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RESEARCH ARTICLE

Associations between lead, cadmium, mercury, and arsenic exposure and alanine aminotransferase elevation in the general adult population: an exposure–response analysis

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Abstract

Cadmium, lead, mercury, and arsenic are among the most toxic environmental contaminants. Serum alanine aminotransferase (ALT) is the most common liver biomarker. This analysis aimed to explore the associations between blood cadmium, lead, mercury, urinary total arsenic, and dimethylarsinic acid and ALT elevation in adults. Data were extracted from 5 National Health and Nutrition Examination Survey cycles (NHANES) 2007–2016. Patients with chronic viral hepatitis and excessive alcohol consumption were excluded. ALT elevation was defined according to the 2017 American College of Gastroenterology Clinical Guideline. Logistic models and restricted cubic splines were adopted to assess the exposure–response relationships. Comparing the highest to lowest quintile of exposure, the multivariable-adjusted odds ratios (95% confidence intervals) of ALT elevation were 1.38 (1.07–1.78) for blood lead ($P_{\text{for trend}}=0.01$), 1.37 (1.16–1.62) for blood mercury ($P_{\text{for trend}}<0.01$), 0.94 (0.78–1.14) for blood cadmium ($P_{\text{for trend}}=0.64$), 1.07 (0.79–1.45) for urinary total arsenic ($P_{\text{for trend}}=0.81$), and 1.25 (0.94–1.66) for urinary dimethylarsinic acid ($P_{\text{for trend}}=0.18$). The associations between blood lead and mercury and ALT elevation were only observed in women. In addition, the associations between urinary total arsenic [1.53 (1.02–2.29), $P_{\text{for trend}}=0.02$] and dimethylarsinic acid [2.17 (1.05–4.49), $P_{\text{for trend}}=0.02$] and ALT elevation were also observed in women. Dose–response analysis showed that there was no safe exposure threshold of blood lead and mercury's toxic effect on ALT elevation, respectively. In conclusion, lead, mercury and arsenic were associated with ALT elevation in adults, and the associations were mainly observed in women.

Keywords Cadmium · Lead · Mercury · Arsenic · Alanine aminotransferase

Introduction

The most common liver biomarkers ordered are serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin (Kwo et al. 2017). ALT is a biomarker of liver injury and is a more specific biomarker of hepatic injury than AST (Kwo et al. 2017). Emerging evidence suggests that ALT elevation is associated with increased liver-related mortality and all-cause mortality (Oh et al. 2016; Karaphillis et al. 2017; Kwo et al. 2017; Schmilovitz-Weiss et al. 2018; Shim et al. 2018). The loss of life expectancy associated with ALT elevation (≥40 IU/L) was up to 5.2 years (Xie et al. 2019). The most recent clinical guideline of the American College of Gastroenterology showed that a true healthy normal ALT level ranges from 29 to 33 IU/L for males and 19 to 25 IU/L for females, and levels above this should be assessed (Kwo et al. 2017). High alcohol consumption, hepatitis B or C infection, and high transferrin saturation are known factors that could lead to elevated aminotransferase levels; however, these factors only contribute to 31.0% of the cases, and 69.0% of the aminotransferase elevation was unexplained in adults (Clark et al. 2003). Chronic liver diseases represent a major world public health problem, and ALT is the best available tool for large-scale screening for chronic liver diseases (Marcellin

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and Kutala 2018). Elevated ALT levels are correlated with the grade of liver necroinflammation (Marcellin and Kutala 2018). Toxic environmental contaminants of cadmium, lead, mercury, and arsenic are among the top 10 chemicals or groups of chemicals of major public health concern (https://www.who.int/ipcs/assessment/public_health/chemicals_phc/en/). Findings from experimental studies showed that exposure to these environmental contaminants could induce oxidative stress, inflammatory responses, DNA damage, and apoptotic cell death in the liver (Souza et al. 2018; Elblehi et al. 2019; Salama et al. 2019).

Recent findings from epidemiological studies on the associations between exposure to these heavy metals and liver injury are not consistent. Occupational lead exposure was not associated with biomarkers of liver injury including ALT in a Turkish population (Can et al. 2008). However, higher levels of arsenic, lead, and cadmium were significantly negatively associated with ALT concentrations in the mining areas in China (Huang et al. 2021). In adolescents, significant associations were found between blood mercury and elevated ALT concentrations in US adolescents (Chen et al. 2019) and between serum lead and elevated ALT concentrations in Iranian adolescents (Poursafa et al. 2014). However, ALT concentrations did not differ significantly across the quartiles of serum mercury in Iranian adolescents (Poursafa et al. 2014). In the general adult population, higher exposure to lead, cadmium, and mercury was positively associated with biomarkers of liver injury including ALT in Korean adults (Kim et al. 2021; Park et al. 2021). A significant correlation was found between higher blood mercury levels and elevated ALT concentrations in women in a pan-India population, while no association was found in men (Sivapandi et al. 2020). Lead and mercury exposures were also associated with biomarkers of liver injury including ALT elevation in US adults (Cave et al. 2010; Obeng-Gyasi 2020). However, the associations between blood cadmium, lead, mercury, urinary total arsenic, and dimethylarsinic acid and ALT elevation have not been reported from the recent NHANES (2011–2016 cycles). In addition, it remains unclear whether there are safe exposure thresholds of cadmium, lead, mercury, and arsenic's toxic effect on ALT elevation, and the dose–response relationships across low levels of exposures (i.e., typical for the general population) are not characterized. Furthermore, given the increased liver-related mortality demonstrated across multiple populations for elevated ALT levels, the most recent clinical guideline of the American College of Gastroenterology utilizes a significantly lower upper limit of normal for ALT (Kwo et al. 2017), defining many more patients as having abnormal ALT levels.

Given the widespread nature of these toxic metal contaminations, it is essential to characterize accurately the associations between these environmental contaminants and ALT elevation defined by the 2017 guideline (Kwo et al. 2017). Therefore, with the hypothesis that toxic environmental contaminants of cadmium, lead, mercury, and arsenic may be associated with ALT elevation, we aimed to determine the dose–response relationships between blood cadmium, lead, mercury, urinary total arsenic, and dimethylarsinic acid and ALT elevation in adults.

Methods

Study population

National Health and Nutrition Examination Survey (NHANES) is a national population-based survey program assessing the health and nutritional status of the civilian general US population, using a complex, multistage, probability sampling design. The NHANES data are released every 2 years. The survey examines about 5000 people in 15 different counties across the country each year. Each 2-year cycle and any combination of 2-year cycles is a nationally representative sample, respectively. The dataset used in this study was obtained by combining the recent 5 NHANES cycles (2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016).

Our population consisted of all adults older than 18 years. The exclusion criteria are as follows: (1) individuals whose biomarker data of cadmium, lead, mercury, and arsenic exposures and ALT are missing; (2) patients with hepatitis B or C; (3) individuals with heavy and very heavy alcohol consumption ($\geq$ 30 g/day) (Bagnardi et al. 2010). These exclusions are known factors contributing to elevated aminotransferase levels and are used to identify suspected cases of nonalcoholic fatty liver disease (Clark et al. 2003).

Cadmium, lead, mercury, and arsenic

Consistent with prior studies (Awata et al. 2017a, b), we evaluated five biomarkers: blood cadmium, lead, mercury, urinary total arsenic, and dimethylarsinic acid. Serum specimens are processed, stored, and shipped to the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA for analysis. Biomarker data are determined with inductively coupled plasma dynamic reaction cell mass spectrometry. All biomarker data were log-transformed to reduce skewness. In addition, urinary metal concentrations were adjusted using the concentration of creatinine in urine to account for the effect of urinary dilution (Awata et al. 2017b). The NHANES quality assurance and quality control protocols meet the 1988 Clinical Laboratory Improvement Act mandates.

ALT data

Serum specimens were processed, stored, and shipped to the Collaborative Laboratory Services, Ottumwa, Iowa for analysis. The test was analyzed on a Beckman Coulter UniCel® DxC800 Synchron Clinical System. The DxC800 used a kinetic rate method to measure ALT activity in serum or plasma. According to the 2017 American College of Gastroenterology Clinical Guideline (Kwo et al. 2017), ALT elevation was defined in men as > 33 IU/L and in women as > 25 IU/L in this analysis.

Covariates

Consistent with prior studies (Cave et al. 2010; Lin et al. 2014), the following covariates were considered: data release cycle, age, sex, race/ethnicity, body mass index (BMI), alcohol consumption, hypertension, diabetes, poverty income ratio, and estimated glomerular filtration rate (eGFR). Subjects were considered hypertensive if they were taking antihypertensive medication, if their mean systolic blood pressure exceeded 130 mmHg, or if their mean diastolic blood pressure exceeded 80 mmHg (mean values of at least two measurements) (Whelton et al. 2018). Diabetes status was determined by self-reported doctor/health professional–diagnosis of diabetes or a glycosylated hemoglobin measurement of ≥ 6.5% (International Diabetes Federation Guideline Development Group 2014). The eGFR was calculated by using the Chronic Kidney Disease Epidemiology Collaboration equation (Levey et al. 2009) and was classified into the following three eGFR categories: (1) normal renal function with eGFR ≥ 90 mL/min/m^2; (2) mildly decreased renal function with eGFR 60–89 mL/min/m^2; and (3) moderately to severely decreased renal function with eGFR < 60 mL/min/m^2) (Jin et al. 2018).

Statistical analysis

The *t* tests were used to compare the mean levels of continuous variables, and chi-square tests were used to compare the distribution of categorical variables. Weighted logistic regression was used to calculate odds ratios (95% confidence intervals) [ORs (95% CIs)] of ALT elevation for each quintile of the exposures. All results were adjusted for data release cycle, age (continuous), sex, race/ethnicity (Mexican–American, other Hispanic, non-Hispanic White, non-Hispanic Black, other race), body mass index (continuous), alcohol consumption (continuous), hypertension, diabetes, poverty income ratio (continuous), and estimated glomerular filtration rate (eGFR) (eGFR ≥ 90 mL/min/m^2, 60–89 mL/min/m^2, eGFR < 60 mL/min/m^2). New multi-year sample weight was computed by simply dividing the 2-year sample weights by 5. Sensitivity analysis was also conducted after excluding pregnant women, obese individuals (BMI ≥ 30 kg/m^2), and patients with diabetes. Tests for trends were performed by entering the categorical variables as continuous variables in the model. The interactions with sex were tested by using cross-product terms of exposure variables and sex. The dose–response relationships between exposure levels and ALT elevation were assessed using a restricted cubic spline function with three knots located at the 5th, 50th, and 95th percentiles of exposure levels, and a *P* value for nonlinearity ($P_{\text{for non-linearity}}$) was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0. In addition, we used multiple linear regression analysis to explore the associations between blood cadmium, lead, mercury, urinary total arsenic, and dimethylarsinic acid and concentrations of other non-specific biomarkers of liver injury (AST, ALP, gamma-glutamyl transferase (GGT) and total bilirubin) (Kwo et al. 2017). Stata 12.0 was used, and statistical significance was determined by *p*-value < 0.05.

Results

A total of 21,407 individuals provided the ALT data. According to the 2017 American College of Gastroenterology Clinical Guideline, and after excluding patients with hepatitis B or C, and individuals with heavy and very heavy alcohol consumption, the weighted prevalence of ALT elevation was 21.16%. The number of individuals included in this analysis was 17,137 for blood cadmium, lead, and mercury; 7,067 for urinary total arsenic; and 7058 for urinary dimethylarsinic acid, respectively. Detailed characteristics of the participants by ALT levels are shown in Table 1.

Blood lead and ALT elevation

Comparing the highest to lowest quintile of blood lead, the multivariable-adjusted OR (95% CI) of ALT elevation was 1.38 (1.07–1.78) ($P_{\text{for tend}} = 0.01$). The association was observed in women [1.61 (1.22–2.11), $P_{\text{for tend}} = 0.02$] but not in men [1.04 (0.75–1.44), $P_{\text{for tend}} = 0.51$] (*P* value for interaction with sex < 0.01). In sensitivity analysis, the positive association between blood lead and ALT elevation was also found in the total sample [1.71 (1.24–2.36), $P_{\text{for tend}} < 0.01$] and in women [1.99 (1.28–3.09), $P_{\text{for tend}} = 0.05$] (Table 2).

Blood cadmium and ALT elevation

Overall, no association was found between blood cadmium and ALT elevation (Table 2).

Table 1 Characteristics of the 2007–2016 NHANES adults by levels of alanine aminotransferase

	Overall	Non-elevation	Elevation	*P*
Male (%)	45.09	43.88	49.72	< 0.01
Age [years]	46.63	47.04	45.06	< 0.01
Race/Hispanic origin (%)				< 0.01
Mexican American	16.99	15.15	24.00	
Other Hispanic	11.30	10.73	13.47	
Non-Hispanic White	40.59	41.41	37.45	
Non-Hispanic Black	20.32	22.06	13.69	
Other race	10.81	10.66	11.39	
Smoked at least 100 cigarettes in life (%)	39.89	40.12	39.04	0.29
Body mass index (kg/m^2)	29.02	28.41	31.32	< 0.01
Hypertension (%)	48.22	46.95	53.07	< 0.01
Diabetes (%)	16.36	12.81	17.52	< 0.01
Alcohol (g/day)	2.74	2.70	2.87	0.13
Poverty income ratio	2.46	2.45	2.47	0.51
eGFR				< 0.01
≥ 90 mL/min/m^2;	64.52	63.31	69.13	
60–89 mL/min/m^2	28.70	29.19	26.84	
< 60 mL/min/m^2	6.78	7.50	4.03	
Exposure biomarkers [G (95% CI)]				
Blood lead (μg/dL)	1.12 (1.11–1.14)	1.10 (1.07–1.12)	1.13 (1.12–1.15)	0.01
Blood cadmium (μg/L)	0.34 (0.33–0.34)	0.31 (0.30–0.32)	0.35 (0.34–0.35)	< 0.01
Blood mercury, total (μg/L)	0.87 (0.86–0.88)	0.85 (0.84–0.87)	0.92 (0.89–0.95)	< 0.01
Urinary arsenic, total (μg/L)	7.85 (7.65–8.06)	7.76 (7.53–7.99)	8.23 (7.77–8.72)	0.79
Urinary dimethylarsinic acid (μg/L)	3.61 (3.53–3.68)	3.54 (3.47–3.62)	3.85 (3.69–4.02)	< 0.01

M arithmetic mean, *G* geometric mean

Blood mercury and ALT elevation

Comparing the highest to lowest quintile of blood mercury, the multivariable-adjusted OR (95% CI) of ALT elevation was 1.37 (1.16–1.62) ($P_{\text{for tend}} < 0.01$). The association was observed in women [1.98 (1.56–2.51), $P_{\text{for tend}} < 0.01$] but not in men [1.03 (0.82–1.29), $P_{\text{for tend}} = 0.76$] ($P$ value for interaction with sex < 0.01). In sensitivity analysis, the positive association between blood mercury and ALT elevation was also found in the total sample [1.55 (1.17–2.06), $P_{\text{for tend}} < 0.01$] and in women [1.97 (1.36–2.87), $P_{\text{for tend}} < 0.01$] (Table 2).

Urinary total arsenic and ALT elevation

Overall, no association was found between urinary total arsenic and ALT elevation. However, an association between urinary total arsenic and ALT elevation was found in women [1.53 (1.02–2.29), $P_{\text{for tend}} = 0.02$] (Table 3).

Urinary dimethylarsinic acid and ALT elevation

Overall, no association was found between urinary dimethylarsinic and ALT elevation. However, an association between urinary dimethylarsinic and ALT elevation was found in women in sensitivity analysis [2.17 (1.05–4.49), $P_{\text{for tend}} = 0.02$] (Table 3).

Dose–response analysis

Dose–response analysis showed that there was no safe exposure threshold of blood lead's toxic effect on ALT elevation, and an initial steep increase in risk of ALT elevation was followed by a platform beyond log-transformed blood lead levels of 0.20 ($P_{\text{for non-linearity}} = 0.01$) (Fig. 1). Dose–response analysis showed that there was no safe exposure threshold of blood mercury's toxic effect on ALT elevation, and a linear relationship was found between blood mercury and ALT elevation ($P_{\text{for non-linearity}} = 0.74$) (Fig. 1). A linear relationship between urinary total arsenic and ALT elevation was found in

Table 2 Associations between blood lead, mercury and cadmium and alanine aminotransferase elevation

	Blood lead		Blood mercury		Blood cadmium	
	OR (95% CI)	Sensitivity analysis	OR (95% CI)	Sensitivity analysis	OR (95% CI)	Sensitivity analysis
Overall						
Quintile 1	1.00	1.00	1.00	1.00	1.00	1.00
Quintile 2	1.19 (1.01–1.39)*	1.28 (1.00–1.62)*	1.10 (0.93–1.30)	1.28 (0.95–1.71)	1.10 (0.93–1.29)	1.15 (0.91–1.47)
Quintile 3	1.29 (1.05–1.59)*	1.39 (1.05–1.83)*	1.14 (0.96–1.36)	1.34 (1.03–1.76)*	1.17 (0.97–1.40)	1.19 (0.93–1.52)
Quintile 4	1.32 (1.07–1.62)*	1.41 (1.07–1.87)*	1.24 (1.05–1.46)*	1.43 (1.08–1.89)*	1.03 (0.83–1.26)	1.00 (0.72–1.39)
Quintile 5	1.38 (1.07–1.78)*	1.71 (1.24–2.36)**	1.37 (1.16–1.62)*	1.55 (1.17–2.06)*	0.94 (0.78–1.14)	1.04 (0.80–1.34)
$P_{\text{for trend}}$	0.01	< 0.01	< 0.01	< 0.01	0.64	0.95
Men						
Quintile 1	1.00	1.00	1.00	1.00	1.00	1.00
Quintile 2	1.10 (0.88–1.38)	1.13 (0.78–1.63)	0.93 (0.72–1.19)	1.32 (0.90–1.95)	1.14 (0.81–1.61)	1.13 (0.75–1.69)
Quintile 3	1.13 (0.88–1.45)	1.20 (0.84–1.72)	0.97 (0.76–1.24)	1.33 (0.92–1.90)	1.14 (0.79–1.66)	1.47 (0.95–2.29)
Quintile 4	1.25 (0.95–1.64)	1.41 (0.99–2.01)	0.97 (0.76–1.22)	1.24 (0.87–1.76)	0.96 (0.66–1.42)	1.11 (0.68–1.80)
Quintile 5	1.04 (0.75–1.44)	1.27 (0.81–2.00)	1.03 (0.82–1.29)	1.23 (0.86–1.77)	0.87 (0.59–1.28)	1.04 (0.66–1.66)
$P_{\text{for trend}}$	0.51	0.16	0.76	0.44	0.15	0.85
Women						
Quintile 1	1.00	1.00	1.00	1.00	1.00	1.00
Quintile 2	1.37 (1.05–1.78)*	1.65 (1.11–2.44)*	1.40 (1.12–1.75)*	1.20 (0.80–1.80)	1.17 (0.91–1.50)	1.12 (0.77–1.63)
Quintile 3	1.13 (0.90–1.42)	1.39 (0.94–2.04)	1.35 (1.05–1.74)*	1.33 (0.94–1.86)	1.14 (0.90–1.45)	1.06 (0.75–1.51)
Quintile 4	1.14 (0.87–1.49)	1.24 (0.78–1.96)	1.62 (1.35–1.94)**	1.60 (1.11–2.29)*	1.10 (0.81–1.50)	0.93 (0.63–1.36)
Quintile 5	1.61 (1.22–2.11)**	1.99 (1.28–3.09)**	1.98 (1.56–2.51)**	1.97 (1.36–2.87)**	0.97 (0.74–1.27)	1.04 (0.73–1.49)
$P_{\text{for trend}}$	0.02	0.05	< 0.01	< 0.01	0.77	0.77

The results were adjusted for data release cycle, age, sex, race/ethnicity, body mass index, smoking, alcohol consumption, hypertension, diabetes, poverty income ratio and estimated glomerular filtration rate

*$P < 0.05$; **$P < 0.01$

women ($P_{\text{for non-linearity}} = 0.94$) (Fig. 1), and a linear relationship was also found between urinary dimethylarsinic acid and ALT elevation in women ($P_{\text{for non-linearity}} = 0.55$) (Fig. 1).

Associations with other biomarkers of liver injury

The associations between blood cadmium, lead, mercury, urinary total arsenic, and dimethylarsinic acid and other non-specific biomarkers of liver injury including AST, ALP, GGT, and total bilirubin are summarized in Supplementary Table 1. Results from the multiple linear regression analysis showed that higher levels of blood cadmium, lead, and mercury were positively associated with concentrations of these non-specific biomarkers of liver injury. However, concentrations of ALP decreased significantly with increasing levels of blood mercury, which should be confirmed further.

Discussion

Based on the 2017 American College of Gastroenterology Clinical Guideline, the prevalence of ALT elevation was 21.16% among individuals without chronic viral hepatitis and excessive alcohol use. Higher levels of exposure to lead, mercury, and arsenic were positively associated with ALT elevation in adults, and the associations were mainly observed in women. Dose–response analysis showed that there was no safe exposure threshold of blood lead and mercury's toxic effect on ALT elevation, respectively.

Given the increased liver-related mortality demonstrated across multiple populations for ALT > 33 IU/L for men and > 25 IU/L for women, the 2017 American College of Gastroenterology Clinical Guideline has opted to utilize a significantly lower upper limit of normal for ALT (Kwo et al. 2017). This analysis indeed identified more patients as having ALT elevation than previous studies (Clark et al. 2003; Ioannou et al. 2006). Blood lead measurement is the preferred method of evaluating lead exposure and its human health effects (National Biomonitoring Program 2021). While urinary lead levels may reflect recently absorbed lead, blood lead levels reflect both recent intake and equilibration with stored lead in other tissues, particularly in the skeleton (National Biomonitoring Program 2021). Previous studies on the lead's toxic effect on liver mainly focused on occupational populations, and ALT levels were higher in high blood lead level group than low blood lead level group (Nakhaee

Table 3 Associations between creatinine-corrected urinary total arsenic and urinary dimethylarsinic acid and alanine aminotransferase elevation

	Urinary total arsenic		Urinary dimethylarsinic acid	
	OR (95% CI)	Sensitivity analysis	OR (95% CI)	Sensitivity analysis
Overall				
Quintile 1	1.00	1.00	1.00	1.00
Quintile 2	1.05 (0.79–1.40)	1.20 (0.76–1.89)	1.00 (0.75–1.33)	0.93 (0.62–1.39)
Quintile 3	0.92 (0.71–1.19)	0.82 (0.53–1.27)	1.07 (0.79–1.44)	1.00 (0.64–1.58)
Quintile 4	1.02 (0.77–1.37)	0.95 (0.61–1.47)	1.06 (0.77–1.45)	0.82 (0.56–1.20)
Quintile 5	1.07 (0.79–1.45)	1.10 (0.75–1.62)	1.25 (0.94–1.66)	1.35 (0.93–1.95)
$P_{\text{for trend}}$	0.81	0.89	0.18	0.29
Men				
Quintile 1	1.00	1.00	1.00	1.00
Quintile 2	1.39 (0.90–2.15)	1.65 (0.91–2.99)	1.17 (0.78–1.74)	0.97 (0.54–1.74)
Quintile 3	1.13 (0.73–1.76)	1.23 (0.62–2.44)	1.43 (0.91–2.25)	1.13 (0.64–2.00)
Quintile 4	1.01 (0.65–1.55)	0.90 (0.45–1.83)	1.15 (0.73–1.81)	0.73 (0.37–1.45)
Quintile 5	0.82 (0.50–1.33)	0.64 (0.34–1.21)	0.94 (0.61–1.46)	0.62 (0.30–1.26)
$P_{\text{for trend}}$	0.24	0.06	1.00	0.16
Women				
Quintile 1	1.00	1.00	1.00	1.00
Quintile 2	1.02 (0.69–1.49)	1.04 (0.58–1.90)	0.85 (0.54–1.33)	1.08 (0.58–2.01)
Quintile 3	0.99 (0.64–1.51)	1.01 (0.57–1.80)	0.97 (0.62–1.51)	0.98 (0.51–1.89)
Quintile 4	1.26 (0.82–1.93)	1.52 (0.82–2.80)	0.99 (0.67–1.47)	1.54 (0.82–2.90)
Quintile 5	1.53 (1.02–2.29)*	1.78 (0.89–3.54)	1.53 (0.98–2.38)	2.17 (1.05–4.49)*
$P_{\text{for trend}}$	0.02	0.06	0.07	0.02

The results were adjusted for data release cycle, age, sex, race/ethnicity, body mass index, alcohol consumption, smoking, hypertension, diabetes, poverty income ratio, and estimated glomerular filtration rate

*$P < 0.05$

et al. 2019). An analysis from the 2003–2004 NHANES showed that the OR (95% CI) of ALT elevation for the highest versus lowest quartiles of blood lead was 1.6 (1.1–2.3) (Cave et al. 2010). In addition, lead exposure was also associated with increased ALT concentrations among the general adult population in Korea (Kim et al. 2021). These findings indicate that low levels of lead exposure are also associated with elevated ALT concentrations in the general population.

In the general population, the blood mercury concentration is due mostly to the dietary intake of organic forms, particularly methyl mercury, and blood mercury levels increase with greater fish consumption (National Biomonitoring Program 2021). A recent study did not find an association between blood mercury and ALT elevation in adolescents overall [quartile 4 vs. quartile 1: 1.19 (0.93–1.41)] (Chen et al. 2019), and another study with only 208 adults also did not find an association between blood mercury and ALT elevation (Choi et al. 2017). However, blood mercury was associated with increased odds of ALT elevation [quartile 4 vs. quartile 1: 3.10 (1.17–8.24)] in 560 elderly participants (Lee et al. 2017). These discrepant findings might arise from the relatively small number of samples and the variation in defining ALT elevation. However, despite the variation in defining ALT elevation, our results are comparable with those from the 2003–2004 NHANES in which blood mercury was associated with increased odds of ALT elevation [quartile 4 vs. quartile 1: 1.6 (1.1–2.4)] (Cave et al. 2010). In addition, blood mercury was also associated with high serum ALT concentrations among the general Korean adults (Kim et al. 2021), and a significant correlation was found between high blood mercury levels and increased ALT concentrations in women in a pan-India population (Sivapandi et al. 2020).

Urinary arsenic levels reflect recent exposures and are moderately to highly correlated with arsenic intakes from drinking water and dietary sources, and urinary arsenic levels have been accepted as a good biomarker of dose (National Biomonitoring Program 2021). Because inorganic arsenic metabolites other than dimethylarsinic acid typically have low frequency of detection (< 40%) (Awata et al. 2017b), we only evaluated biomarker levels of urinary dimethylarsinic acid in our study. The reports on arsenic exposure and the risk of ALT elevation are very limited. Among adolescents and adults, the OR (95% CI) of ALT elevation for quartile 4 vs. quartile 1 of inorganic arsenic was 2.0 (1.2–3.4) (Frediani et al. 2018). The association between urinary dimethylarsinic acid and ALT elevation deserves to be confirmed further. Blood cadmium reflects both recent and cumulative exposures (National Biomonitoring Program

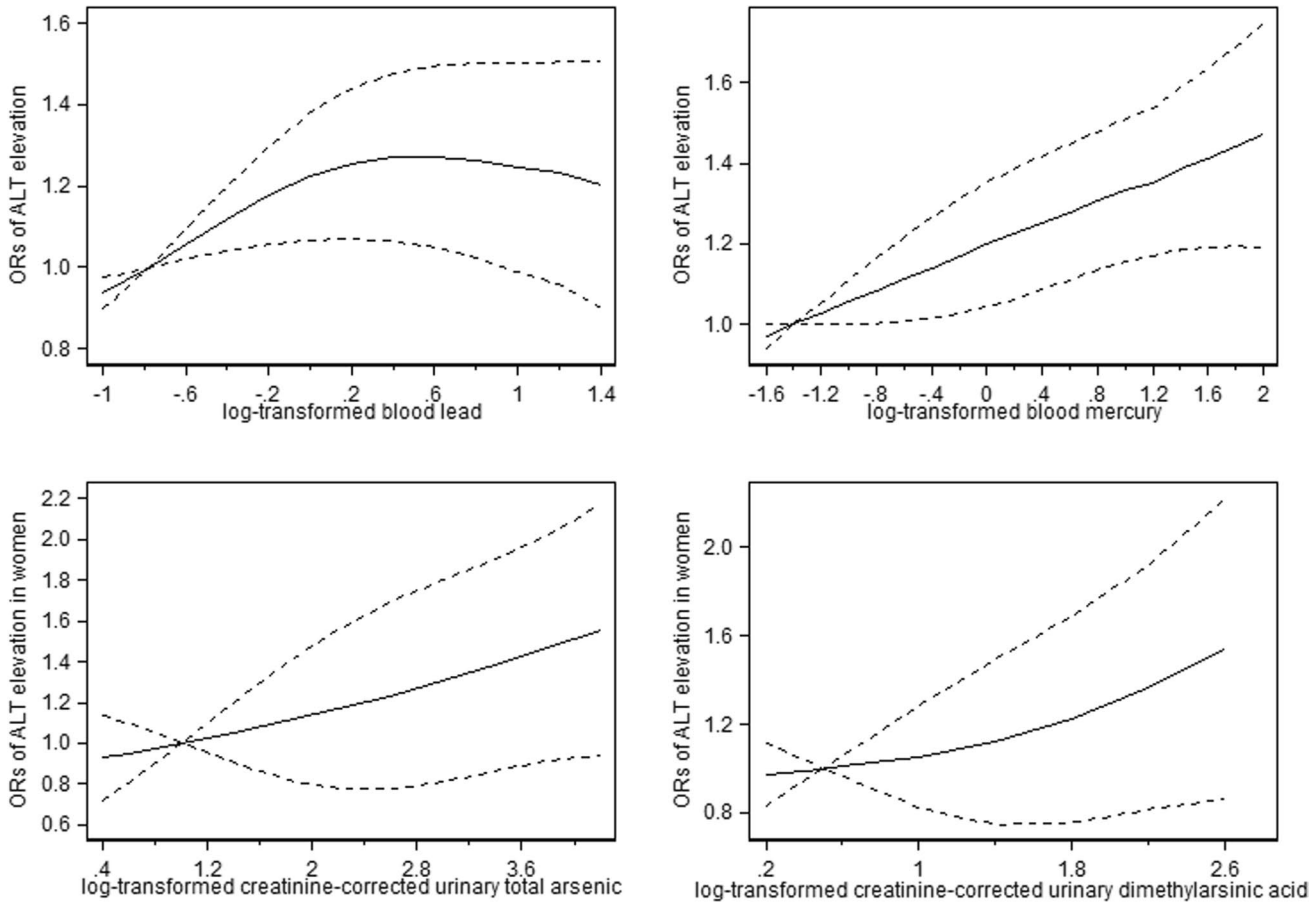

Fig. 1 The dose–response analysis between blood lead, mercury, urinary total arsenic, and dimethylarsinic acid and odds of ALT elevation. The middle line and upper and lower lines represent the estimated odds ratio and its 95% confidence interval, respectively

2021). Findings from the Korean NHANES showed that the odds for ALT elevation increased significantly with increasing levels of cadmium exposure (Kang et al. 2013; Park et al. 2021; Han et al. 2022), and urinary cadmium was also associated with high serum ALT concentrations (Kim et al. 2021). However, no association between blood cadmium and ALT elevation was found in our analysis. The inconsistent finings might arise from the fact that blood concentration of cadmium among the Koreans (0.94 μg/L) (Kang et al. 2013) is much higher than the level in this study (0.34 μg/L).

The general mechanisms that apply to all toxic metals center on oxidative stress (Solenkova et al. 2014; Hassan et al. 2019; Khafaga et al. 2019; Samak et al. 2020). By binding to sulfhydryl groups of proteins like glutathione, these metals could increase the intracellular concentration of reactive oxygen species. The consequences include promotion of lipid peroxidation, cell membrane damage, DNA damage, and oxidation of aminoacids in proteins (Solenkova et al. 2014). The associations between toxic metals and aminotransferase elevation were only observed in women in this analysis; however, the levels of toxic metals exposure did not differ materially by sex (Table 2). Gender differences in metal exposure and health effects are highly neglected research areas, and the possible reasons have been discussed elsewhere (Vahter et al. 2002, 2007). Increased endogenous lead exposure has been demonstrated in women during periods of increased bone turnover (Vahter et al. 2002). Women are more affected than men following exposure to methylmercury at adult age, while males seem to be more sensitive to exposure during early development (Vahter et al. 2002). Regarding arsenic, some data also indicate gender differences in the biotransformation by methylation (Vahter et al. 2002). Furthermore, female rats were also reported more susceptible to mercury than were males in experimental studies (Thomas et al. 1982; Tamashiro et al. 1986), and some data also reported that women are more susceptible to other adverse health effects related with these toxic metals like hypertension (da Cunha et al. 2018) and renal diseases (Sun et al. 2019).

This study had several strengths. We evaluated the associations between four toxic metal contaminants and ALT elevation with a large number of participants from 5

NHANES cycles. This is the first study to quantitatively examine the non-linear dose–response relationships between these four metals and ALT elevation in the general population. There are also several limitations. First, reverse causality should be of concern because of the cross-sectional study design of NHANES. However, the magnitude of associations, the consistent findings found in women and after sensitivity analysis, the biological gradient (does-response analysis), and the theoretical biological plausibility do meet several of the Hill criteria for causation (Hill 2015). Second, high transferrin saturation is associated with higher levels of ALT; however, transferrin saturation is not available, and it is not used as an exclusion criteria in this analysis. Finally, we only adopted ALT as the main biomarker of liver injury in this analysis. However, ALT is the most common liver injury biomarker and a more specific marker of hepatic injury than AST, ALP, GGT, and bilirubin (Kwo et al. 2017). In addition, blood cadmium, lead, and mercury were also positively associated with concentrations of these biomarkers of liver injury. However, the inverse association between blood mercury levels and ALP concentrations should be confirmed further.

In conclusion, high levels of exposure to arsenic, lead, and mercury were associated with ALT elevation, and the associations were mainly found in women. Dose–response analysis showed that there was no safe exposure threshold of blood lead and mercury's toxic effect on ALT elevation, respectively. These findings could have important policy and scientific implications. Developing evidence-based public health guidelines and interventions to reduce human exposure to these contaminants are prioritized regarding the primary prevention of ALT elevation in the general population. Causality should be confirmed further by prospective cohort studies.

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Author contribution Xiaoming Zhou and Yijun Feng: conceptualization, data curation, analysis and writing; Li Gong and Zonglin Gong: writing; Yijun Feng: review and supervision.

Availability of data and materials The data presented in this study are openly available in the NHANES: https://www.cdc.gov/nchs/nhanes/.

Declarations

Ethics approval and consent to participate The NHANES is approved by the National Center for Health Statistics Research Ethics Review Board (Protocol #2011–17), and informed consent is obtained from all participants.

Consent for publication Informed consent was obtained from all subjects in the NHANES.

Competing interests The authors declare no competing interests.

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