424 (72.10)	3921 (69.04)	4303 (71.32)	4042 (76.26)	4364 (78.35)	4160 (76.33)	4191 (79.84)	31,725 (74.21)		0.035
High school or equivalent	709 (15.02)	730 (15.37)	997 (17.56)	977 (16.19)	745 (14.06)	764 (13.72)	638 (11.71)	595 (11.34)	6155 (14.40)		0.386
Less than high school	690 (14.62)	595 (12.53)	761 (13.40)	753 (12.48)	513 (9.68)	442 (7.94)	652 (11.96)	463 (8.82)	4869 (11.39)		0.174
PIR[a]										< 0.001	
High	1155 (24.48)	1299 (27.35)	1419 (24.99)	1464 (24.27)	1314 (24.79)	1424 (25.57)	1268 (23.27)	1347 (25.66)	10,690 (25.01)		0.536
Medium	2678 (56.75)	2608 (54.92)	3080 (54.23)	3183 (52.76)	2628 (49.58)	2864 (51.42)	2951 (54.15)	2912 (55.48)	22,904 (53.58)		0.536
Low	886 (18.78)	842 (17.73)	1180 (20.78)	1386 (22.97)	1358 (25.62)	1282 (23.02)	1231 (22.59)	990 (18.86)	9155 (21.42)		0.711
BMI[b] ($kg/m^{2)}$	27.20 (24.22–31.25)	27.20 (24.46–31.60)	27.52 (24.53–31.80)	27.55 (24.70–32.08)	27.20 (24.24–31.81)	27.37 (24.36–32.02)	27.85 (24.84–32.73)	28.07 (25.05–33.07)	27.47 (24.53–32.04)	< 0.001	0.042

Table 1 (continued)

Characteristics	Cycles of NHANES									*P*	$P_{for\ trend}$
	2003–2004 (n = 4719)	2005–2006 (n = 4749)	2007–2008 (n = 5679)	2009–2010 (n = 6033)	2011–2012 (n = 5300)	2013–2014 (n = 5570)	2015–2016 (n = 5450)	2017–2018 (n = 5249)	Total (n = 42,749)		
Physical activity										< 0.001	
Vigorous	998 (21.15)	1311 (27.61)	1085 (19.11)	1107 (18.35)	1169 (22.06)	1217 (21.85)	1340 (24.59)	1220 (23.24)	9748 (22.80)		0.063
Moderate	183 (3.88)	118 (2.48)	1349 (23.75)	1592 (26.39)	1447 (27.30)	1533 (27.52)	1296 (23.78)	1211 (23.07)	8428 (19.72)		0.711
None	3538 (74.97)	3320 (69.91)	3245 (57.14)	3334 (55.26)	2684 (50.64)	2820 (50.63)	2814 (51.63)	2818 (53.69)	24,573 (57.48)		0.063
Smoking										< 0.001	
Current smoker	1109 (23.50)	1006 (21.18)	1241 (21.85)	1287 (21.33)	1042 (19.66)	1156 (20.75)	1050 (19.27)	1004 (19.13)	8895 (20.81)		0.536
Ex-smoker	1274 (27.00)	1193 (25.12)	1405 (24.74)	1466 (24.30)	1202 (22.68)	1238 (22.23)	1198 (21.98)	1170 (22.29)	10,146 (23.73)		0.266
None	2336 (49.50)	2550 (53.70)	3033 (53.41)	3280 (54.37)	3056 (57.66)	3176 (57.02)	3202 (58.75)	3075 (58.58)	23,708 (55.46)		0.063
Alcohol consumption										0.037	
Heavy drinking	596 (12.63)	615 (12.95)	758 (13.35)	870 (14.42)	647 (12.21)	731 (13.12)	714 (13.10)	675 (12.86)	5606 (13.11)		0.536
None	4123 (87.37)	4133 (87.03)	4917 (86.58)	5161 (85.55)	4651 (87.75)	4838 (86.86)	4734 (86.86)	4567 (87.01)	37,124 (86.84)		0.711

[a]PIR, poverty to income ratio; [b]BMI, body mass index

Table 2 Geometric means and geometric standard deviations of heavy metals by each cycle of NHANES (2003–2018)

Heavy metals	Cycles of NHANES																$P_{for\ trend}$[d]
	2003–2004		2005–2006		2007–2008		2009–2010		2011–2012		2013–2014		2015–2016		2017–2018		
	n	Mean (SD)[#]	n	Mean (SD)[#]	n	Mean (SD)[#]	n	Mean (SD)[#]	n	Mean (SD)[#]	n	Mean (SD)[#]	n	Mean (SD)[#]	n	Mean (SD)[#]	
In urine																	
Total arsenic (μg/L)	777	11.60 (3.29)	1379	10.11 (3.24)	1661	8.95 (2.99)	1879	10.10 (3.26)	1862	8.89 (3.40)	NA*	NA*	NA*	NA*	NA*	NA*	0.005
Dimethylarsonic acid (μg/L)	753	4.40 (2.27)	1358	4.16 (2.16)	1638	3.92 (2.18)	1884	3.90 (2.40)	1859	4.09 (2.45)	1747	3.49 (2.20)	1716	3.54 (2.26)	1611	3.43 (2.26)	0.009
Monomethylarsonic acid (μg/L)	646	0.87 (1.69)	1382	0.85 (1.57)	1639	0.85 (1.57)	1882	0.83 (1.61)	NA*	NA*	1708	0.43 (2.43)	NA*	NA*	NA*	NA*	0.007
Barium (ng/mL)	756	1.26 (2.61)	1305	1.37 (2.80)	1609	1.31 (2.72)	1798	1.34 (2.63)	1790	1.14 (2.65)	1714	1.00 (2.77)	1680	1.04 (2.82)	1608	0.91 (2.92)	0.035
Cadmium (ng/mL)	690	0.29 (2.67)	1348	0.26 (2.74)	1658	0.27 (2.64)	1857	0.25 (2.63)	1842	0.25 (2.90)	1739	0.19 (2.96)	1699	0.21 (2.86)	1608	0.22 (2.75)	0.024
Cobalt (ng/mL)	686	0.32 (2.26)	1351	0.37 (2.32)	1647	0.35 (2.15)	1853	0.34 (2.26)	1835	0.31 (2.27)	1746	0.38 (2.26)	1696	0.40 (2.24)	1608	0.40 (2.30)	0.135
Cesium (ng/mL)	774	4.84 (2.10)	1366	4.65 (2.02)	1660	4.43 (1.95)	1856	4.09 (1.96)	1852	3.92 (1.99)	1746	3.95 (1.99)	1705	4.04 (2.02)	1608	4.24 (1.97)	0.108
Lead (ng/mL)	724	0.72 (2.15)	1212	0.71 (2.30)	1536	0.58 (2.36)	1744	0.54 (2.37)	1714	0.47 (2.44)	1649	0.34 (2.53)	1624	0.35 (2.51)	1608	0.33 (2.44)	0.001
Antimony (ng/mL)	292	0.14 (1.66)	1344	0.07 (2.29)	1646	0.06 (2.15)	1834	0.05 (2.21)	1850	0.05 (2.03)	1738	0.04 (2.37)	1694	0.05 (2.32)	1608	0.05 (2.32)	0.023

Table 2 (continued)

Heavy metals	Cycles of NHANES																$P_{for\ trend}$[d]
	2003–2004		2005–2006		2007–2008		2009–2010		2011–2012		2013–2014		2015–2016		2017–2018		
	n	Mean (SD)[#]	n	Mean (SD)[#]	n	Mean (SD)[#]	n	Mean (SD)[#]	n	Mean (SD)[#]	n	Mean (SD)[#]	n	Mean (SD)[#]	n	Mean (SD)[#]	
Thallium (ng/mL)	625	0.16 (2.12)	1342	0.15 (2.06)	1641	0.14 (2.07)	1843	0.14 (2.06)	1824	0.15 (2.05)	1723	0.14 (2.14)	1684	0.15 (2.07)	1608	0.16 (2.03)	1.000
Tungsten (ng/mL)	625	0.06 (2.74)	1338	0.08 (2.77)	1623	0.09 (2.79)	1816	0.07 (2.68)	1809	0.07 (2.73)	1712	0.05 (2.95)	1672	0.06 (2.80)	1608	0.06 (2.73)	0.248
Uranium (ng/mL)	785	0.01 (2.14)	1368	0.01 (2.66)	1665	0.01 (2.74)	1861	0.01 (2.71)	1863	0.01 (2.48)	1751	0.01 (2.97)	1706	0.01 (2.66)	NA*	NA*	0.190
In blood																	
Cadmium (μg/L)	2063	0.43 (2.56)	3896	0.40 (2.16)	4642	0.42 (2.15)	5445	0.38 (2.16)	3509	0.47 (2.06)	2267	0.35 (2.29)	2254	0.34 (2.28)	4651	0.34 (2.36)	0.046
Lead (μg/dL)	2887	1.77 (1.90)	4297	1.50 (2.01)	5016	1.51 (1.88)	5516	1.33 (1.94)	4289	1.20 (2.00)	2402	1.07 (2.00)	2343	1.02 (2.02)	4779	0.98 (2.03)	0.002
Total mercury (μg/L)	3251	1.16 (2.81)	4382	0.97 (2.54)	5140	0.92 (2.58)	5617	0.99 (2.61)	4470	1.06 (2.72)	2510	0.91 (2.74)	2460	0.88 (2.71)	4889	0.79 (2.77)	0.035

[#]Mean (SD), geometric means and geometric standard deviations; **NA*, not applicable

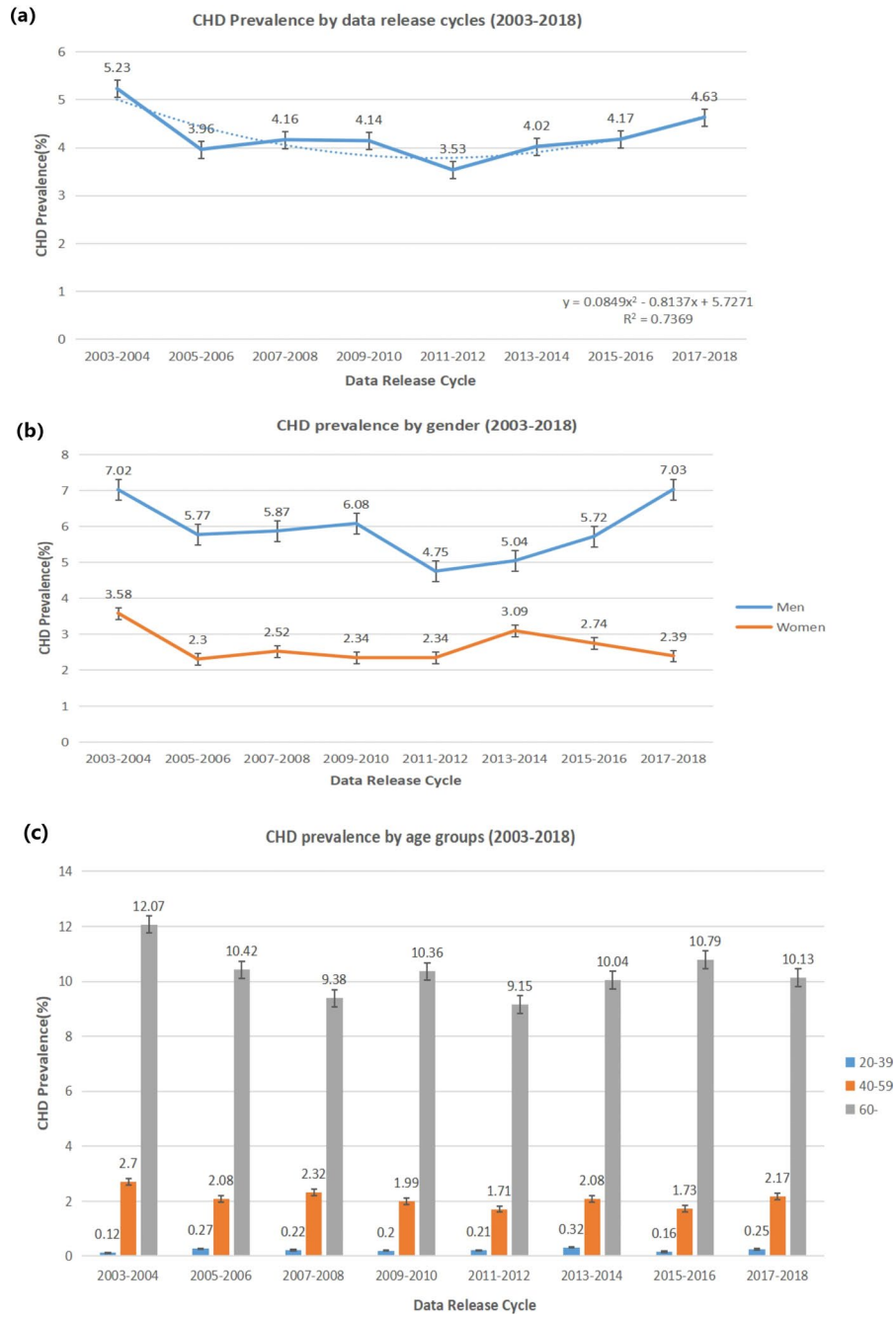


Fig. 1 CHD[#] prevalence from 2003 to 2018 in NHANES. [#]*CHD*, coronary heart disease

The explained variance ratio (first two heavy metals) was 0.973 and 0.107.

To provide a comprehensive analysis, we performed PCA for heavy metals every two years from 2005 to 2010, considering different CHD statuses (in Supplementary Fig. 1). However, it is important to note that the measurements for total arsenic and monomethylarsonic acid were absent after 2010, preventing us from disaggregating the data for 2011–2018.

Moreover, based on the different CHD statuses (Supplementary Table 3), the content of barium and thallium in urine as well as cadmium and lead in

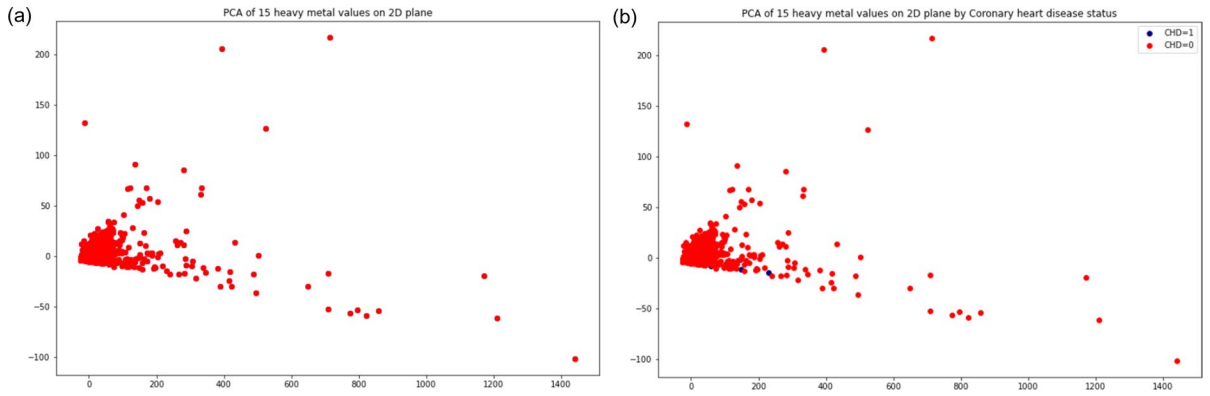


Fig. 2 PCA[#] of 15 heavy metal values on 2D plane. [#]*PCA*, principal component analysis; *CHD*, coronary heart disease

both urine and blood showed a significant difference ($P < 0.05$).

Correlation coefficients between heavy metal exposure and corresponding CHD prevalence

The corresponding CHD prevalences by data release cycles based on each heavy metal all showed a fluctuating trend ($P_{\text{for trend}} > 0.05$). The Spearman's rank correlation coefficients (r ranging from -0.238 to 0.910) between 15 heavy metals and their corresponding CHD prevalence correlations are reported in Supplementary Table 1 and Fig. 3. There was, in particular, a significant correlation between total arsenic ($r = 0.900$, $P = 0.037$), monomethylarsonic acid ($r = 0.900$, $P = 0.037$), cesium ($r = 0.786$, $P = 0.021$) and thallium ($r = 0.762$, $P = 0.028$) in urine and CHD by data release cycle (Fig. 3). Other heavy metals were not associated with their corresponding CHD prevalence.

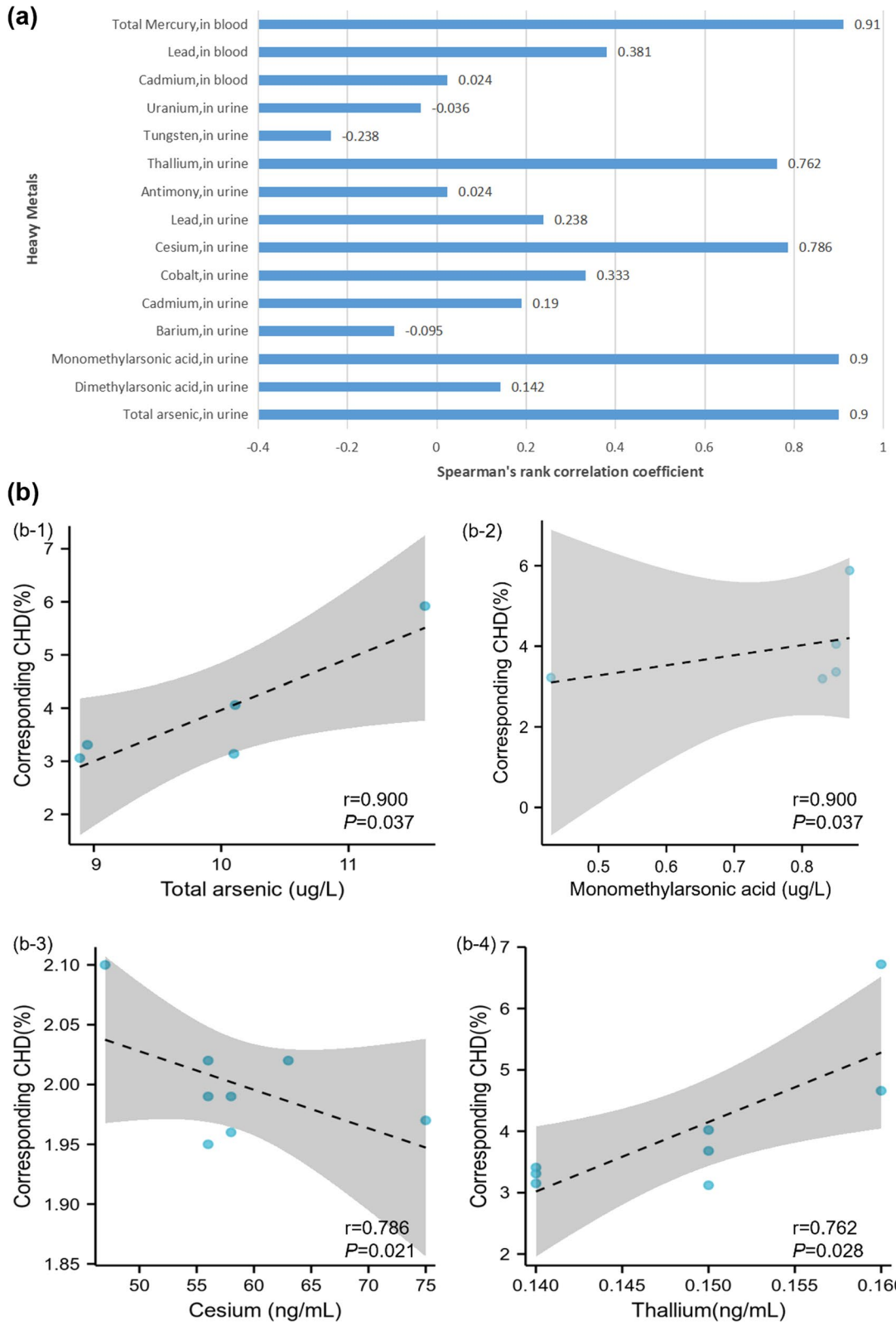
Overall, there was a reasonable level of concordance between the trend of change in heavy metal exposure and the variability in CHD prevalence among the four heavy metals. We separately illustrate the association between total arsenic, monomethylarsonic acid, cesium, and thallium in urine with their corresponding CHD prevalence from 2003 to 2018 in Fig. 4. With regard to total arsenic exposure in urine, the level increased to 10.1 μg/L in 2009–2010, but, by contrast, the corresponding CHD prevalence decreased from 3.31 to 3.14%. Figure 4-c, comparing the level of cesium exposure in urine in 2005–2006, 2011–2012, and 2017–2018 with other years, reveals variation in the corresponding CHD prevalence. Figure 4-d shows that in 2011–2012 there was a noticeable increase in the level of thallium exposure in urine, although the corresponding prevalence of CHD gradually decreased.

Association between heavy metals and CHD

The ORs of association between the different models of heavy metal exposure with CHD were estimated separately by the LR model, as reported in Table 3. After adjusting for potential variables, the ORs and 95% CI of total arsenic, monomethylarsonic acid, cesium, and thallium in urine with CHD were 1.003 (1.000–1.010), 1.010 (1.001–1.014), 0.995 (0.990–0.998) and 1.004 (1.002–1.014), respectively. The results of ORs were similar to the correlation coefficients between heavy metal exposure and corresponding CHD prevalence.

Discussion

In our large sample population-based cross-sectional study, we investigated the relationship between 15 metals and CHD among 42,749 participants. Based on our study, the total arsenic, dimethylarsonic acid, monomethylarsonic acid, barium, cadmium, lead, and antimony in urine, and cadmium and lead in blood, showed significant decreasing trends over the 16 years. In particular, total


(a)
Heavy Metals
Total Mercury,in blood
Lead,in blood
Cadmium,in blood
Uranium,in urine
Tungsten,in urine
Thallium,in urine
Antimony,in urine
Lead,in urine
Cesium,in urine
Cobalt,in urine
Cadmium,in urine
Barium,in urine
Monomethylarsonic acid,in urine
Dimethylarsonic acid,in urine
Total arsenic,in urine
0.91
0.381
0.024
-0.036
-0.238
0.762
0.024
0.238
0.786
0.333
0.19
-0.095
0.9
0.142
0.9
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1
Spearman's rank correlation coefficient
(b)
(b-1)
Corresponding CHD(%)
r=0.900
P=0.037
Total arsenic (ug/L)
(b-2)
Corresponding CHD(%)
r=0.900
P=0.037
Monomethylarsonic acid (ug/L)
(b-3)
Corresponding CHD(%)
r=0.786
P=0.021
Cesium (ng/mL)
(b-4)
Corresponding CHD(%)
r=0.762
P=0.028
Thallium(ng/mL)

◂**Fig. 3** Correlation between metal content and corresponding CHD[#] prevalence by Spearman's rank (NHANES, 2003–2018), [#]*CHD*, coronary heart disease

arsenic, monomethylarsonic acid, and thallium in urine showed a positive relationship with CHD, while cesium in urine revealed a negative relationship with CHD.

Through a literature search we found that previous studies had noted a positive correlation between CHD and arsenic in blood and its constituents, in line with our findings (Hannon et al., 2020; Liu et al., 2022; Marrugo-Madrid et al., 2022). An animal study also revealed that arsenic exposure during pregnancy in mice mothers had a teratogenic effect on the heart, significantly increasing the occurrence of cardiac abnormalities (Richter et al., 2022). Even arsenic and monomethylarsonic acid could pass from breast milk to human offspring, causing cardiac development issues (Pierezan et al., 2022).

Thallium was recognized as a potential environmental pollutant and an "invisible health killer" by the United States Environmental Protection Agency (USEPA) (Xiao et al., 2004). Simultaneously, the priority constraint list mentions thallium in the European Water Framework Directive (EWFD) as the predominant hazardous waste (Lennartson, 2015). In earlier research, thallium exhibited a nonlinear association with disorders of the cardiovascular system, similar to this research (Sacks et al., 2018). Moreover, studies have inferred that urine thallium concentrations over 4.5–6 g/L could lead to early health damage in humans (Xu et al., 2019); however, the mechanisms underlying the associations of thallium or cesium exposure with CHD are still unknown due to the paucity of conclusive evidence (Wi et al., 2019).

It is worth stating that the potential causes of the variability between levels of heavy metal exposure and CHD prevalence are complicated. The United States paid a great deal of attention to environmental

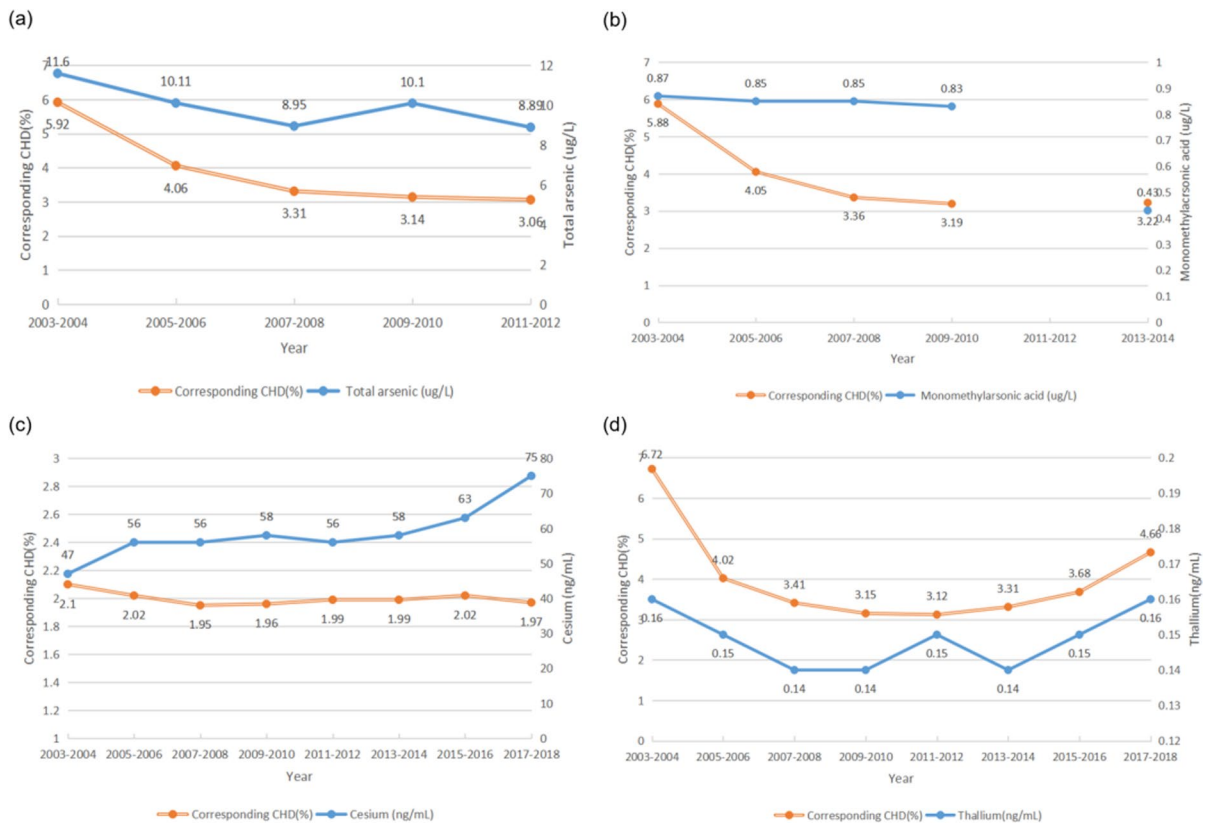


Fig. 4 Relationship between metal content and corresponding CHD[#] prevalence (NHANES, 2003–2018), [#]*CHD*, coronary heart disease

Table 3 Association between heavy metals and CHD[#] (NHANES, 2003–2018)

Heavy metal	OR* (95% CI)		
	Model 1	Model 2	Model 3
Total arsenic, in urine	1.002 (1.001–1.008)	1.003 (1.002–1.010)	1.003 (1.000–1.010)
Monomethylarsonic acid, in urine	1.004 (1.002–1.017)	1.004 (1.001–1.017)	1.010 (1.001–1.014)
Cesium, in urine	0.997 (0.987–0.990)	0.993 (0.990–0.997)	0.995 (0.990–0.998)
Thallium, in urine	1.023 (1.013–1.033)	1.005 (1.001–1.015)	1.004 (1.002–1.014)

Model 1 unadjusted

Model 2 adjusted for age and gender

Model 3 adjusted for model 2 plus BMI, race, educational level, poverty-to-income ratio, smoking, alcohol consumption, and physical activity

[#]*CHD*, coronary heart disease; **OR*, odds ratio

health issues from 2009 to 2013, with the administration and competent institutions establishing a range of environmental policy instruments to support and promote environmental restoration (Li et al., 2014; Skubała & Zaleski, 2012; Smieja-Król et al., 2010). Although policies and intervention initiatives directly led to a decline in heavy metal exposure, the corresponding CHD prevalences reported varied (Jia et al., 2020; Miller et al., 2017). Considering the impact of an accumulation of heavy metals on human health, however, the level of heavy metals' exposure decreasing in the short-term would not change CHD prevalence. Even though the decrease in prevalence of CHD showed some time lag, this phenomenon suggests that the findings from our study are more accurate.

Further, there are many studies of clinical treatment after exposure to heavy metals (Ganz et al., 2020; Haschka et al., 2021; Kattamis et al., 2022; Morales & Xue, 2021; Wang et al., 2017). Chelation therapy, a typical treatment for heavy metal toxicity, entails offering patients detoxifying illegal substances to help with the elimination of heavy metal ions (Balali-Mood et al., 2021; Kattamis et al., 2022; Morales & Xue, 2021). Nevertheless, due to restrictions and possible adverse reactions, the utilization of chelating compounds should be considered cautiously. The oxidation and breakdown of heavy metals can be enhanced by nutritional support through the consumption of especially valuable vitamins and minerals, such as vitamin C, selenium, and zinc, which could decrease the detrimental effects of heavy metals on health (Ganz et al., 2020; Haschka et al., 2021; Zhang et al., 2022). A nutritious meal plan, frequent exercise, and staying away from outside sources of heavy metals are other lifestyle changes that are essential for minimizing the risk and seriousness of heavy metal exposure (Duan et al., 2023; Santos et al., 2022).

The current study has several potential strengths. First, the study was notable for its assessment of levels of heavy metals' exposure over a period of 16 years with a substantial sample size, making the results more realistic and reliable. Second, though these findings were reproducible in our study, the trend of heavy metal exposure levels or prevalence of CHD both had strong data support, thus laying a solid foundation for other researchers to explore the relationship between heavy metals and disease in the future. Finally, our study comprehensively investigated the relationship between heavy metals' exposure and CHD prevalence, providing a scientific reference to guide further management of the levels of heavy metal exposure in the environment.

There are several limitations to our research, however. First, before 2015 the identification of CHD relied on participants' responses in an interview questionnaire in NHANES, meaning that a portion of the resulting data was based on participants' memories. Information bias was likely to appear in the reported data, self-reported results tending to be different from actual clinical diagnoses. Second, due to limitations in the study method, we were not able to infer a causal relationship between disease and dosage of heavy metals' exposure. Moreover, participants with other comorbidities were not excluded, possibly increasing the influence of confounding factors in our study and affecting the accuracy of its results. Finally, due to the

absence of heavy metal sub-test data for total arsenic, monomethylarsonic acid, and uranium in urine since 2012 in NHANES, we were unable to continue collecting data for analyses. Moreover, we discovered that monomethylarsonic acid, and dimethylarsonic acid showed no relationship with CHD (2003–2012), but lead in urine and total mercury in blood had a relationship with CHD (2003–2012), which was contrary to the correlation (2003–2018) (Supplementary Table 2). The absence of data may affect our results. We will therefore persist in requiring ongoing research in future studies because we realize the importance of continually updating data for analyzing and interpreting findings.

Conclusion

When examining the NHANES data between 2003 and 2018, we found that the trends of total arsenic, dimethylarsonic acid, monomethylarsonic acid, barium, cadmium, lead, and antimony in urine and blood decreased, while the exposure levels of cobalt, cesium, thallium, tungsten, and uranium in urine followed a constant trend. CHD prevalence, however, fluctuated. Moreover, total arsenic (2003–2012), monomethylarsonic acid, and thallium in urine all showed positive relationships with CHD, while cesium in urine showed a negative relationship with CHD. In the future, we need to control total arsenic, monomethylarsonic acid, thallium, and cesium exposure levels in the environment.

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Author contributions Under the guidance of Professor DH, all authors helped organize and arrange the data for the article, while XL completed the majority of the writing. DZ made a lot of helpful suggestions. YZ was in charge of assessing the article's reliability. All authors have agreed to the article's final draft.

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Data availability Our data is available on reasonable request for other researchers.

Declarations

Conflict of interest We have no competing interests.

Ethical approval US NHANES already-available data was offered to every researcher. All the participants signed the consent form.

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