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RESEARCH ARTICLE

Environmental exposure to metals and the risk of high blood pressure: a cross-sectional study from NHANES 2015–2016

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Abstract

Exposure to metal pollution can be caused from inhalation, ingestion, or absorption from air, water, or food. Chronic exposure to trace amounts of metals can lead to high blood pressure, or hypertension, and other chronic diseases. The rationale of our study was to determine if there was a correlation between nineteen forms of urinary metal concentrations and high blood pressure, defined as ≥ 130 mm Hg systolic or ≥ 80 mm Hg diastolic, in the adult US population, to understand the possible impacts of metal exposure on humans. Five types of urinary arsenic species and fourteen types of urinary metals were studied to examine their correlation with high blood pressure. We used the dataset from the 2015–2016 National Health and Nutrition Examination Survey (NHANES) for the study. A specialized complex survey design analysis package was used in analyzing the NHANES data. We used pairwise *t* tests and the logit regression models to study the correlation between urinary arsenic (five types) and urinary metal (fourteen types) concentrations and high blood pressure. The total study population analyzed included 4037 adults aged 20 years and older, of whom 57.9% of males and 51.7% of females had high blood pressure. Urinary arsenous acid (OR: 2.053, 95% CI: 1.045, 4.035), tin (OR: 1.983, 95% CI: 1.169, 3.364), and cesium (OR: 2.176, 95% CI: 1.013, 4.675) were associated with increased odds of high blood pressure. The other four types of urinary arsenic and twelve types of urinary metals were not associated with high blood pressure. Our results determined that exposure to environmental metals such as arsenous acid, tin, and cesium can be associated with high blood pressure. Further investigation is suggested to support our findings.

Keywords Urinary metals · Urinary arsenic · Blood pressure · Cesium · Tin · Environmental pollution

Introduction

Environmental metals exist in air, water, and soil. The main routes of environmental metal exposure occur from ingestion of contaminated food and water, inhalation of contaminated air, and skin absorption. Chronic low dose exposure to environmental metals can cause disease and is a public health hazard (Rahman et al. 2020a; Wu et al. 2018). Many studies have associated heavy metals with high blood pressure (Hawkesworth et al. 2013; Telisman et al. 2001). Some studies have shown significant associations between cardiovascular disease (CVD) and exposure to arsenic, cadmium, mercury, and lead, while other studies found no significant association between these toxic metals and CVD risk (Yang et al. 2020). Prevalence of high blood pressure increases with age including 7.5% among adults aged 18–39 and 63.1% among those aged 60 and over (Fryar et al. 2017). Metals including arsenic, tin, cadmium, lead, and mercury have been associated with high blood pressure (Miao et al. 2020; Wang et al. 2018; Shiue et al., 2014b; Shiue and Hristova 2014; Abhyankar et al. 2012; Houston 2007; Hallenbeck 1984) although some studies show mixed results (Shiue 2014a; Jones et al. 2011). It has been reported that certain metals, including selenium, vanadium, and manganese are needed for maintaining blood pressure. Deficiencies can decrease oxidative defenses leading to increased adverse effects from toxicants. Excess levels can lead to negative effects on the cardiovascular system (Wu et al. 2018).

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Several studies have analyzed metals through different exposures and their relationship to high blood pressure (Abhyankar et al. 2012; Kobal et al. 2004). Arsenic exposure can be measured by different methods. In analyzing arsenic exposure from drinking water, a systematic review determined an increasing trend in odds of high blood pressure with increasing arsenic exposure (Abhyankar et al. 2012). Indoor air pollution from coal combustion and indoor smoking can include trace and major metal elements, including tin (Wang et al. 2018). Cesium levels in the environment are low; however, cesium chloride is a homeopathic cancer therapy causing some individuals to have significant exposures (McGinnis et al. 2016). Lead exposure has been linked to cardiac and vascular damage leading to an increased risk of CVD (Miao et al. 2020). In occupational studies, mercury miners with chronic exposure were seen to have a weak correlation between systolic blood pressure and mercury exposure (Kobal et al. 2004). Furthermore, high blood pressure is a complex medical condition leading to a global mortality rate of 13%. It is estimated to contribute to 25% of myocardial infarctions and has been associated with lifestyle habits, including tobacco smoking, lack of physical activity, and alcohol consumption (Cuschieri et al. 2017). The cost of high blood pressure is high for both individuals and society (Shiue 2014b). The mean annual medical expenditure for patients with high blood pressure is $9089. Compared to individuals without high blood pressure, patients with high blood pressure had 2.5 times the inpatient costs, almost double the outpatient costs, and triple the prescription costs. The cost of patients with high blood pressure in the USA results in an annual cost of approximately $131 billion per year more than that of the non-hypertensive population (Kirkland et al. 2018).

The purpose of this study is to evaluate the association between increased blood pressure and urinary toxic metals in the general US population using the 2015–2016 NHANES dataset, which is the most recent NHANES dataset published by the CDC that includes urinary speciated arsenic. The current study aims to assess the link with environmental metal exposure (arsenous acid, arsenobetaine, dimethylarsinic acid, monomethylarsonic acid, total arsenic, mercury, barium, cadmium, cobalt, cesium, molybdenum, manganese, lead, antinomy, tin, strontium, thallium, tungsten, and uranium) assessed with urine samples and the risk of high blood pressure in the human population.

Methods

Data sources

The data for this project was taken from the 2015–2016 NHANES dataset, a long-standing study conducted by the National Center for Health Statistics (NCHS) which is a part of the Centers for Disease Control and Prevention (CDC). It combines interviews and physical examinations of children and adults throughout the USA to determine their health and nutritional status (CDC 2017a).

The NHANES data files used for the response factors were BPX_I—Blood pressure measurements and BPQ_I—Blood pressure questionnaire (CDC 2017c; CDC 2017b). The NHANES data files used for the urinary arsenic and urinary metals data which were used as the primary variates were UAS_I—Speciated urinary arsenic, UTAS_I—Total Urinary arsenic, UMS_I—Urinary metals, and UHG_I—Urinary mercury (CDC 2018a; CDC 2018b; CDC 2018c; CDC 2018d). The creatinine concentration used to normalize the urinary arsenic and metal concentrations came from the NHANES data file ALB_CR_I (CDC 2019a). The data for the covariates came from the NHANES data files ALQ_I—Alcohol consumption, BMX_I—Body mass index, and DEMO_I—Demographic data, COT_I—Serum cotinine (CDC 2018e; CDC 2017d; CDC 2017e; CDC 2019b).

NHANES was approved by the Research Ethics Review Board of the NCHS. As this is a public-use dataset, this study was exempt from additional review by an institutional review board.

Data cleaning

The data cleaning consisted of four primary steps: (1) removing all missing responses, (2) categorizing the continuous covariate variables, (3) normalizing the concentration of the urinary chemical species by the creatinine concentration, and (4) creating the binary categorical variable for high blood pressure. Missing responses in the demographic data, BMI, serum continine, and alcohol consumption were removed, and the reduced dataset was used for all subsequent modeling. If any one of these variables was missing, the entire response was eliminated. Missing responses for urinary arsenic and urinary metals were removed from the complete dataset just prior to creation of the logit regression model.

The continuous variables age, family income to poverty ratio (FIPR), and body mass index (BMI) were converted into categorical factors. Age was converted into a three-level categorical variable with the levels $20 \le \text{age1} \le 40$, $41 \le \text{age2} \le 65$, and $65 < \text{age3}$ as in prior studies (Rahman et al. 2020b). FIPR was converted into a three-level categorical variable: $0 \le \text{FIPR1} \le 130\%$, $130\% \le \text{FIPR2} \le 350\%$, and $350\% < \text{FIPR3}$. The BMI was converted into a four-level categorical variable with underweight: $\text{BMI} < 18.5$, normal weight: $18.5 \le \text{BMI} < 24.9$, overweight: $24.9 \le \text{BMI} < 30.0$, and obese: $30.0 \le \text{BMI}$ per the CDC definitions (CDC 2020).

Natural variation in urine dilution was addressed by taking the urinary arsenic and metals species concentrations and dividing them by the creatinine concentration (Jones et al.

2011). No attempt was made to make the concentration units consistent; the values provided in the NHANES data were used directly. Once the concentration had been normalized, they were then $\log_{10}$ transformed to create a more nearly normal distribution of the concentrations.

The categorical binary variable for high blood pressure was set so that the respondent was deemed to have high blood pressure if any of the following criteria were true: the average of the 2nd, 3rd, and (if present) 4th systolic blood pressure readings was greater than or equal to 130 mm Hg, or the average of the 2nd, 3rd, and (if present) 4th diastolic blood pressure readings was greater than or equal to 80 mm Hg, or they were taking prescribed medicine for high blood pressure (Jones et al. 2011).

Statistical analysis

The statistical analysis was done in R version 3.6.3 using programs from the *survey* package to account for the complex design used in the construction of the NHANES survey (R Core Team 2020; Lumley 2004; Lumley 2010; Lumley 2020). Specifically, from the *survey* package, the functions *svyby*, *svymean*, *svyttest*, *svydesign*, and *svyglm* were used to calculate the unweighted occurrences of responses, the weighted mean of the responses, the weighted pairwise *t* tests of the responses, the survey design object, and the logit regression models, respectively. Additional R functions and packages used to simplify the programing included: the function *nhanes_load_data* in the package *RNHANES* was used to download the data files from the NHANES website and store them locally as comma separated values (*.csv) files (Susmann 2016). The functions *optimalCutoff*, *misClassError*, *sensitivity*, and *specificity* in the package *InformationValue* were used to calculate the quality metrics of the logit regression models, while the function *plotROC* from the same function was used to calculate the ROC curves used for visual model assessment (Prabhakaran 2016).

Logit regression modeling

The discussion below gives an overview of the approach to modeling the correlation between the concentration of selected urinary compounds and high blood pressure. The basic approach is to construct a logit regression model using the assumed covariate factors to predict high blood pressure and then add to that basic model the urinary compounds one at a time to determine whether or not there is a correlation between the urinary compound and high blood pressure. Each of these is discussed in more detail below.

Covariate-factor modeling

Since the demographic dataset is much larger than the arsenic and metal datasets, the initial covariate-factor models were developed using just the demographic dataset to gain insight into how these factors correlated with high blood pressure. Two models were considered. The first was constructed using just the main effects of the covariate factors; the second included the main effects and all the two-factor interactions except those associated with family income to poverty ratio, serum cotinine level, and alcohol consumption.

The metrics that were used to assess the goodness-of-fit of the models were fraction mismatched—the total number of predictions that were incorrect divided by the total number of predictions. Sensitivity, also called the true positive rate—the proportion of actual positives which were correctly identified as such and were complementary to the false negative rate. Sensitivity = true positives / (true positive + false negative) (Vadakkanmarveettil 2015). Specificity, also called the true negative rate—the proportion of negatives which were correctly identified as such. Specificity was complementary to the false positive rate. Specificity = true negatives / (true negative + false positives) (Prabhakaran 2016). Area under the ROC curve—this was an aggregated metric that evaluated how well the logistic regression model classified positive and negative outcomes at all possible cutoffs. It ranges from 0.5 to 1, and the larger it is the better ("Interpreting Logistic ROC Curves," n.d.). The results of the logit regression for the main-effects model are given in Table 1.

Results

Preliminary data review: covariate factors

The responses are presented for the complete demographic dataset as well as for urinary cotinine concentration and alcohol consumption in Table 2. For each covariate, the total number of respondents of each group of each categorical variable is given along with the corresponding percentage and the percentage within the categorical variable that had high blood pressure (% HBP).

In summary of these results: the difference in gender is statistically significant with a higher percentage of men having high blood pressure than women. Non-Hispanic black have the highest percentage of individuals with high blood pressure (58.3%), while other Hispanic have the lowest (42.5%). However, the results for Mexican American, Other Hispanic, Non-Hispanic Asian, and Other were not statistically different at the α=0.05 level. On the other hand, the frequency of high blood pressure in Non-Hispanic whites (50.3%) was statistically different from the other groups except for Non-Hispanic Asian. For highest educational level

Table 1 Logit regression model coefficients, the corresponding odds ratios, and lower and upper confidence levels (LCL and UCL, respectively) for a model that includes only main effects

Category	Variable	Model Coefficients			Odds Ratio		
		Value	LCL	UCL	Value	LCL	UCL
Intercept		-1.494	-1.986	-1.001	0.032	0.010	0.100
Gender	Male						
	Female	-0.442	-0.695	-0.189	0.361	0.202	0.647
Race/Ethnicity	Mexican American						
	Other Hispanic	-0.011	-0.337	0.314	0.975	0.461	2.061
	Non-Hispanic White	0.250	0.003	0.498	1.780	1.007	3.147
	Non-Hispanic Black	0.700	0.456	0.945	5.015	2.858	8.801
	Non-Hispanic Asian	0.688	0.366	1.010	4.871	2.320	10.228
	Other	0.494	-0.110	1.098	3.119	0.776	12.540
Highest Level of Education	Less than 9th grade						
	Some 9th-12th grade	-0.412	-0.929	0.105	0.387	0.118	1.272
	HS or GED graduate	-0.185	-0.539	0.169	0.653	0.289	1.474
	Some college/AA degree	-0.275	-0.702	0.151	0.530	0.199	1.417
	College graduate	-0.472	-0.848	-0.095	0.338	0.142	0.803
Marital Status	Married						
	Widowed	0.688	0.277	1.100	4.880	1.891	12.590
	Divorced	0.099	-0.159	0.358	1.257	0.694	2.278
	Separated	0.457	-0.098	1.013	2.865	0.797	10.296
	Never Married	0.043	-0.314	0.400	1.104	0.485	2.510
	Living with partner	0.012	-0.268	0.292	1.028	0.539	1.961
Age	20-39						
	40-64	1.426	1.121	1.730	26.657	13.225	53.734
	65 and above	2.246	1.848	2.644	176.268	70.455	440.995
Family Income to Poverty Ratio	0% to 130%						
	130% to 350%	-0.127	-0.327	0.074	0.747	0.471	1.185
	Over 350%	-0.185	-0.446	0.077	0.654	0.358	1.193
Body Mass Index	Normal weight						
	Underweight	-0.280	-1.142	0.582	0.525	0.072	3.822
	Overweight	0.561	0.338	0.784	3.638	2.177	6.080
	Obese	1.161	0.955	1.368	14.495	9.014	23.309
Serum Cotinine Concentration	Below LLoD (ng/mL)						
	Above LLoD (ng/mL)	0.061	-0.229	0.351	1.151	0.590	2.246
Alcohol Consumption	<12 drinks last year						
	≥12 drinks last year	-0.034	-0.257	0.190	0.925	0.553	1.547

Note: Factors that are significant at a=0.05 are highlighted in grey.

achieved, generally the higher the level of education, the smaller the percentage of respondents with high blood pressure. There are statistically significant differences between the groups within the marital status category with those never married or living with a partner having the lowest percentage of individuals with high blood pressure and those separated having the highest. There are statistically significant differences in all three age categories with the youngest having the lowest percentage of individuals with high blood pressure and those above age 65 having the highest percentage. There is no statistically significant difference in the family income to poverty ratio groups. There is a statistically significant difference in the BMI groups with the higher the BMI, the higher the percentage of individuals with high blood pressure. There is no statistically significant difference in the serum cotinine concentration groups or in the alcohol consumption groups.

In the columns of the percentage of individuals with high blood pressure, those within the same category with the same

Table 2 Summary statistics for the covariates used in the study of high blood pressure

Category	Variable	Sample statistics				Population statistics
		N	%	N_{HBP}	$\%_{HBP}$	$\%_{HBP}$
Gender	Male	2005	49.7%	1160	57.9% a	52.8% a
	Female	2032	50.3%	1050	51.7% b	47.4% a
Ethnicity	Mexican American	709	17.6%	371	52.3% a	43.7% a
	Other Hispanic	515	12.8%	274	53.2% a	42.5% a
	Non-Hispanic White	1453	36.0%	784	54.0% a	50.3% b
	Non-Hispanic Black	801	19.8%	508	63.4% b	58.3% c
	Non-Hispanic Asian	413	10.2%	193	46.7% a	46.2% ab
	Other	146	3.6%	80	54.8% ab	53.2% abc
Education	No high school	441	10.9%	304	68.9% c	61.8% c
	Some high school	441	10.9%	245	55.6% a	49.4% ab
	High school graduate	906	22.4%	524	57.8% a	54.9% ac
	Some college	1235	30.6%	652	52.8% ab	51.4% a
	College graduate	1014	25.1%	485	47.8% b	44.0% b
Marital status	Married	2062	51.1%	1165	56.5% c	51.5% b
	Widowed	289	7.2%	233	80.6% a	79.1% a
	Divorced	437	10.8%	288	65.9% b	58.1% b
	Separated	136	3.4%	85	62.5% bc	63.3% b
	Never married	724	17.9%	278	38.4% d	35.9% c
	Living with partner	389	9.6%	161	41.4% d	37.9% c
Age	20–44	1310	32.4%	339	25.9% c	25.3% c
	45–59	1761	43.6%	1087	61.7% a	57.2% a
	60 and older	966	23.9%	784	81.2% b	75.3% b
FIPR	0 to 130%	1270	31.5%	745	58.7% b	51.6% a
	130 to 350%	1624	40.2%	880	54.2% a	50.0% a
	Over 350%	1143	28.3%	585	51.2% a	49.3% a
BMI	Normal weight	1007	24.9%	402	39.9% a	33.4% a
	Underweight	56	1.4%	14	25.0% a	22.3% a
	Overweight	1316	32.6%	723	54.9% b	50.2% b
	Obese	1658	41.1%	1071	64.6% c	61.7% c
Cotinine concentration	Below LLoD (ng/mL)	1357	33.6%	754	55.6% a	50.4% a
	Above LLoD (ng/mL)	2680	66.4%	1456	54.3% a	49.8% a
Alcohol consumption	12 drinks or fewer	2810	69.6%	1507	53.6% a	49.3% a
	More than 12 drinks	1227	30.4%	703	57.3% b	52.6% a

letter following the numerical value are not statistically different at the α=0.05 level. For the categories with only two levels, this was determined using a χ^2 test on the appropriate contingency table. For categories with more than two levels, this was determined using a Tukey analysis based on a linear model using only the variables within that category as the independent factors.

The results for the two-factor interaction model are not presented here due to the large number of terms in the model, 270 in total. However, the model did indicate several significant 2-factor interaction terms along with decreasing the number of significant main effects.

The two-factor model does a better prediction of correctly predicting positive results (i.e., having high blood pressure) than does the main-effects only model. The two-factor interaction and the main-effects models have similar abilities to predict negative results. The two-factor interaction model misclassifies 26% of the responses, while the main-factor model misclassifies 28% of the responses. As expected, there is a tradeoff in sensitivity and specificity. As the sensitivity decreases, the specificity increases. The values of the sensitivity and specificity are functions not only of the logit regression model but also the cutoff value used to split the continuous response into the binary prediction response. In this work, the

cutoff values were determined using the *optimalCutoff* function in the R package *InformationValue* (Prabhakaran 2016). The area under the ROC curve (not presented) is higher for the two-factor interaction model than it is for the main-effects model.

Complete modeling summary

Using a covariate model with just main effects, the model coefficients and odds ratios as well as their 95% confidence intervals for the arsenic and metal compounds are given in Table 3. These results show that one of the arsenic compounds and two of the metals are statistically correlated with high blood pressure at the a=0.05 level. Model coefficients and odds ratios are not given for any models for arsenic acid and arsenocholine because the NHANES database did not have sufficient data to create a logit regression model because of the large number of terms in the model.

The model coefficients and odds ratios as well as their 95% confidence intervals using two-factor interaction modes for the arsenic and metal compounds are given in Table 4. These results show that none of the arsenic compounds and two of the metals are statistically correlated with high blood pressure at the a=0.05 level. The only two species significantly correlated with high blood pressure are cesium and tin.

A second two-factor interaction model was also created to study the effect of the choice of interaction terms on the results. The second two-factor interaction model included the main effects and interaction terms associated with age to see if this would more accurately model how high blood pressure develops as individuals age. Specifically, the interaction terms included age × gender, age × race/ethnicity, age × education, age × marital status, and age × BMI. The results for this covariate model are given in Table 5. Using this model, only two metals are significantly correlated with high blood pressure: cesium and tin, the same two that were significant in the prior two-factor model.

A fourth model was created that used the main effects and gender related two-factor interactions, specifically: gender × age, gender × race/ethnicity, gender × education, gender × marital status, and gender × BMI. The results for this covariate model are given in Table 6. Using this model, only two metals are significantly correlated with high blood pressure: cesium and tin, the same two that were significant in the prior two-factor models.

Finally, a fifth model was created that used the main effects and body mass index-related two-factor interactions, specifically: BMI × gender, BMI × age, BMI × education, and BMI × marital status. The results for this covariate model are given in Table 7. Using this model, arsenous acid, cesium, and tin are significantly correlated with high blood pressure.

Table 3 Summary of logit model regressions with only main effects for the covariates for the correlation of arsenic and metal compounds, measured in μg/L, on high blood pressure

Species		N	Model Coefficient			Odds Ratio		
			Value	LCL	UCL	Value	LCL	UCL
Arsenic Compounds	Arsenous Acid	686	0.719	0.044	1.395	2.053	1.045	4.035
	Arsenobetaine	656	0.080	-0.420	0.580	1.083	0.657	1.785
	Dimethylarsinic Acid	80	0.385	-0.372	1.142	1.470	0.690	3.134
	Monomethylarsonic Acid	114	0.431	-0.309	1.170	1.538	0.734	3.223
	Total Arsenic	148	0.264	-0.291	0.819	1.302	0.748	2.268
Metals	Mercury	182	-0.143	-0.558	0.272	0.867	0.572	1.313
	Barium	216	-0.067	-0.381	0.247	0.935	0.683	1.280
	Cadmium	250	0.453	-0.236	1.141	1.572	0.790	3.130
	Cobalt	284	0.419	-0.214	1.052	1.521	0.807	2.864
	Cesium	318	0.777	0.013	1.542	2.176	1.013	4.675
	Molybdenum	352	0.116	-0.582	0.814	1.123	0.559	2.257
	Manganese	386	0.311	-0.404	1.025	1.364	0.668	2.787
	Lead	420	0.075	-0.692	0.843	1.078	0.501	2.323
	Antinomy	454	0.332	-0.386	1.050	1.394	0.680	2.858
	Tin	488	0.685	0.156	1.213	1.983	1.169	3.364
	Strontium	522	0.061	-0.347	0.468	1.062	0.707	1.597
	Thallium	556	-0.023	-0.839	0.793	0.977	0.432	2.211
	Tungsten	590	0.442	-0.195	1.078	1.555	0.823	2.939
	Uranium	624	0.342	-0.305	0.990	1.408	0.737	2.692

Note: Terms that are statistically significant at a=0.05 are highlighted in grey. LCL: Lower Confidence Level. UCL: Upper Confidence Level.

Table 4 Summary of logit model regressions including selected two-factor interaction terms for the covariates for the correlation of arsenic and metal compounds, measured in μg/L, on high blood pressure

Species		Model Coefficient			Odds Ratio		
		Value	LCL	UCL	Value	LCL	UCL
Arsenic Compounds	Arsenous Acid	0.607	-0.118	1.332	1.834	0.889	3.787
	Arsenobetaine	0.027	-0.478	0.533	1.028	0.620	1.704
	Dimethylarsinic Acid	0.343	-0.390	1.076	1.409	0.677	2.933
	Monomethylarsonic Acid	0.423	-0.259	1.106	1.527	0.772	3.022
	Total Arsenic	0.262	-0.292	0.817	1.300	0.747	2.263
Metals	Mercury	-0.111	-0.499	0.278	0.895	0.607	1.320
	Barium	-0.039	-0.369	0.290	0.961	0.692	1.337
	Cadmium	0.568	-0.176	1.311	1.764	0.839	3.709
	Cobalt	0.509	-0.173	1.192	1.664	0.841	3.294
	Cesium	0.829	0.057	1.600	2.290	1.059	4.955
	Molybdenum	0.097	-0.616	0.810	1.102	0.540	2.249
	Manganese	0.158	-0.651	0.968	1.172	0.522	2.632
	Lead	0.060	-0.750	0.870	1.062	0.473	2.387
	Antinomy	0.306	-0.430	1.041	1.357	0.650	2.833
	Tin	0.718	0.176	1.260	2.051	1.193	3.525
	Strontium	0.130	-0.288	0.548	1.139	0.750	1.729
	Thallium	0.044	-0.732	0.820	1.045	0.481	2.271
	Tungsten	0.445	-0.192	1.083	1.561	0.826	2.952
	Uranium	0.371	-0.260	1.001	1.449	0.771	2.722

Note: Terms that are statistically significant at a=0.05 are highlighted in grey. LCL: Lower Confidence Level. UCL: Upper Confidence Level.

Table 5 Summary of logit model regressions including age-related two-factor interaction terms for the covariates for the correlation of arsenic and metal compounds, measured in μg/L, on high blood pressure

Species		Model Coefficient			Odds Ratio		
		Value	LCL	UCL	Value	LCL	UCL
Arsenic Compounds	Arsenous Acid	0.385	-0.258	1.028	1.470	0.773	2.796
	Arsenobetaine	-0.010	-0.630	0.609	0.990	0.533	1.838
	Dimethylarsinic Acid	0.341	-0.349	1.032	1.407	0.705	2.806
	Monomethylarsonic Acid	0.352	-0.286	0.991	1.422	0.751	2.693
	Total Arsenic	0.259	-0.300	0.818	1.296	0.741	2.267
Metals	Mercury	-0.040	-0.401	0.321	0.961	0.670	1.378
	Barium	-0.062	-0.341	0.217	0.940	0.711	1.242
	Cadmium	0.474	-0.245	1.193	1.606	0.783	3.296
	Cobalt	0.371	-0.263	1.004	1.449	0.769	2.730
	Cesium	0.777	0.063	1.490	2.175	1.066	4.439
	Molybdenum	0.012	-0.767	0.791	1.012	0.464	2.206
	Manganese	0.033	-0.769	0.836	1.034	0.463	2.308
	Lead	-0.008	-0.870	0.855	0.992	0.419	2.351
	Antinomy	0.255	-0.458	0.968	1.290	0.632	2.632
	Tin	0.800	0.257	1.344	2.226	1.293	3.835
	Strontium	0.051	-0.309	0.411	1.053	0.734	1.509
	Thallium	0.001	-0.734	0.736	1.001	0.480	2.088
	Tungsten	0.449	-0.159	1.056	1.566	0.853	2.876
	Uranium	0.426	-0.227	1.078	1.531	0.797	2.940

Note: Terms that are statistically significant at a=0.05 are highlighted in grey. LCL: Lower Confidence Level. UCL: Upper Confidence Level.

Discussion

Our study analyzed the relationship between nineteen urinary metals (arsenous acid, arsenobetaine, dimethylarsinic acid, monomethylarsonic acid, total arsenic, mercury, barium, cadmium, cobalt, cesium, molybdenum, manganese, lead, antinomy, tin, strontium, thallium, tungsten, and uranium) and their effect on high blood pressure in US adults using the 2015–2016 NHANES dataset. Among five different models, it was observed that urinary arsenous acid, cesium, and tin all had statistically significant associations with high blood pressure, defined as ≥130 mm Hg systolic, ≥80 mm Hg diastolic, or patients on antihypertensive medications. High blood pressure affects approximately one-third of American adults, and nearly 1 billion people worldwide (Shiue 2014b; Wu et al. 2018). The American Heart Association (AHA) categorizes high blood pressure into several groups. Elevated systolic blood pressure ranges from 120 to 129 mm Hg, stage 1 hypertension ranges 130–139 mm Hg, and stage 2 hypertension includes ≥140 mm Hg (AHA 2019). Based on the 2017 American College of Cardiology (ACC) guidelines, we defined high blood pressure as stage 1 or greater, defined as a systolic pressure of ≥130 mm Hg and/or a diastolic pressure of ≥80 mm Hg, or patients on antihypertensive medications (Flack and Adekola 2020; Whelton et al. 2018).

Studies have shown mixed results regarding the association between arsenic and high blood pressure. Jones et al. (2011) found no association between total arsenic minus arsenobetaine, DMA, or arsenobetaine and systolic or diastolic high blood pressure using 2003–2008 NHANES data. High blood pressure was measured as ≥140 mm Hg systolic, ≥90 mm Hg diastolic, a physician diagnosis, or use of antihypertensive medication (Jones et al. 2011). In our study, we also found no association between DMA and arsenobetaine and high blood pressure. Chen et al. (1995) studied arsenic exposure through well water consumption measuring the concentration of arsenic in the water. They determined that in residents in villages where long-term arseniasis was hyperendemic, there was a 1.5-fold increase in age and sex adjusted high blood pressure compared to residents in non-endemic areas, with high blood pressure measured as ≥160 mm Hg systolic, ≥95 mm Hg diastolic, or treatment with antihypertensive drugs. A significant dose-response relationship between high blood pressure and average arsenic concentration in drinking water was found even after adjustment for age and sex. This study did not identify what form of arsenic was found in drinking water and therefore does not show whether a certain form of speciated arsenic could be responsible for the high blood pressure (Chen et al. 1995).

Table 6 Summary of logit model regressions including gender-related two-factor interaction terms for the covariates for the correlation of arsenic and metal compounds, measured in μg/L, on high blood pressure

Species		Model Coefficient			Odds Ratio		
		Value	LCL	UCL	Value	LCL	UCL
Arsenic Compounds	Arsenous Acid	0.629	-0.102	1.360	1.875	0.903	3.895
	Arsenobetaine	0.104	-0.413	0.620	1.109	0.662	1.859
	Dimethylarsinic Acid	0.385	-0.399	1.168	1.469	0.671	3.215
	Monomethylarsonic Acid	0.515	-0.309	1.339	1.674	0.734	3.814
	Total Arsenic	0.260	-0.327	0.846	1.297	0.721	2.331
Metals	Mercury	-0.166	-0.590	0.259	0.847	0.554	1.296
	Barium	-0.074	-0.383	0.235	0.928	0.682	1.264
	Cadmium	0.497	-0.223	1.218	1.644	0.800	3.381
	Cobalt	0.556	-0.103	1.214	1.743	0.902	3.368
	Cesium	0.828	0.098	1.559	2.290	1.103	4.754
	Molybdenum	0.092	-0.619	0.803	1.096	0.539	2.232
	Manganese	0.293	-0.441	1.027	1.340	0.643	2.792
	Lead	0.081	-0.738	0.899	1.084	0.478	2.458
	Antinomy	0.355	-0.432	1.141	1.426	0.649	3.131
	Tin	0.684	0.093	1.275	1.981	1.097	3.577
	Strontium	0.070	-0.393	0.532	1.072	0.675	1.702
	Thallium	0.008	-0.779	0.795	1.008	0.459	2.214
	Tungsten	0.460	-0.198	1.118	1.584	0.820	3.059
	Uranium	0.355	-0.304	1.015	1.427	0.738	2.759

Note: Terms that are statistically significant at a=0.05 are highlighted in grey. LCL: Lower Confidence Level. UCL: Upper Confidence Level.

Table 7 Summary of logit model regressions including BMI-related two-factor interaction terms for the covariates for the correlation of arsenic and metal compounds, measured in μg/L, on high blood pressure

Species		Model Coefficient			Odds Ratio		
		Value	LCL	UCL	Value	LCL	UCL
Arsenic Compounds	Arsenous Acid	0.616	0.019	1.214	1.852	1.019	3.367
	Arsenobetaine	-0.047	-0.603	0.509	0.954	0.547	1.663
	Dimethylarsinic Acid	0.478	-0.279	1.235	1.613	0.757	3.438
	Monomethylarsonic Acid	0.327	-0.534	1.188	1.387	0.586	3.281
	Total Arsenic	0.245	-0.285	0.776	1.278	0.752	2.172
Metals	Mercury	-0.125	-0.475	0.224	0.882	0.622	1.251
	Barium	-0.069	-0.338	0.201	0.934	0.713	1.222
	Cadmium	0.442	-0.179	1.064	1.556	0.836	2.897
	Cobalt	0.372	-0.230	0.975	1.451	0.794	2.651
	Cesium	0.826	0.112	1.541	2.285	1.118	4.668
	Molybdenum	0.068	-0.598	0.735	1.070	0.550	2.085
	Manganese	0.368	-0.230	0.966	1.444	0.794	2.627
	Lead	-0.047	-0.917	0.823	0.954	0.400	2.277
	Antinomy	0.363	-0.440	1.165	1.437	0.644	3.206
	Tin	0.665	0.171	1.159	1.944	1.186	3.188
	Strontium	-0.014	-0.476	0.448	0.986	0.621	1.565
	Thallium	0.038	-0.762	0.839	1.039	0.467	2.313
	Tungsten	0.426	-0.145	0.997	1.531	0.865	2.710
	Uranium	0.470	-0.198	1.138	1.600	0.820	3.121

Note: Terms that are statistically significant at a=0.05 are highlighted in grey. LCL: Lower Confidence Level. UCL: Upper Confidence Level.

Our study presented an association with arsenous acid, which is an inorganic form of arsenic. Jones et al. (2011) did not analyze arsenous acid because the limits of detection for arsenite, arsenate, and methylarsonate, which reflect inorganic arsenic exposure, were too high for the population that had an overall low to moderate exposure of inorganic arsenic. Arsenous acid shares the same oxidation state of arsenite of +3, whereas arsenic acid and arsenate are +5 (Jekel and Amy 2006). Arsenous acid, among other inorganic forms of arsenic, are considered toxic and can lead to adverse health effects (Caldwell et al. 2009). Jones et al. (2011) analyzed total arsenic, DMA, and arsenobetaine. Arsenous acid and other forms of inorganic arsenic are methylated to metabolites like DMA and MMA and distributed to the body. Jones et al. (2011) did find a small association between DMA and high blood pressure only in certain subgroups, including BMI ≥30 kg/m^2 and in never-smokers; however, the overall sample did not show a significant association. Our study found a positive association between arsenous acid and high blood pressure but none between DMA and high blood pressure. It has been suggested that arsenic acts on blood pressure levels via oxidative stress, inflammation, endothelial dysfunction, and nitric oxide inhibition (Wu et al. 2018).

There is minimal literature regarding the effect of tin exposure on blood pressure in humans. Wang et al. (2018) studied 367 subjects, all housewives in China exposed to indoor air pollution primarily due to coal combustion and passive smoking. A positive correlation with high blood pressure was found with arsenic, lead, and rare earth element levels in hair samples; a negative correlation was found with trace elements including chromium, cobalt, nickel, tin, and alkaline earth metals: calcium, magnesium, and barium (Wang et al. 2018). Lan et al. (2021) found no significant association between tin and systolic or diastolic blood pressure. In contrast, Shiue (2014b) found a significant association between high blood pressure and tin; our study also supports these findings.

Few studies have analyzed the effect of cesium on humans. A study using 1999–2012 NHANES data found a negative association between urinary cesium and diastolic blood pressure, showing that urinary cesium lowered diastolic blood pressure (McGinnis et al. 2016). However, Shiue and Hristova (2014) determined an increased odds of high blood pressure with cesium exposure using 2009–2012 NHANES data. Their study defined high blood pressure as ≥140 mm Hg systolic or ≥90 mm Hg diastolic. Shiue (2014b) also found a positive association between cesium and high blood pressure using 2011–2012 NHANES data. In addition, in Brazil, Rodrigues et al. (2017) studied a group of victims with radioactive exposure to cesium-137. It was determined that the prevalence of high blood pressure was similar in the

radioactivity victims as the general population. This was conflicting to our results of an increased odds of high blood pressure with cesium exposure; however, their sample size was only 102 participants, and it was not adjusted for smoking (Rodrigues et al. 2017). In our results, the correlations with tin and cesium observed with the two-factor model remained consistent with the main-effect model associations. Furthermore, all other metals were not found to have an association with high blood pressure in our study. Shiue (2014a) found no association between mercury and high blood pressure but did find significant associations with cobalt, lead, antimony, and tungsten using 2009–2010 NHANES data. Wu et al. (2018), however, found no association between lead and cadmium and high blood pressure.

Within the study group, certain demographic groups had statistically significant higher odds of having high blood pressure. These included Non-Hispanic Whites, Non-Hispanic Blacks, Non-Hispanic Asians, widows, individuals over 40, and those who are overweight or obese. On the other hand, females and college graduates were statistically more likely to have lower blood pressure. Jones et al. (2011) found that compared to subjects without high blood pressure, participants with high blood pressure were more likely to be older, female, white, and less educated. These results were similar to ours with the exception of race and sex, wherein our study determined that the ethnic group with the smallest percentage of individuals with high blood pressure were Other Hispanics (42.5%) but that was statistically not different from Mexican American (43.7%), non-Hispanic Asians (46.2%), and Other (53.2%) and that males were more likely than females to have high blood pressure. This was also observed in Wu et al. (2018) where males were significantly more likely to have high blood pressure. Feng et al. (2012) found that BMI was strongly associated with high blood pressure, which was also supported by our results.

Strengths and limitations

This study was conducted using the NHANES dataset, leading to a large sample size of 4037 adults, which was representative of the US population including a sample of several races, ages, and health statuses. Exposures to nineteen different metals were analyzed, which provides a thorough evaluation of many different exposures that an individual could experience simultaneously. High blood pressure affects a large portion of the population in the USA, determining potential causes that can help to improve health and reduce healthcare expenditures in the USA.

Our study is only applicable to the adult population and is a cross-sectional design; therefore, we cannot determine causality. In addition, the sources of exposures are unknown and not accounted for. Our study does not designate which participants had occupational exposure, and therefore the public health implications of reducing exposure in certain populations are limited. We also did not study the impact of combined metal exposure, such as the interaction of specific metals with each other. Future prospective studies are needed to determine causation and the source of metal exposures.

Conclusions

Arsenous acid, cesium, and tin are likely to contribute to high blood pressure in adults in the USA. Using the 2015–2016 NHANES dataset, no other urinary environmental metals were associated with high blood pressure among the nineteen included in this study.

Availability of data and material The datasets analyzed during the current study are available in the NHANES repository provided by the CDC to the public [https://wwwn.cdc.gov/nchs/nhanes/ContinuousNhanes/Default.aspx?BeginYear=2015] (CDC/National Center for Health Statistics 2020).

Author's contribution HHR conceptualized the study and contributed to the introduction and discussion. SMM conducted the data analysis and contributed to the drafting of the paper. DN contributed to the methods section and drafting of the paper. All authors read and approved the final manuscript.

Declarations

Ethics approval and consent to participate Not applicable. This study uses only secondary data analyses without any personal information identified using statistical data from the NHANES website; no further ethical approval for conducting the present study is required.

Consent to participate Consent was given by all the authors.

Competing interests The authors declare no competing interests.

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