scientific reports

Check for updates

OPEN

Association between blood heavy metal element and all-cause mortality in asthmatic adults: a cohort study

Jiaxin Liao[1,4], Jun Wen[1,4]✉, Chengcheng Wei[2,3,4], Rongjuan Zhuang[1,4], Mohan Giri[1] & Shuliang Guo[1]✉

Asthma start, development, and exacerbation have all been linked in numerous studies to exposure to a variety of metal elements. However, there is still a dearth of epidemiological data linking heavy metal exposure to death in asthmatics. The investigation included 2432 eligible adults with asthma. The study examined the possible correlation between blood heavy metal levels and all-cause mortality. This was done by utilizing Cox proportional hazards models, restricted cubic spline (RCS), threshold effect models, and CoxBoost models. Subgroup analyses were conducted to investigate the associations between blood metal levels and all-cause mortality among distinct asthmatic populations. An inverse association was found between blood selenium and all-cause mortality in asthmatics, while blood manganese showed a positive association with all-cause mortality. However, there were no significant connections found between blood lead, cadmium, mercury, and all-cause mortality via multivariate Cox proportional hazard models. In model 3, after accounting for all factors, all-cause mortality dropped by 10% for every additional 10 units of blood selenium (μg/L) and increased by 6% for every additional unit of blood manganese (μg/L). The RCS and threshold effect model found a U-shaped correlation between blood selenium, blood manganese, and all-cause mortality. The lowest all-cause mortality among asthmatics was observed when blood selenium and manganese were 188.66 μg/L and 8.47 μg/L, respectively. Our investigation found a U-shaped correlation between blood selenium levels, blood manganese levels, and all-cause mortality in asthmatic populations. Optimizing dietary selenium intake and effectively managing manganese exposure could potentially improve the prognosis of asthma.

Keywords Metal, Selenium, Manganese, Asthma, Mortality, CoxBoost

Abbreviations

NHANES	National health and nutrition examination survey
Pb	Lead
Cd	Cadmium
Hg	Mercury
Se	Selenium
Mn	Manganese
RCS	Restricted cubic splines
NDI	National death index
CDC	Centers for disease control and prevention
NCHS	National center for health statistics
PIR	Poverty to income ratio
BMI	Body mass index

[1]Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing Medical University, Chongqing, China. [2]Department of Urology, The First Affiliated Hospital of Chongqing Medical University, Chongqing Medical University, Chongqing, China. [3]Department of Urology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China. [4]These authors contributed equally: Jiaxin Liao, Jun Wen, Chengcheng Wei and Rongjuan Zhuang. ✉email: wencej@stu.cqmu.edu.cn; guoshul666@163.com

CVD	Cardiovascular disease
COPD	Chronic obstructive pulmonary disease
ICD	International statistical classification of diseases
CI	Confidence interval

Asthma is characterized by sporadic and diverse symptoms (such as difficulty breathing, chest constriction, wheezing, coughing, and production of phlegm) caused by bronchospasm and inflammation of the airways[1]. Currently, the global prevalence of this condition exceeds 350 million individuals, and it has been steadily increasing over the past few decades. Moreover, it is directly accountable for causing around 250,000 annual fatalities due to asthma[2,3]. Although most patients can be effectively treated, a considerable number of individuals with asthma fail to attain long-term control, resulting in a substantial economic burden. According to research, it is projected that the United States will experience economic losses of 963 billion dollars due to adult asthma in the next 20 years[4].

The incidence and mortality rates of asthma are significantly linked to poverty and its related factors, which encompass limited access to healthcare and exposure to environmental elements such as allergens, tobacco smoke, air pollution, and a lack of beneficial microbial exposure[5]. Heavy metals are extensively utilized and distributed in the environment, and they can enter animal, human, and plant cells by being consumed by food, water, or air intake[6]. Lead, cadmium, mercury, and manganese are heavy metals found in polluted environments. These metals can enter the lungs and bloodstream through inhalation and ingestion. They can act individually or in combination to affect biological processes, including inflammation and oxidative stress pathways. These processes contribute to lung damage, such as asthma, and result in the premature deaths of millions of people annually[7–12].

Lead is a significant air pollutant that directly disrupts the immune system and triggers an elevation in inflammatory mediators inside the body. This, in turn, results in the development of allergic asthma[13]. Empirical investigations have demonstrated that inhaling lead causes an elevation in IgE and histamine levels in animals that have been sensitized. Additionally, it leads to an increase in inflammatory indicators such as the total count of white blood cells, and exacerbates the severity of asthma, both during the advancement of the disease and after its symptoms have become apparent[14]. Our prior research indicates that long-term exposure to lead may be linked to immune system abnormalities in adults with asthma and can affect the onset, progression, and worsening of asthma[15]. An investigation conducted in the United States revealed that adult individuals who smoke have an elevated susceptibility to wheeze and asthma following exposure to elevated levels of cadmium. Additionally, exposure to cadmium or lead adversely impacts lung function in non-smoking adults[16]. Furthermore, scientific literature has documented a correlation between levels of mercury in the blood and the likelihood of school-aged children acquiring asthma. This link also impacts several aspects of asthma, including wheezing, the use of asthma medication, and respiratory hyperresponsiveness[17]. Experimental findings indicate that manganese exhibits cytotoxicity towards bronchial epithelial cells (BEAS-2B) when cultivated in vitro at various doses. This leads to the release of interleukins, which serve to attract immune system cells[18]. Nevertheless, certain investigations have indicated that optimal levels of manganese can mitigate, to some extent, specific asthma symptoms[19].

Asthma has been linked to both environmental contaminants and deficiencies in micronutrients. Selenium is a micronutrient that has a multifaceted relationship with asthma. It is connected not only to the connection between selenium levels, glutathione peroxidase (GPX) activity, and oxidative stress but also to the balance between Th1 and Th2 immune responses[20]. Research has indicated that low levels of selenium in the overall population are linked to an increased likelihood of developing asthma. Additionally, supplementing with selenium has been found to enhance lung function in individuals with asthma[21–23].

Current research has yielded, there have been limited studies that have specifically investigated the impact of various types of heavy metal exposure on the overall mortality rate in adult patients with asthma. This study utilized data from the National Health and Nutrition Examination Survey (NHANES) conducted between 2011 and 2018. We established specific criteria to select asthmatic individuals who met the requirements of the study and examined the relationship between certain elements (lead, cadmium, mercury, manganese, and selenium) and all-cause mortality in adults with asthma. We conducted a thorough investigation to determine if this correlation varies among different populations.

Materials and methods

Study data and population

The Centers for Disease Control and Prevention (CDC) carried out the NHANES, a vital scientific endeavor that methodically evaluates the health and nutritional condition of both American adults and children. The CDC, responsible for supplying extensive health statistics for the country, has received official permission for NHANES methodology from the Research Ethics Review Board of the National Center for Health Statistics (NCHS). NHANES guaranteed participant rights by obtaining informed written consent from all individuals who participated in the study. All methods in this study were carried out in accordance with relevant guidelines/regulations. The data we collected from NHANES covered the time frame between 2011 and 2018. Figure 1 illustrates that NHANES had a participation of 39,156 people from 2011 to 2018. Adhering to specific inclusion and exclusion criteria, our study population excluded: (1) individuals under 18 years old (n = 15,331); (2) individuals without asthma or with missing data (n = 20,213); (3) those lacking blood heavy metal data (n = 1174); (4) those with missing follow-up data (n = 6). Finally, our investigation involved a huge sample of 2432 asthmatic adults in the USA.

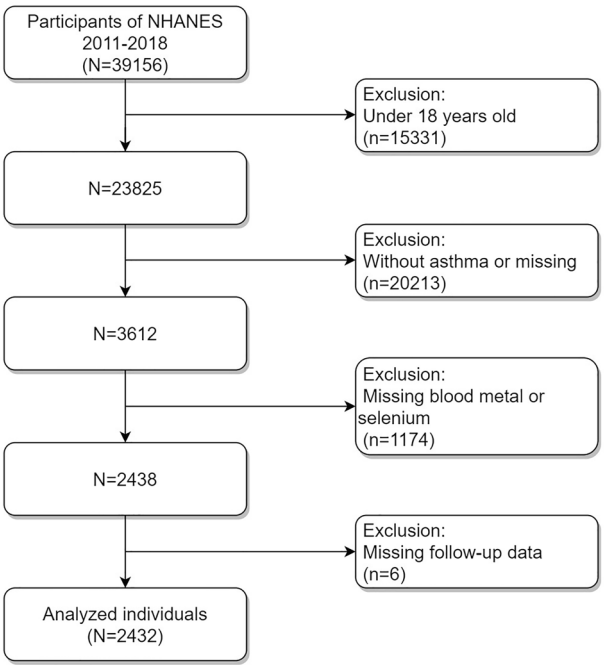

Figure 1. Flow diagram delineating the participant selection protocol for the investigated cohort.

Measurement of blood metal

The exposures of whole-blood lead (Pb), cadmium (Cd), mercury (Hg), selenium (Se), and manganese (Mn) were measured using inductively coupled plasma-dynamic reaction mass spectrometry (ICP-DRC-MS) on either an ELAN 6100 DRC Plus or ELAN DRC II instrument (PerkinElmer Instruments, Headquarters Office, 710 Bridgeport Ave., Shelton, CT 06,484–4794) at the CDC's National Center for Environmental Health. Concentrations that were too low to be detected (below the limit of detection, LOD) were estimated by using the value of LOD divided by the square root. Detailed information about laboratory quality assurance and monitoring can be found on the NHANES website.

Assessment of mortality

We employed unique study identifiers and performed probabilistic matching with the National Death Index (NDI) as of December 31, 2018, to ascertain the vital status of our participants. The NCHS provided additional information on the matching methodology. In addition, we used the 10th edition of the International Statistical Classification of Diseases (ICD) ten to determine mortality status. We primarily focused on all-cause mortality.

Covariates

In order to address the potential confounding effects of diverse factors, we incorporated numerous covariates into our investigation. The covariates considered in the analysis were gender (male and female), age, ethnicity (non-Hispanic white, non-Hispanic black, other race), levels of education (less than high school, high school, more than high school), poverty-to-income ratio (PIR), status in marriage (married, single, living with a partner), body mass index (BMI), smoking status (smoker: individuals with a history of smoking over 100 cigarettes; non-smoker: individuals with a history of smoking less than 100 cigarettes), intake of alcohol, serum cotinine, hypertension history (Yes, No), diabetes history (Yes, No), cardiovascular disease (CVD) history (Yes, No), chronic obstructive pulmonary disease (COPD) history (Yes, No), malignancy history (Yes, No), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, and urine creatinine. Asthma status was ascertained using standardized questionnaires presented during participants' visits, employing the query, "Have you ever been diagnosed with asthma by a physician or other healthcare professional?" Participants who answered positively were classified as having a diagnosis of asthma. Participants' CVD was verified based on self-reported physician diagnoses obtained through individual interviews using a standardized questionnaire to evaluate medical conditions. The participants were queried about whether they had ever received information from a physician or other healthcare professional regarding their diagnosis of congestive heart failure, coronary heart disease, angina pectoris, heart attack, or stroke. An affirmative answer to any of these items categorized an individual as having CVD.

Statistical analysis

Statistical analyses were performed utilizing R software (version 4.2.0). A significance threshold of $p < 0.05$ was established. In order to tackle the intricate sampling design of the NHANES, sample weights were implemented. Utilizing the chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables, baseline

characteristics among groups were compared according to survival outcome. In the beginning, we developed three Cox proportional hazards regression models to assess the independent association between each blood heavy metal and all-cause mortality in individuals with asthma, while also accounting for numerous covariates. Following this, metals that demonstrated statistical significance were chosen for analysis using trend tests and Cox regression. Multiple imputation was used to handle variables with missing values, ensuring that the total proportion of missing values for each covariate was less than 10%. In order to investigate the association between blood heavy metals and all-cause mortality, we utilized restricted cubic splines (RCS) and a threshold effect model to assess both linear and non-linear relationships. When dealing with a nonlinear connection, the inflection point was identified by methodically evaluating all potential values and choosing the inflection point with the greatest probability. Subsequently, a two-piecewise Cox proportional risk model was utilized to examine the association between blood metals and the probability of all-cause death, separately on each side of the inflection point. Stratified studies were performed to investigate the correlation between blood metals and overall mortality in various groups of people with asthma. Finally, the CoxBoost algorithm model was employed to thoroughly assess the relative impact of each metal on the status of survival.

Ethical approval and consent to participate

Before implementing the data collection techniques and conducting thorough health examinations, all participants finished informed consent voluntarily. The NHANES study protocol received approval from the Research Ethics Review Board of the NCHS (Ethical approval number: Protocol #2011-17, Protocol #2018-01).

Results

Baseline characteristics based on survival status of study individuals

Provided in Table 1 were the baseline characteristics of people involved in the cohort study (N = 2432), grouped according to their survival outcomes. The individuals with asthma under analysis displayed an average age of 45.91 years, with 57.46% being female. The median period of follow-up for all asthmatics was 57.89 months. Significant variations were observed in the distributions of age, educational level, PIR, smoking status, history of hypertension, diabetes, CVD, COPD and malignancy, serum creatinine, blood lead, and blood cadmium among different survival outcome groups. A comparison between individuals who deceased and those who survived revealed that the former were more likely to be elderly, have a lower education level, possess a reduced PIR, engage in smoking, have a history of hypertension, diabetes, CVD, COPD, and malignancy, and exhibit elevated levels of serum creatinine, blood lead, and blood cadmium.

Association between blood metals and all-cause mortality

The analysis of both univariate and multivariate Cox proportional hazard models (Table 2) revealed a significant inverse connection between blood selenium levels and all-cause mortality in individuals with asthma. However, the levels of manganese in the blood showed a significant positive relationship only with all-cause mortality when analyzed using multivariate Cox proportional hazard models (models 2 and 3). Significantly, there were no apparent connections between blood lead, cadmium, mercury, and all-cause mortality in model 3. In model 3, after accounting for various factors such as sex, age, race, education, marital status, and more, it was found that all-cause mortality decreased by 10% for every additional 10 units of blood selenium (μg/L). Conversely, the all-cause mortality increased by 6% for every additional unit of blood manganese (μg/L). In addition, the trend test (Table 3) indicated a potential linear correlation between blood selenium and all-cause mortality in model 3 (p for trend < 0.05), while suggesting a potential non-linear correlation between blood manganese and all-cause mortality in model 3 (p for trend > 0.05). Besides, we found no significant correlation between blood selenium, lead, cadmium, mercury, manganese levels and respiratory disease-related mortality in multivariate Cox proportional hazards regression models (Supplementary Table 1).

Restricted cubic splines (RCS) and threshold effect model

Our investigation utilized RCS and a threshold effect model to investigate the association between blood selenium, blood manganese, and all-cause mortality in persons with asthma. The objective was to ascertain whether the relationships were linear. The analysis, including all covariates, showed a U-shaped relationship between blood selenium, blood manganese, and all-cause mortality(Figures 2A,B). The non-linearity and overall p-values were both below 0.05, demonstrating a non-linear association between blood selenium, blood manganese, and all-cause mortality. Following that, a threshold effect analysis was performed to determine the points of inflection. The inflection points for blood selenium and manganese were determined as 188.66 and 8.47, respectively, based on log-likelihood ratio p-values that were less than 0.05. These inflection points corresponded to the lowest all-cause mortality among asthmatics. Table 4 demonstrates significant disparities between model A (the single-line model) and model B (the segmented regression model). The segmented regression model provided a more reasonable explanation for the non-linear association between blood manganese, selenium, and all-cause mortality in persons with asthma.

Subgroup analysis

Subgroup analyses were carried out to evaluate the links between blood selenium, blood manganese, and all-cause mortality in various asthmatic populations. The outcomes, grouped by gender, age, race, BMI, history of hypertension, diabetes, CVD, COPD, and malignancy, appeared in Table 5. A negative link was shown between blood selenium levels and all-cause mortality in asthmatic adults over the age of 60 who were non-Hispanic white, had a BMI below 30, and did not have hypertension or malignancy. In addition, those with asthma who had high levels of manganese in their blood, especially females, individuals of other race, those with hypertension

	Survival	Death	*P* value
Sex (%)			0.4670
Male	42.25	46.32	
Female	57.75	53.68	
Age (years old)	43.61 ± 0.57	63.07 ± 2.04	< 0.0001
Race (%)			0.0842
Non-Hispanic White	66.08	72.22	
Non-Hispanic Black	12.51	14.97	
Other Race	21.41	12.81	
Education (%)			< 0.0001
Less than high school	13.29	29.03	
High school	22.29	27.59	
More than high school	64.42	43.39	
Marital status (%)			0.1134
Married	51.16	41.31	
Single	41.76	53.29	
Living with a partner	7.08	5.40	
Poverty-to-income-ratio	2.50 (1.18 ,4.62)	1.38 (0.81 ,2.51)	< 0.0001
BMI (kg/m2)	30.43 ± 0.29	30.49 ± 0.82	0.9489
Smoking status (%)			0.0015
Smoker	44.57	62.51	
Non-smoker	55.43	37.49	
Alcohol intake (gm)	12.48 ± 0.95	12.91 ± 4.23	0.9224
Serum cotinine (ng/mL)	0.04 (0.01 ,31.60)	0.15 (0.01 ,106.00)	0.1732
Hypertension (%)			< 0.0001
No	65.46	29.99	
Yes	34.54	70.01	
Diabetes (%)			< 0.0001
No	89.67	66.47	
Yes	10.33	33.53	
CVD history (%)			< 0.0001
No	89.29	57.98	
Yes	10.71	42.02	
COPD history (%)			< 0.0001
No	90.59	67.25	
Yes	9.41	32.75	
Malignancy history (%)			< 0.0001
No	87.96	70.92	
Yes	12.04	29.08	
AST (U/L)	22.00 (18.00, 26.00)	22.00 (20.00, 31.00)	0.1171
ALT (U/L)	26.00 (17.00, 55.00)	37.00 (16.00, 61.00)	0.0797
Serum creatinine (umol/l)	73.37 (62.76, 85.75)	82.21 (63.65, 97.24)	0.0165
Urine creatinine (umol/L)	9635.60 (5215.60, 15,381.60)	8398.00 (5215.60, 13,790.40)	0.0812
Blood selenium (ug/L)	194.33 ± 1.03	186.99 ± 4.54	0.1133
Blood lead (ug/dL)	0.81 (0.52, 1.27)	1.25 (0.78, 2.11)	< 0.0001
Blood cadmium (ug/L)	0.26 (0.16, 0.51)	0.53 (0.28, 0.76)	0.0299
Blood mercury (ug/L)	0.66 (0.35, 1.38)	0.58 (0.34, 1.21)	0.1084
Blood manganese (ug/L)	9.93 ± 0.09	9.82 ± 0.55	0.8488

Table 1. The study population's baseline characteristics based on survival status. The continuous data was presented as means ± SD or median (IQR). The categorical variable data was displayed as proportions.

and CVD, and those without a history of COPD or malignancy, had a higher risk of mortality from all-cause compared to those with lower levels of blood manganese.

The relative effect of each variable by the CoxBoost model

To assess the relative impact of each blood metal level on the survival status of the study population, we employed the CoxBoost algorithm model. This model evaluated the positive and negative effects of blood lead, cadmium,

	Model 1	Model 2	Model 3
	HR (95% CI) *P* value	HR (95% CI) *P* value	HR (95% CI) *P* value
Blood selenium (ug/L)	0.98 (0.97, 0.99) < 0.0001	0.98 (0.98, 0.99) < 0.0001	0.99 (0.98, 0.99) 0.0006
Blood lead (ug/dL)	1.21 (1.14, 1.28) < 0.0001	1.08 (0.96, 1.20) 0.1921	1.02 (0.91, 1.14) 0.7473
Blood cadmium (ug/L)	1.14 (0.96, 1.35) 0.1339	1.18 (0.98, 1.42) 0.0779	1.00 (0.76, 1.31) 0.9732
Blood mercury (ug/L)	0.90 (0.80, 1.02) 0.1114	0.86 (0.75, 0.99) 0.0341	0.93 (0.82, 1.06) 0.2818
Blood manganese (ug/L)	0.98 (0.94, 1.03) 0.5364	1.06 (1.01, 1.11) 0.0242	1.06 (1.01, 1.11) 0.0123

Table 2. Association between blood metals and all-cause mortality in asthmatic adults. Model 1 adjusted none. Model 2 adjusted sex, age, and race. Model 3 adjusted sex, age, race, educational level, marital state, PIR, BMI, smoking state, alcohol intake, hypertension history, diabetes history, CVD history, COPD history, malignancy history, serum cotinine, AST, ALT, serum creatinine, and urine creatinine.

	Model 1	Model 2	Model 3
	HR (95% CI) *P* value	HR (95% CI) *P* value	HR (95% CI) *P* value
Blood selenium (ug/L)	0.98 (0.97, 0.99) < 0.0001	0.98 (0.98, 0.99) < 0.0001	0.99 (0.98, 0.99) 0.0006
Blood selenium tertiles			
T1 (85.15–181.50)	Reference	Reference	Reference
T2 (181.51–200.86)	0.30 (0.19, 0.47) < 0.0001	0.32 (0.20, 0.51) < 0.0001	0.38 (0.24, 0.62) < 0.0001
T3 (200.87–371.76)	0.43 (0.29, 0.65) < 0.0001	0.44 (0.29, 0.67) 0.0001	0.53 (0.35, 0.81) 0.0036
P for trend	< 0.0001	< 0.0001	0.0013
Blood manganese (ug/L)	0.98 (0.94, 1.03) 0.5364	1.06 (1.01, 1.11) 0.0242	1.06 (1.01, 1.11) 0.0123
Blood manganese tertiles			
T1 (1.57–7.95)	Reference	Reference	Reference
T2 (7.97–10.63)	0.67 (0.44, 1.03) 0.0666	0.90 (0.59, 1.38) 0.6396	0.92 (0.59, 1.42) 0.6993
T3 (10.64–33.94)	0.83 (0.56, 1.24) 0.3657	1.40 (0.93, 2.12) 0.1092	1.50 (0.98, 2.29) 0.0643
P for trend	0.3342	0.142	0.0854

Table 3. Association between blood selenium and blood manganese with all-cause mortality in the asthmatic adults. Model 1 adjusted none. Model 2 adjusted sex, age, and race. Model 3 adjusted sex, age, race, educational level, marital state, PIR, BMI, smoking state, alcohol intake, hypertension history, diabetes history, CVD history, COPD history, malignancy history, serum cotinine, AST, ALT, serum creatinine, and urine creatinine. We grouped blood selenium and blood manganese by tertile.T1-T3: Grouped by tertiles.

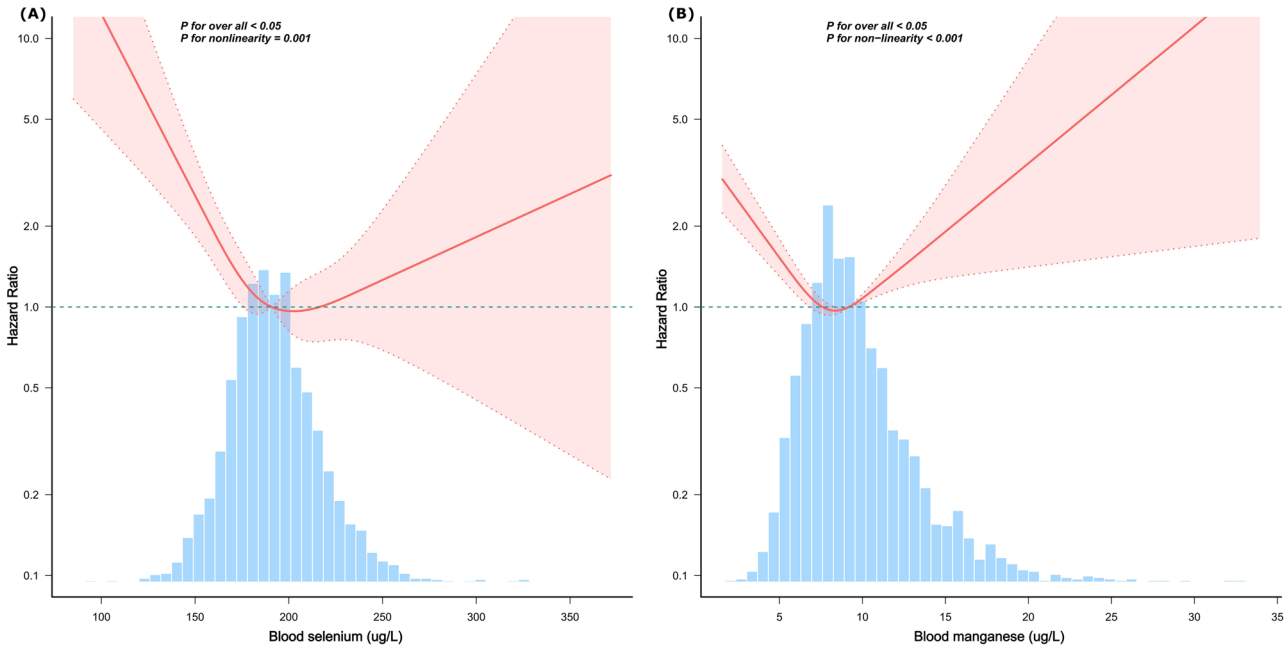

Figure 2. Association between blood selenium (A), blood manganese (A), and all-cause mortality in asthmatic adults. The red solid line and red area correspond to the HR and their corresponding 95%CI, separately.

	Blood selenium	Blood manganese
	HR (95% CI) *P* value	HR (95% CI) *P* value
Model A		
Linear effect	0.99 (0.98, 0.99) 0.0006	1.06 (1.01, 1.11) 0.0123
Model B		
Inflection point (K)	188.66	8.47
< K	0.97 (0.96, 0.98) < 0.0001	0.89 (0.77, 1.03) 0.1260
> K	1.01 (1.00, 1.02) 0.2377	1.11 (1.05, 1.17) 0.0002
P for log likelihood ratio	< 0.001	0.018

Table 4. Threshold effect analysis of blood selenium and blood manganese with all-cause mortality. Model A and B all adjusted sex, age, race, educational level, marital state, PIR, BMI, smoking state, alcohol intake, hypertension history, diabetes history, CVD history, COPD history, malignancy history, serum cotinine, AST, ALT, serum creatinine, and urine creatinine.

Subgroup	Blood selenium	Blood manganese
	HR (95% CI) *P* value	HR (95% CI) *P* value
Sex		
Male	0.99 (0.98, 1.00) 0.0468	1.05 (0.97, 1.12) 0.2112
Female	0.98 (0.97, 0.99) 0.0021	1.08 (1.01, 1.15) 0.0308
Age		
< 40	1.01 (0.98, 1.03) 0.5560	1.12 (0.98, 1.29) 0.0919
40–60	0.98 (0.97, 1.00) 0.0759	1.00 (0.90, 1.12) 0.9461
≥ 60	0.98 (0.98, 0.99) 0.0007	1.04 (0.98, 1.11) 0.1499
Race		
Non-hispanic white	0.99 (0.98, 1.00) 0.0066	1.01 (0.94, 1.09) 0.7305
Non-hispanic black	0.99 (0.98, 1.00) 0.2087	1.03 (0.91, 1.16) 0.6623
Other race	0.99 (0.97, 1.01) 0.1962	1.13 (1.05, 1.22) 0.0011
BMI		
< 25	0.98 (0.96, 1.00) 0.0218	1.10 (0.99, 1.21) 0.0816
25–30	0.98 (0.97, 1.00) 0.0102	1.01 (0.91, 1.11) 0.8907
≥ 30	0.99 (0.98, 1.00) 0.1532	1.07 (1.00, 1.14) 0.0521
Hypertension		
No	0.99 (0.97, 1.00) 0.0784	1.00 (0.89, 1.12) 0.9931
Yes	0.99 (0.98, 1.00) 0.0081	1.08 (1.03, 1.14) 0.0024
Diabetes		
No	0.99 (0.98, 1.00) 0.0062	1.06 (1.00, 1.13) 0.0585
Yes	0.99 (0.98, 1.00) 0.0169	1.06 (0.98, 1.14) 0.1753
CVD history		
No	0.99 (0.98, 1.00) 0.0479	1.03 (0.96, 1.10) 0.3712
Yes	0.99 (0.97, 1.00) 0.0255	1.08 (1.01, 1.16) 0.0302
COPD history		
No	0.99 (0.98, 1.00) 0.0148	1.07 (1.01, 1.13) 0.0214
Yes	0.98 (0.97, 1.00) 0.0070	1.03 (0.94, 1.13) 0.5180
Malignancy history		
No	0.99 (0.98, 1.00) 0.0061	1.06 (1.00, 1.12) 0.0483
Yes	0.99 (0.98, 1.00) 0.1539	1.05 (0.95, 1.17) 0.3062

Table 5. Stratified associations for blood selenium, blood manganese and all-cause mortality in asthmatics. Above analyses adjusted for sex, age, race, education level, marital state, PIR, BMI, smoking state, alcohol intake, hypertension, diabetes, CVD history, COPD history, malignancy history, serum cotinine, AST, ALT, serum creatinine, and urine creatinine. The model was not adjusted for the stratification variable in any of the cases.

mercury, selenium, and manganese on the risk of all-cause mortality in asthmatics. The results of the CoxBoost model, illustrated in Figure 3, revealed that blood metals with a positive impact on mortality risk, in descending order of effect size, were lead and cadmium. Conversely, blood metals associated with a decreased risk of death, in descending order of effect size, were selenium. Due to its minimal effect, manganese was not visually

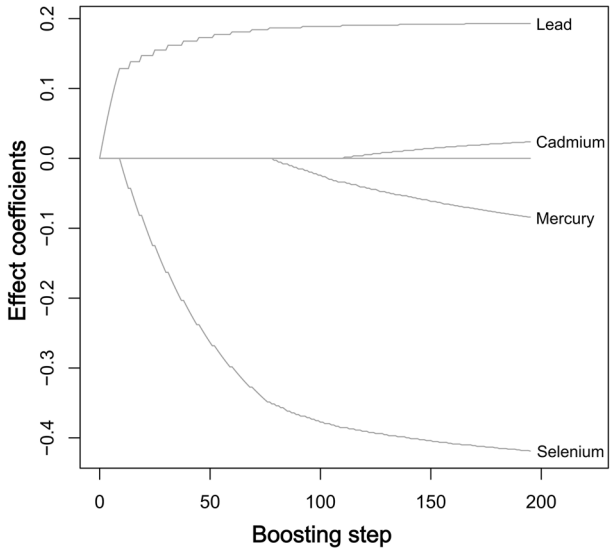

Figure 3. The CoxBoost model assessed the positive and negative effects of each blood metal level in relation to the survival outcome of the follow-up.

represented in Figure 3. Among the selected metals, selenium exhibited the most substantial impact on the survival status of individuals with asthma.

Discussion

Heavy metal contamination is a highly significant environmental issue in the modern world. As humans occupy the highest position in the food chain, they will unavoidably consume different types of heavy metals as a result of the bioconcentration effect[24]. Asthma is a prevalent chronic respiratory condition characterized by persistent inflammation of the airways and increased sensitivity to various stimuli from many sources[25,26]. Several studies have indicated an association between the exposure to specific heavy metal ions and the occurrence of asthma. In a meta-analysis of children's hypersensitivity diseases, Wang et al. discovered a correlation between copper exposure and childhood asthma[27]. Similarly, Miyazaki et al.[28] observed that exposure to mercury and manganese during pregnancy heightened the likelihood of asthma in early childhood. Furthermore, there exists a link between the presence of heavy metals and the likelihood of developing active asthma. Wu et al. discovered a favorable correlation between elevated levels of mercury and lead in the bloodstream and the occurrence of wheezing events in children diagnosed with asthma[29]. Patients afflicted with asthma face an elevated risk of mortality. Osvald et al. observed a noteworthy rise in overall mortality among individuals with asthma compared to those without the condition, particularly among children and young people[30]. Nevertheless, there is limited research on the association between exposure to heavy metals and mortality in individuals with asthma. Therefore, we undertook this study to investigate whether heavy metal exposure acts as a contributing factor to the risk of death in asthma patients.

A total of 2432 participants who had asthma were assessed for the study based on predetermined exclusion criteria. We documented the correlation between blood metal concentrations and all-cause mortality in adult asthmatics by examining their blood concentrations of selenium, various metal elements, and related clinical indicators. After adjusting for multiple variables, our study found that blood manganese levels were significantly positively correlated with all-cause mortality in asthmatics. However, univariate analysis and analysis adjusted for certain variables suggested that blood lead and blood mercury levels might be related to mortality in asthma patients. Both univariate and multivariate analyses revealed a negative connection between blood selenium level and all-cause mortality in asthma patients. It was inaccurate to conclude, however, that a longer life for asthma was associated with lower blood manganese levels and higher blood selenium levels, based alone on these findings. We established nonlinear models of all-cause mortality and blood selenium or blood manganese, respectively, using restricted cubic splines. The results showed a U-shaped correlation: patients who had either a concentration too high or too low would have a higher risk of dying, while there was a certain concentration that reduced that risk, which was also supported by the threshold effect model.

One of the most important microelements in the human body, manganese is primarily needed as an enzyme cofactor for enzymes like manganese superoxide dismutase (Mn-SOD) and is present in a variety of metalloproteins[31]. One of the essential components of the mitochondrial antioxidant system, Mn-SOD, may generate superoxide radicals at a disproportionate rate and protect the mitochondria from damage brought on by a range of oxidants[32]. Furthermore, manganese contributes to the structure of the enzymes pyruvate carboxylase[33], arginase[34], and glutamine synthetase[35]. Low manganese levels have been linked to an increase in NO and a decrease in arginase activity, which increases airway responsiveness in asthmatic children[19]. On the other hand, an excessive buildup of manganese may also be detrimental to human health. Overdosing on manganese is considered cytotoxic and linked to several neurodegenerative illnesses[36]. Exposure to manganese may

cause a pathological increase in the intracellular autophagic process, impairing cellular energy metabolism among other processes[37]. In asthmatics, metabolic anomalies like those brought on by high manganese concentrations can harm the airways and raise the chance of death.

Another one of the necessary microelements is selenium. Glutathione peroxidase[38], iodothyronine deiodinase[39], selenoprotein P[40], and thioredoxin reductases[41], among other selenoproteins, are examples of selenium's functional forms. These enzymes are involved in the regulation of antioxidants, DNA synthesis, thyroid hormone metabolism, and numerous other biological processes. Research has revealed that blood selenium concentrations are lower in asthma sufferers than in healthy individuals[42]. Because it controls the activity of immune cells such T helper cells, selenium may have an impact on the development of asthma[22]. Significantly, a high selenium intake has toxicological consequences on the human body that harm the respiratory, digestive, and cardiovascular systems, among other organs[43,44].

It is well known that heavy metals such as lead, cadmium, and mercury have an impact on human health[6,7,13]. However, this study found that certain heavy metal elements do not appear to be significantly associated with all-cause mortality in asthma patients. This may be because the effects of these elements are masked or balanced under the influence of multiple confounding factors, and the effects of these elements may require more complex mechanisms to explain. Selenium and manganese showed a significant correlation with all-cause mortality in asthma patients due to the impact on the overall health status of patients. However, the two and other elements such as lead, cadmium, and mercury were not significantly related to respiratory system-related mortality. This may be because these elements do not directly damage or act on the respiratory system and thus cannot effectively affect the incidence and severity of respiratory diseases.

Unlike other studies, ours focused on explaining the relationship—which had not been previously documented by other researchers—between blood heavy metal concentrations and all-cause mortality in asthmatics. After selecting the two elements with the highest correlation—manganese and selenium—we analyzed the remaining elements using Cox proportional hazard models. We discovered that asthma patients would have a higher risk of mortality if there were either excessively high or low amounts of the two components. This provides valuable insights for establishing specific reference levels for blood selenium and manganese concentrations in asthmatic patients, as well as helping these patients modify their dietary regimens and toxic exposure.

Our investigation does, however, still have certain shortcomings. First off, the majority of the study participants were asthmatics from the United States. Data from other nations still need to be further incorporated because there are regional variations in environmentally induced heavy metal exposure. Secondly, the medical care that the research participants received was not considered in the study. Third, a large number of confounding variables may still exist and may not have been taken into account. Unquestionably, systematic asthma treatment plays a significant role in enhancing asthma patients' prognosis. Nonetheless, knowing the body's levels of selenium, manganese, and other elements may help with more effective medical care. The prognosis of patients may be improved by maintaining certain levels of selenium and manganese through dietary adjustments and manganese exposure.

Conclusion

The investigation identified a U-shaped correlation between the levels of selenium and manganese in the blood of adult asthmatics and their risk of all-cause mortality. This discovery indicates that both excessive and insufficient levels of manganese and selenium have harmful effects on the longevity of patients with asthma. Our research contributes to the understanding of the relationship between levels of heavy metals in the blood and the risk of death in individuals with asthma. Moreover, our findings suggest that modifying the amount of selenium in the diet and managing exposure to manganese could potentially improve the prognosis for individuals with asthma.

Data availability

All accessible data is available on the official NHANES website (http://www.cdc.gov/nchs/nhanes/index.htm).

Received: 6 April 2024; Accepted: 14 August 2024
Published online: 03 September 2024

References

1. Porsbjerg, C., Melén, E., Lehtimäki, L. & Shaw, D. Asthma. *Lancet* **401**, 858–873 (2023).
2. Stern, J., Pier, J. & Litonjua, A. A. Asthma epidemiology and risk factors. *Semin. Immunopathol.* **42**, 5–15 (2020).
3. Forno, E. *et al.* Asthma in the americas: An update: A joint perspective from the Brazilian thoracic society, Canadian thoracic society, Latin American thoracic society, and American thoracic society. *Ann. Am. Thorac. Soc.* **19**, 525–535 (2022).
4. Yaghoubi, M., Adibi, A., Safari, A., FitzGerald, J. M. & Sadatsafavi, M. The projected economic and health burden of uncontrolled asthma in the United States. *Am. J. Respir Crit. Care Med.* **200**, 1102–1112 (2019).
5. Suárez-Medina, R. *et al.* Prevalence and risk factors for wheeze, decreased forced expiratory volume in 1 s and bronchoconstriction in young children living in Havana, Cuba: A population-based cohort study. *BMJ Open* **10**, e034192 (2020).
6. Nguyen, H. D. Effects of mixed heavy metals on obstructive lung function: Findings from epidemiological and toxicogenomic data. *Environ. Geochem. Health* **45**, 8663–8683 (2023).
7. Esposito, S. *et al.* Possible molecular mechanisms linking air pollution and asthma in children. *BMC Pulm. Med.* **14**, 31 (2014).
8. Karmaus, W. *et al.* Immune function biomarkers in children exposed to lead and organochlorine compounds: A cross-sectional study. *Environ. Health* **4**, 5 (2005).
9. Hsieh, C.-Y., Jung, C.-R., Lin, C.-Y. & Hwang, B.-F. Combined exposure to heavy metals in PM2.5 and pediatric asthma. *J. Allergy. Clin. Immunol.* **147**, 2171-2180.e13 (2021).
10. Zeng, X. *et al.* Heavy metals in PM2.5 and in blood, and children's respiratory symptoms and asthma from an e-waste recycling area. *Environ. Pollut.* **210**, 346–353 (2016).
11. Yuan, Y. *et al.* In vitro toxicity evaluation of heavy metals in urban air particulate matter on human lung epithelial cells. *Sci. Total Environ.* **678**, 301–308 (2019).

12. Manisalidis, I., Stavropoulou, E., Stavropoulos, A. & Bezirtzoglou, E. Environmental and health impacts of air pollution: A Review. *Front. Public Health* **8**, 14 (2020).
13. Boskabady, M. *et al.* The effect of environmental lead exposure on human health and the contribution of inflammatory mechanisms, a review. *Environ. Int.* **120**, 404–420 (2018).
14. Farkhondeh, T., Boskabady, M. H., Kohi, M. K., Sadeghi-Hashjin, G. & Moin, M. Lead exposure affects inflammatory mediators, total and differential white blood cells in sensitized guinea pigs during and after sensitization. *Drug Chem. Toxicol.* **37**, 329–335 (2014).
15. Wen, J., Wang, C., Giri, M. & Guo, S. Association between serum folate levels and blood eosinophil counts in American adults with asthma: Results from NHANES 2011–2018. *Front. Immunol.* **14**, 1134621 (2023).
16. Yang, G. *et al.* Serum cadmium and lead, current wheeze, and lung function in a nationwide study of adults in the United States. *J. Allergy Clin. Immunol. Pract.* **7**, 2653-2660.e3 (2019).
17. Kim, K.-N., Bae, S., Park, H. Y., Kwon, H.-J. & Hong, Y.-C. Low-level mercury exposure and risk of asthma in school-age children. *Epidemiology* **26**, 733–739 (2015).
18. Pascal, L. E. & Tessier, D. M. Cytotoxicity of chromium and manganese to lung epithelial cells in vitro. *Toxicol. Lett.* **147**, 143–151 (2004).
19. Kocyigit, A., Zeyrek, D., Keles, H. & Koylu, A. Relationship among manganese, arginase, and nitric oxide in childhood asthma. *Biol. Trace. Elem. Res.* **102**, 11–18 (2004).
20. Zajac, D. Mineral micronutrients in Asthma. *Nutrients* **13**, 4001 (2021).
21. Kocyigit, A., Armutcu, F., Gurel, A. & Ermis, B. Alterations in plasma essential trace elements selenium, manganese, zinc, copper, and iron concentrations and the possible role of these elements on oxidative status in patients with childhood asthma. *Biol. Trace. Elem. Res.* **97**, 31–41 (2004).
22. Norton, R. L. & Hoffmann, P. R. Selenium and asthma. *Mol. Aspects Med.* **33**, 98–106 (2012).
23. Hu, G. & Cassano, P. A. Antioxidant nutrients and pulmonary function: The Third national health and nutrition examination survey (NHANES III). *Am. J. Epidemiol.* **151**, 975–981 (2000).
24. Rakib, M. R. J. *et al.* A comprehensive review of heavy metal pollution in the coastal areas of Bangladesh: Abundance, bioaccumulation, health implications, and challenges. *Environ. Sci. Pollut. Res. Int.* **29**, 67532–67558 (2022).
25. Mims, J. W. Asthma: Definitions and pathophysiology. *Int. Forum Allergy Rhinol.* **5**(Suppl 1), S2-6 (2015).
26. Gans, M. D. & Gavrilova, T. Understanding the immunology of asthma: Pathophysiology, biomarkers, and treatments for asthma endotypes. *Paediatr. Respir. Rev.* **36**, 118–127 (2020).
27. Wang, J., Yin, J., Hong, X. & Liu, R. Exposure to heavy metals and allergic outcomes in children: A systematic review and meta-analysis. *Biol. Trace Elem. Res.* **200**, 4615–4631 (2022).
28. Miyazaki, J. *et al.* Prenatal exposure to selenium, mercury, and manganese during pregnancy and allergic diseases in early childhood: The Japan Environment and Children's study. *Environ. Int.* **179**, 108123 (2023).
29. Wu, K.-G., Chang, C.-Y., Yen, C.-Y. & Lai, C.-C. Associations between environmental heavy metal exposure and childhood asthma: A population-based study. *J. Microbiol. Immunol. Infect.* **52**, 352–362 (2019).
30. Caffrey, O. E. *et al.* Asthma and all-cause mortality in children and young adults: A population-based study. *Thorax* **75**, 1040–1046 (2020).
31. Jomova, K. *et al.* Essential metals in health and disease. *Chem. Biol. Interact* **367**, 110173 (2022).
32. Murley, J. S., Kataoka, Y., Weydert, C. J., Oberley, L. W. & Grdina, D. J. Delayed radioprotection by nuclear transcription factor kappaB -mediated induction of manganese superoxide dismutase in human microvascular endothelial cells after exposure to the free radical scavenger WR1065. *Free Radic. Biol. Med.* **40**, 1004–1016 (2006).
33. Kimura, M., Ujihara, M. & Yokoi, K. Tissue manganese levels and liver pyruvate carboxylase activity in magnesium-deficient rats. *Biol. Trace Elem Res.* **52**, 171–179 (1996).
34. Keni, S. & Punekar, N. S. Contribution of arginase to manganese metabolism of Aspergillus niger. *Biometals* **29**, 95–106 (2016).
35. Kim, G. W. *et al.* Glutamine synthetase as a therapeutic target for cancer treatment. *Int. J. Mol. Sci.* **22**, 1701 (2021).
36. Pfalzer, A. C. & Bowman, A. B. Relationships between essential manganese biology and manganese toxicity in neurological disease. *Curr. Environ. Health Rep.* **4**, 223–228 (2017).
37. Gorojod, R. M. *et al.* The autophagic- lysosomal pathway determines the fate of glial cells under manganese- induced oxidative stress conditions. *Free Radic. Biol. Med.* **87**, 237–251 (2015).
38. Ursini, F. *et al.* Dual function of the selenoprotein PHGPx during sperm maturation. *Science* **285**, 1393–1396 (1999).
39. de Oliveira, C. R. *et al.* Low urinary selenium levels are associated with iodine deficiency in Brazilian schoolchildren and adolescents. *Endocrine* **73**, 609–16 (2021).
40. Zheng, X. *et al.* Selenoprotein P expression in glioblastoma as a regulator of ferroptosis sensitivity: Preservation of GPX4 via the cycling-selenium storage. *Sci. Rep.* **14**, 682 (2024).
41. Reeves, M. A. & Hoffmann, P. R. The human selenoproteome: Recent insights into functions and regulation. *Cell Mol. Life Sci.* **66**, 2457–2478 (2009).
42. Guo, C.-H., Liu, P.-J., Hsia, S., Chuang, C.-J. & Chen, P.-C. Role of certain trace minerals in oxidative stress, inflammation, CD4/CD8 lymphocyte ratios and lung function in asthmatic patients. *Ann. Clin. Biochem.* **48**, 344–351 (2011).
43. Hadrup, N. & Ravn-Haren, G. Acute human toxicity and mortality after selenium ingestion: A review. *J. Trace Elem. Med. Biol.* **58**, 126435 (2020).
44. Hadrup, N. & Ravn-Haren, G. Toxicity of repeated oral intake of organic selenium, inorganic selenium, and selenium nanoparticles: A review. *J. Trace Elem. Med. Biol.* **79**, 127235 (2023).

Author contributions

J.W. participated in the study design, data extraction, statistical analysis, drafting and revision of the manuscript. J.X.L. performed the study design, statistical analysis, and drafted and revised the manuscript. C.C.W. conducted the study design and the data extraction, and revised the manuscript. R.J.Z. carried out statistical analysis and drafted the manuscript. M.G. carried out the data extraction and revised the manuscript. S.L.G. took part in the study design, management, and revision of the paper. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-70250-8.

Correspondence and requests for materials should be addressed to J.W. or S.G.