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ENVIRONMENTAL EXPOSURE AND PULMONARY DISEASE

Urinary Metals, Arsenic, and Polycyclic Aromatic Hydrocarbon Exposure and Risk of Self-reported Emphysema in the US Adult Population

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Abstract

Purpose Metal and chemical exposure can cause acute and chronic respiratory diseases in humans. The purpose of this analysis was to analyze 14 types of urinary metals including mercury, uranium, tin, lead, antimony, barium, cadmium, cobalt, cesium, molybdenum, manganese, strontium, thallium, tungsten, six types of speciated arsenic, total arsenic and seven forms of polycyclic aromatic hydrocarbons (PAHs), and the link with self-reported emphysema in the US adult population.

Methods A cross-sectional analysis using the 2011–2012, 2013–2014 and 2015–2016 National Health and Nutrition Examination Survey datasets was conducted. A specialized weighted complex survey design analysis package was used in analyzing the data. Multivariate logistic regression models were used to assess the association between urinary metals, arsenic, and PAHs and self-reported emphysema among all participants and among non-smokers only. Models were adjusted for lifestyle and demographic factors.

Results A total of 4,181 adults were analyzed. 1-Hydroxynaphthalene, 2-hydroxynaphthalene, 3-hydroxyfluorene, 2-hydroxyfluorene, 1-hydroxypyrene, and 2 & 3-hydroxyphenanthrene were positively associated with self-reported emphysema. Positive associations were also observed in cadmium and cesium with self-reported emphysema. Among non-smokers, quantiles among 2-hydroxynaphthalene, arsenocholine, total urinary arsenic, cesium, and tin were associated with increased odds of self-reported emphysema. Quantiles among 1-hydroxyphenanthrene, cadmium, manganese, lead, antimony, thallium, and tungsten were associated with an inverse relationship with self-reported emphysema in non-smokers.

Conclusion The study determined that six types of urinary PAHs, cadmium, and cesium are positively associated with self-reported emphysema. Certain quantiles of 2-hydroxynaphthalene, arsenocholine, total urinary arsenic, cesium, and tin are positively associated with self-reported emphysema among non-smokers.

Keywords Polycyclic aromatic hydrocarbons · Heavy metals · Arsenic · Emphysema · NHANES · Non-smoker

Introduction

Emphysema is an airflow limitation due to parenchymal destruction in which there is destruction and enlargement of the gas-exchanging surfaces of alveoli distal to the terminal bronchiole [1]. Emphysema is a subtype of chronic obstructive pulmonary disease (COPD), which is characterized by persistent respiratory symptoms due to abnormalities in the airway and alveoli often due to exposure to noxious particles or gases [2–5]. The most common cause of emphysema is cigarette smoking.

Polycyclic aromatic hydrocarbons (PAHs) are chemicals that contain fused aromatic rings and are organic in nature, containing hydrogen and carbon molecules [6]. The principal source of PAHs is the partial combustion of organic materials, in addition to exhaust from vehicles, smoking tobacco, agricultural burning, occupational sources, smoked and grilled food, and coal tar in the United States (US) [7]. Correlational studies in humans have found associations with PAH exposure and multiple chronic diseases in humans

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including emphysema, impaired respiratory function, lung cancer, and ischemic heart disease [8–12].

Exposure to cadmium can occur through food and through accumulation in tobacco plants, resulting in tobacco smoking being an important route of exposure in the human population. Cadmium accumulates inside the lungs, which chronically can lead to smoking-related lung diseases including emphysema and chronic bronchitis [13]. Exposure to cadmium in occupational settings has been associated with impaired lung function and emphysema [14, 15]. Furthermore, arsenic is a naturally occurring element and metalloid found in earth's crust. It can contaminate groundwater sources, creating a public health threat [16]. Low–moderate arsenic exposure has been linked with lower lung function and emphysema [17]. Cesium exposure has been attributed to drinking water and prior nuclear accidents and has been associated with several health conditions [18–21]. There is minimal literature regarding cesium exposure, particularly in relation to its effect on lung function [19, 22].

The purpose of this study is to analyze the association between urinary PAHs, arsenic (speciated and total), and metal exposure and self-reported emphysema in the US adult population among all participants and non-smokers. The study uses the National Health and Nutrition Examination Survey (NHANES) dataset including six forms of urinary PAHs, seven forms of urinary speciated arsenic, and 14 urinary metals to determine the association with self-reported emphysema.

Methods

The 2011–2012, 2013–2014, and 2015–2016 NHANES datasets were used. NHANES is a national study evaluating the health and nutritional status of children and adults in the US. Demographic, laboratory, examination, and questionnaire data were collected as part of the datasets [23].

For emphysema data, the variable "MCQ160G" in medical conditions (MCQ_G), (MCQ_H), and (MCQ_I) datasets was used [24–26]. Patients were asked on a questionnaire, "Ever told you had emphysema?" [31]. For urinary metals data, the metals—urine (UHM_G), (UM_H), and (UM_I) datasets including urinary barium, cadmium, cesium, cobalt, manganese, molybdenum, lead, antimony, strontium, thallium, tin, tungsten, and uranium were used [27–29] in addition to mercury data: inorganic, urine (UHG_G), mercury—urine (UHG_H), and (UHG_I) datasets [30–32]. Both urinary and blood cadmium are used as biomarkers to assess exposure and body burden of cadmium. Urinary cadmium is considered to reflect the kidney burden of cadmium, while blood cadmium is often considered the best to reveal recent cadmium exposure [33–36]. Urinary total and speciated arsenic datasets including total arsenic, arsenous acid, arsenic acid, arsenobetaine, arsenocholine, dimethylarsinic acid (DMA), and monomethylarsonic acid (MMA) including arsenics—total and speciated—urine (UAS_G), arsenic—total—urine (UTAS_H), arsenics—speciated—urine (UAS_H), arsenic—total—urine (UTAS_I) and speciated arsenics—urine (UAS_I) were used [37–41]. For PAH data including 1-hydroxynapthalene, 2-hydroxynapthalene, 3-hydroxyfluorene, 2-hydroxyfluorene, 1-hydroxyphenanthrene, 1-hydroxypyrene, 2-hydroxyphenanthrene & 3-hydroxyphenanthrene, Polyaromatic Hydrocarbons (PAHs)—Urine (PAH_G), (PAH_H), and (PAH_G) datasets were used [42–44]. The NHANES datasets included utilized urinary samples, which were consistent throughout all PAHs, arsenic, and metals. Therefore, to accurately compare the association with emphysema, we used urinary rather than blood samples [45, 46]. Adults $\geq$ 20 years were included in the study.

The following demographics and data files were used as covariates: gender (male, female), race/ethnicity (Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian, other race multi-racial), marital status (married, widowed, divorced, separated, never married, living with partner), highest level of education achieved (no high school, some high school, high school graduate, some college, college graduate), age (20–44, 45–59, 60 and older), family income to poverty ratio (FIPR) (<1.5, 1.5–3.5, >3.5), BMI (normal weight, underweight, overweight, obese) (underweight: BMI <18.5, normal weight: $18.5 \leq$ BMI ≤ 24.9, overweight: $25.0 \leq$ BMI ≤ 29.9, and obese: $30.0 \leq$ BMI), serum cotinine (below lower limit of detection (LLoD), above LLoD), and alcoholic drink in last 12 months (no, yes), and country of birth (USA, other) [2, 21, 47–55]. Smoking was controlled for through the variable cotinine. Cotinine is used as a determinant of smoking status as it is the main metabolite of nicotine biotransformation [56, 57].

For the non-smoker analysis, the data were censored by eliminating all participants who had smoked more than 100 cigarettes in their lifetime using the NHANES variable "SMQ020—smoked at least 100 cigarettes in life" in the datasets smoking—cigarette use (SMQ_G), (SMQ_H), and (SMQ_I) [64–66]. Once the data had been reduced to include only non-smokers, the urinary concentrations of PAHs, arsenic, and metal species were normalized by the urinary creatine concentration. The data were then categorized into quantiles by each urinary species. The first quantile included those with concentrations of the urinary species that were below the LLOD. Each quantile typically had between 630 and 660 data points depending on which species was being modeled. Demographic data for non-smokers was analyzed but not presented.

R version 3.6.3 was used for the statistical analysis. Data was cleaned and missing responses removed. Concentrations

Table 1 Summary statistics for demographics related to self-reported emphysema

Category	Variable	Sample					Population	
		N total	% total	N with emphysema	% with emphysema		% with emphysema	
Gender	Male	2101	50.3	83	4.0	a	4.2	a
	Female	2080	49.7	153	7.4	b	7.8	b
Race/ethnicity	Mexican American	551	13.2	17	3.1	bc	2.4	bc
	Other Hispanic	448	10.7	22	4.9	abc	4.2	abc
	Non-Hispanic White	1695	40.5	139	8.2	a	7.0	a
	Non-Hispanic Black	868	20.8	45	5.2	b	5.1	ab
	Non-Hispanic Asian	487	11.6	4	0.8	c	0.8	c
	Other race multi-racial	132	3.2	9	6.8	abc	6.7	abc
Marital status	Married	2091	50.0	87	4.2	c	5.4	c
	Widowed	294	7.0	25	8.5	ab	10.1	ab
	Divorced	451	10.8	54	12.0	a	10.9	a
	Separated	123	2.9	11	8.9	abc	6.8	abc
	Never married	856	20.5	41	4.8	bc	4.3	c
	Living with partner	366	8.8	18	4.9	bc	5.0	bc
Highest education level achieved	No high school	373	8.9	21	5.6	ab	7.9	a
	Some high school	495	11.8	35	7.1	a	6.8	a
	High school graduate	904	21.6	62	6.9	a	8.8	a
	Some college	1282	30.7	84	6.6	a	7.2	a
	College graduate	1127	27.0	34	3.0	b	2.5	b
Age	20–44	1840	44.0	71	3.9	b	3.6	c
	45–60	999	23.9	62	6.2	a	6.6	a
	60 and older	1342	32.1	103	7.7	a	9.6	b
Family income to poverty ratio (FIPR)	Less than 1.5	1355	32.4	107	7.9	b	8.3	a
	1.5–3.5	1530	36.6	82	5.4	a	7.0	a
	Over 3.5	1296	31.0	47	3.6	a	3.8	b
BMI	Normal weight	1161	27.8	38	3.3	a	3.3	b
	Underweight	60	1.4	2	3.3	ab	6.3	ab
	Overweight	1362	32.6	72	5.3	a	6.2	a
	Obese	1598	38.2	124	7.8	b	7.7	a
Serum cotinine	Below LLoD	1304	31.2	56	4.3	a	5.0	a
	Above LLoD	2877	68.8	180	6.3	b	6.5	a
Alcoholic drink last 12 months	No	1139	27.2	58	5.1	a	6.3	a
	Yes	3042	72.8	178	5.9	a	5.9	a
Country of birth	USA	2990	71.5	207	6.9	a	6.7	a
	Other	1191	28.5	29	2.4	b	1.9	b

Variables within a category in the columns labeled "% with Emphysema" that are followed by the same letter are not statistically different at the $\alpha = 0.05$ level

of PAHS, arsenic, and metals were normalized with creatinine concentrations [58] and a binary categorical variable was created for self-reported emphysema. Data was used as directly reported by NHANES, concentrations were then normalized and $\log_{10}$ transformed. Programs from the *survey* package and *svyby*, *svymean*, *svyttest*, *svydesign*, and *svyglm* functions were used for data analysis and to calculate pairwise t-tests and logit regression models [59–62]. The function *nhanes_load_data* in the package *RNHANES* was used in downloading and processing data [63].

Table 2 Demographic odds ratios and their 95% confidence intervals (CI) related to self-reported emphysema

Category	Variable	Odds ratio	95% CI	*P* value
Gender	Male			
	Female	0.531	0.280, 1.009	0.0594
Race/ethnicity	Mexican American			
	Other Hispanic	0.771	0.266, 2.235	0.6341
	Non-Hispanic White	1.854	0.809, 4.252	0.1515
	Non-Hispanic Black	**0.119**	**0.038, 0.375**	**0.0007**
	Non-Hispanic Asian	1.545	0.220, 10.834	0.6634
	Other race multi-racial	1.102	0.285, 4.258	0.8888
Marital status	Married			
	Widowed	1.437	0.664, 3.109	0.3620
	Divorced	1.538	0.686, 3.448	0.3013
	Separated	**10.462**	**2.772, 39.479**	**0.0011**
	Never married	1.197	0.418, 3.427	0.7396
	Living with partner	1.432	0.513, 3.998	0.4961
Highest education level achieved	No high school			
	Some high school	0.651	0.249, 1.705	0.3870
	High school graduate	0.577	0.253, 1.314	0.1967
	Some college	**0.348**	**0.141, 0.859**	**0.0266**
	College graduate	0.419	0.109, 1.605	0.2103
Age	20–44			
	45–60	**6.306**	**2.051, 19.384**	**0.0024**
	60 and older	**29.776**	**9.395, 94.370**	**0.0000**
Family income to poverty ratio (FIPR)	Less than 1.5			
	1.5–3.5	0.555	0.245, 1.256	0.1642
	Over 3.5	**0.150**	**0.045, 0.497**	**0.0032**
BMI	Normal weight			
	Underweight	**0.000**	**0.000, 0.000**	**0.0000**
	Overweight	0.753	0.344, 1.651	0.4828
	Obese	0.925	0.439, 1.951	0.8394
Serum cotinine	Below LLoD			
	Above LLoD	**3.532**	**1.524, 8.186**	**0.0050**
Alcoholic drink last 12 months	No			
	Yes	1.584	0.625, 4.019	0.3376
Country of birth	USA			
	Other	**0.136**	**0.045, 0.415**	**0.0010**

Odds ratios which are bolded are statistically different at the $\alpha = 0.05$ level

LLOD lower limit of detection

Results

Among three NHANES datasets, 2,026 participants were included in reduced sample. Several significant demographic findings were determined among those who identified as being diagnosed with emphysema in the past (Tables 1 and 2). Marital status of separated, ages 45–59 and 60 years and older, and serum cotinine above the LLOD were seen to have an increased odds of self-reported emphysema, as seen in Table 2. Race of Non-Hispanic Black, some college, FIPR over 3.5, underweight BMI, and country of birth outside USA were found to have an inverse relationship with self-reported emphysema.

Figures 1, 2, and 3 display the $\log_{10}$ and median normalized concentration distributions of urinary metals, arsenic, and PAHs in the sample population. For all the species studied, the concentration distributions were non-normal even in the transformed space with high concentration outliers. For some of the species, e.g., 2-hydroxyfluorene, the distributions were bimodal.

All PAHs analyzed (Table 3), 1-hydroxynaphthalene, 2-hydroxynaphthalene, 3-hydroxyfluorene,

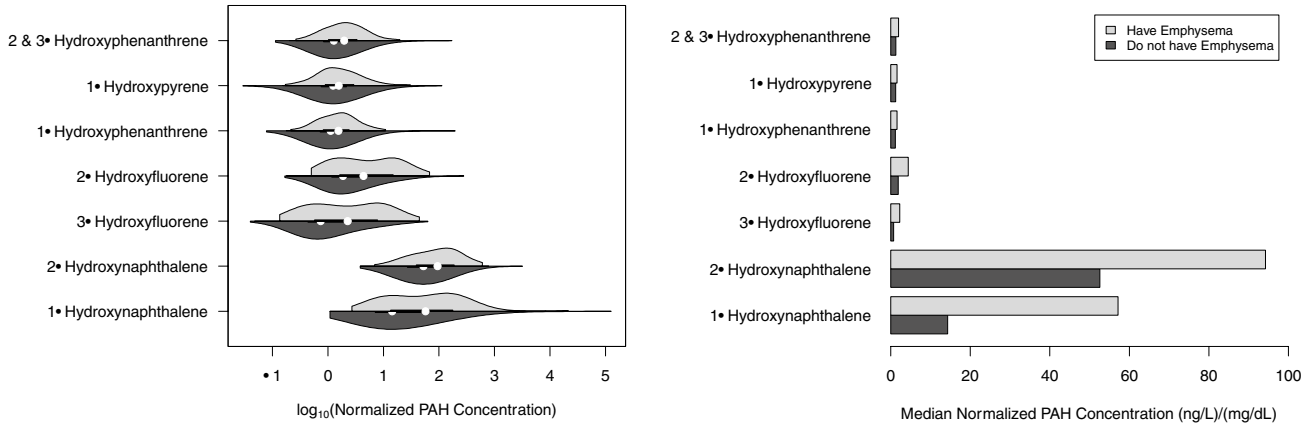

Fig. 1 Concentration distribution (left) and dose–response plot (right) of participants with self-reported emphysema for seven forms of PAH

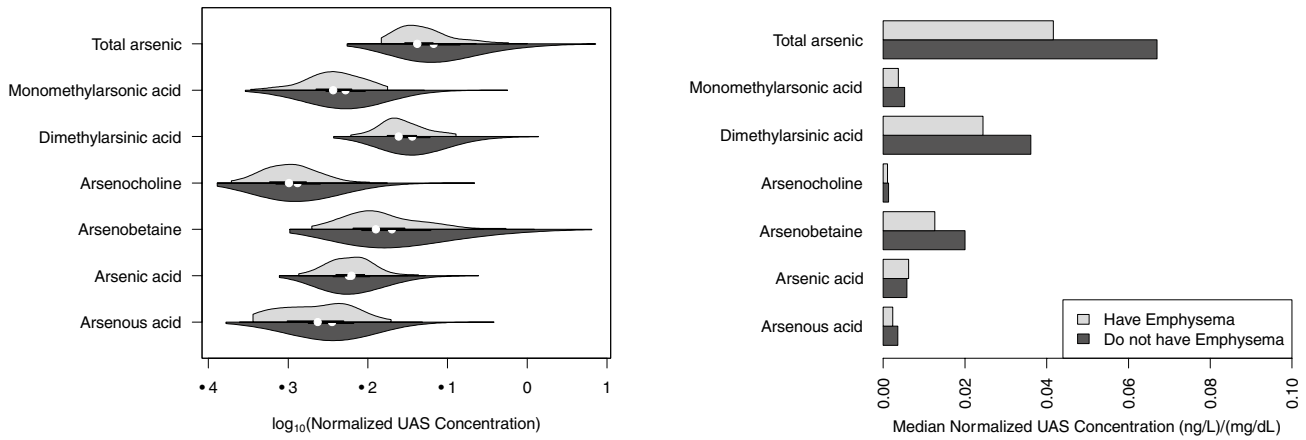

Fig. 2 Concentration distribution (left) and dose–response plot (right) of participants with self-reported emphysema for seven forms of urinary arsenic

2-hydroxyfluorene, 1-hydroxypyrene, and 2 & 3-hydroxyphenanthrene, with the exception of 1-hydroxyphenanthrene, were found to have an increased odds of self-reported emphysema. Therefore, there was an increased odds of self-reported emphysema given the exposure to 1-hydroxynaphthalene, 2-hydroxynaphthalene, 3-hydroxyfluorene, 2-hydroxyfluorene, 1-hydroxypyrene, and 2 & 3-hydroxyphenanthrene, compared to the odds of self-reported emphysema occurring in the absence of these PAH exposures. Among urinary arsenic species (Table 4), urinary arsenobetaine and total urinary arsenic had significant inverse associations with self-reported emphysema. Urinary arsenobetaine and total urinary arsenic exposure revealed reduced odds of self-reported emphysema compared with no exposure to these species. Among urinary metals (Table 5), cadmium and cesium were both found to have an increased odds of self-reported emphysema. There was increased odds of self-reported emphysema with exposure to cadmium and cesium compared to the odds of self-reported emphysema with no exposure. No other urinary arsenic or metal species were found to have significant associations with self-reported emphysema.

Of the PAH compounds studied in non-smokers (Table 6), only the 2nd and 4th quartiles of 2-hydroxynaphthalene had odds ratios that were statistically significant (OR 20.73, 95% CI 1.59–269.73 and OR 42.42, 95% CI 1.25–1435.96 respectively). On the other hand, only the 3rd quartile of 1-hydroxyphenanthrene had odds ratios that were statistically less than one.

Of the urinary arsenic compounds studied (Table 7), both arsenocholine and total urinary arsenic had odds ratios that were significantly different than one. In both cases, the odds ratios were very large. This is most likely due to the few respondents with self-reported emphysema and a low measured concentration of the arsenic species, i.e., the data for the 1st quartile (see Fig. 2) were entirely due to those who did not report having emphysema.

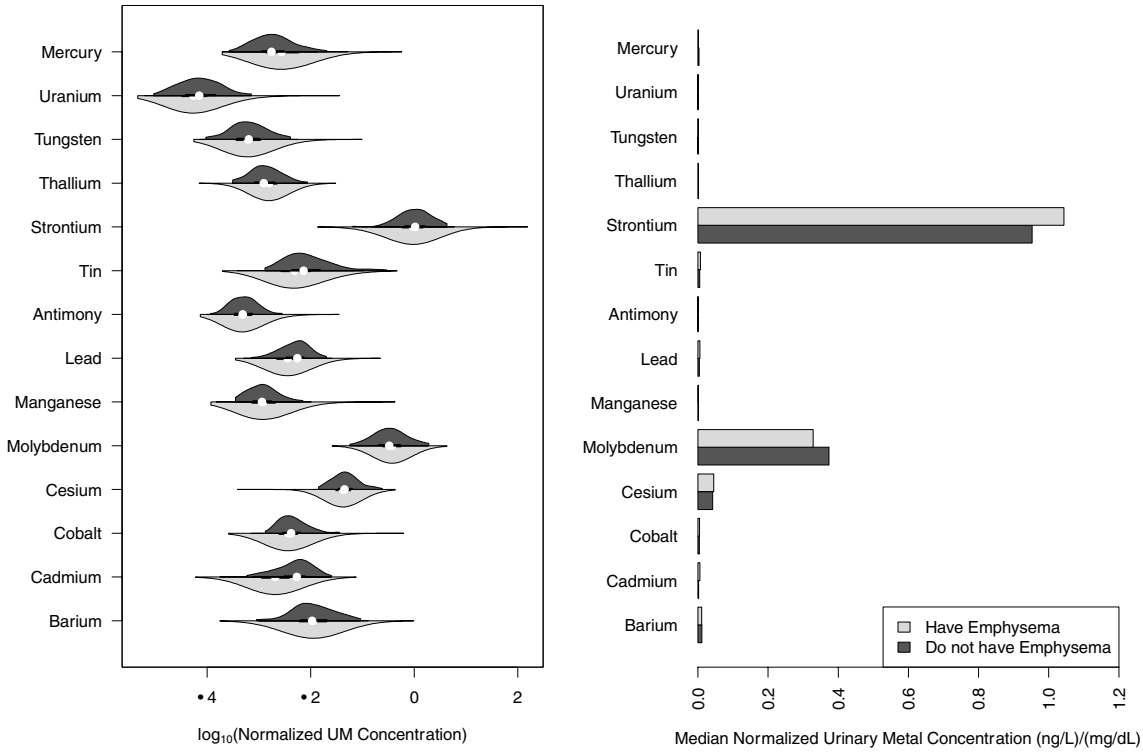

Fig. 3 Concentration distribution (left) and dose–response plot (right) of participants with self-reported emphysema for 14 forms of urinary metals

Table 3 Urinary PAHs adjusted odds ratios and their 95% confidence intervals (CI) related to self-reported emphysema

Urinary PAH compound	Odds ratio	95% CI	*P* value
1-Hydroxynaphthalene	**1.637**	**1.141, 2.349**	**0.010**
2-Hydroxynaphthalene	**3.438**	**1.484, 7.963**	**0.006**
3-Hydroxyfluorene	**2.780**	**1.399, 5.523**	**0.005**
2-Hydroxyfluorene	**3.457**	**1.586, 7.538**	**0.003**
1-Hydroxyphenanthrene	3.067	0.992, 9.482	0.058
1-Hydroxypyrene	**3.010**	**1.632, 5.552**	**0.001**
2 & 3-Hydroxyphenanthrene	**4.804**	**1.657, 13.929**	**0.006**

Odds ratios which are bolded are statistically different at the $\alpha = 0.05$ level. Adjusted for gender, race/ethnicity, education level, marital status, age, FIPR, BMI, cotinine level, alcohol consumption and country of birth in the multifactor logit regression

Of the 14 urinary metal compounds studied (Table 8), only cesium (all three quartiles) and the 3rd and 4th quartiles of tin had odds ratios that were statistically significantly greater than one. Conversely, cadmium, manganese, antimony, thallium, and tungsten all had odds ratios for at least one quartile that was significantly smaller than one.

Discussion

This study found an association among PAHs and self-reported emphysema, with six of seven PAHs studied having a significant positive association ($P < 0.05$) including 1-hydroxynaphthalene, 2-hydroxynaphthalene, 3-hydroxyfluorene, 2-hydroxyfluorene, 1-hydroxypyrene, and 2 & 3-hydroxyphenanthrene. Shiue [8] analyzed the association among PAHs and emphysema using NHANES 2011–2012 data. Significant positive associations between emphysema and 2-hydroxyfluorene and 3-hydroxyfluorene were found; concordant findings were found among 2-hydroxyfluorene, 3-hydroxyfluorene, and 1-hydroxyphenanthrene. No association was found among the other forms of PAHs. Among those with self-reported emphysema who were non-smokers, there was increased odds among some quartiles with 2-hydroxynaphthalene, similar to the original group, and a protective factor for 1-hydroxyphenanthrene. The NHANES datasets, used in this study, did not include 9-hydroxyfluorene and 4-hydroxyphenanthrene which were included in the dataset in Shiue's study [8]. This study did, however, find a positive association among 1-hydroxynaphthalene, 2-hydroxynaphthalene, 1-hydroxypyrene, and 2 &

Table 4 Urinary speciated arsenic adjusted odds ratios and their 95% confidence intervals (CI) related to self-reported emphysema

Urinary arsenic compound	Odds ratio	95% CI	*P* value
Urinary arsenous acid	0.819	0.450, 1.489	0.516
Urinary arsenic acid	1.103	0.474, 2.565	0.821
Urinary arsenobetaine	**0.533**	**0.309, 0.921**	**0.029**
Urinary arsenocholine	0.759	0.391, 1.472	0.418
Urinary dimethylarsinic acid (DMA)	0.457	0.152, 1.373	0.170
Urinary monomethylarsonic acid (MMA)	0.672	0.244, 1.849	0.446
Total urinary arsenic	**0.400**	**0.182, 0.878**	**0.027**

Odds ratios which are bolded are statistically different at the $\alpha = 0.05$ level. Adjusted for gender, race/ethnicity, education level, marital status, age, FIPR, BMI, cotinine level, alcohol consumption and country of birth in the multifactor logit regression

Table 5 Urinary metals adjusted odds ratios and their 95% confidence intervals (CI) related to self-reported emphysema

Urinary metal compound	Odds ratio	95% CI	*P* value
Barium	0.759	0.443, 1.299	0.319
Cadmium	**7.440**	**2.095, 26.427**	**0.003**
Cobalt	2.100	0.825, 5.348	0.126
Cesium	**9.045**	**2.083, 39.283**	**0.005**
Molybdenum	0.582	0.191, 1.778	0.347
Manganese	0.573	0.246, 1.335	0.203
Lead	1.111	0.501, 2.463	0.797
Antimony	0.720	0.364, 1.425	0.350
Tin	1.005	0.575, 1.757	0.986
Strontium	1.726	0.809, 3.684	0.165
Thallium	2.804	0.669, 11.754	0.165
Tungsten	1.019	0.418, 2.484	0.968
Uranium	0.915	0.442, 1.896	0.812
Mercury	0.597	0.331, 1.075	0.092

Odds ratios which are bolded are statistically different at the $\alpha = 0.05$ level. Adjusted for gender, race/ethnicity, education level, marital status, age, FIPR, BMI, cotinine level, alcohol consumption and country of birth in the multifactor logit regression

3-hydroxyphenanthrene which were not significant in Shiue [8].

In mice studies, co-exposure to tobacco smoke and arsenite significantly induced emphysema-like lesions, characterized by enlarged alveolar spaces and destruction of alveolar structure [67]. Arsenic exposure in humans has been correlated with increased incidence of chronic bronchitis, chronic cough, shortness of breath and obstructive lung diseases [68–71]. Arsenobetaine and arsenocholine, organic forms of speciated arsenic, are the major forms of arsenic in most fish, which is non-toxic and not metabolized. The findings in this study are likely attributed to consumption of seafood rather than inorganic forms of arsenic, which are the main forms in drinking water [72]. In contrast, arsenocholine and total urinary arsenic had significant increased odds for emphysema in the non-smoker group. A previous study [73] utilizing 2003–2006 NHANES data found no association in low or high quintiles between organic arsenic and emphysema.

Cadmium has been linked to emphysema most commonly due to smoking [74]. Mannino et al. [75] determined a significant association between reduced forced expiratory volumes in 1 s (FEV_1) and cadmium in current and former smokers, but not in never smokers. However, that study only evaluated COPD, rather than emphysema specifically. This study found a positive association among urinary cadmium and self-reported emphysema using NHANES 2011–2016 data. It is suggested that prolonged exposure to cadmium contributes to airway inflammation likely due to the induction of oxidative stress, cadherin activity, and impaired DNA repair and apoptosis [76–82]. In contrast to the overall group, the non-smoker group was found to have an inverse association with emphysema among multiple quartiles. This is likely due to alterative sources of cadmium as compared to smokers exposed to cadmium in cigarettes.

The association among cesium and emphysema has been relatively unreported in literature [19]. Almulla et al. [83] determined an association among cesium levels and immune biomarkers in immune inflammatory pathways. In studies from the 1986 Chernobyl disaster, radioactive Cesium 137 was linked to pediatric obstructive and restrictive lung function. This study found a statistically significant association with cesium among all participants (OR 9.045, 95% CI 2.083–39.283) and in the 2nd, 3rd, and 4th quantiles among non-smokers.

Table 6 Urinary PAHs adjusted odds ratios and their 95% confidence intervals (CI), and associated *P* values related to self-reported emphysema in non-smokers

Urinary PAH compound	Quantile	Odds ratio	95% CI	*P* value
1-Hydroxynaphthalene	2nd	4.26	0.36, 50.51	0.2306
	3rd	0.79	0.03, 22.25	0.8850
	4th	1.72	0.14, 21.09	0.6570
2-Hydroxynaphthalene	2nd	**20.73**	**1.59, 269.73**	**0.0181**
	3rd	0.40	0.02, 9.75	0.5584
	4th	**42.42**	**1.25, 1435.96**	**0.0323**
3-Hydroxyfluorene	2nd	1.83	0.25, 13.25	0.5306
	3rd	2.44	0.28, 21.56	0.4006
	4th	0.66	0.04, 10.04	0.7544
2-Hydroxyfluorene	2nd	0.08	0.00, 1.65	0.0893
	3rd	0.57	0.10, 3.39	0.5158
	4th	0.19	0.02, 2.13	0.1627
1-Hydroxyphenanthrene	2nd	6.00	0.47, 75.79	0.1497
	3rd	**0.00**	**0.00, 0.00**	**0.0000**
	4th	1.11	0.16, 7.77	0.9120
1-Hydroxypyrene	2nd	2.57	0.09, 71.88	0.5594
	3rd	8.90	0.47, 167.81	0.1293
	4th	1.39	0.06, 35.00	0.8323
2 & 3-Hydroxyphenanthrene	2nd	4.26	0.36, 50.51	0.2306
	3rd	0.79	0.03, 22.25	0.8850
	4th	1.72	0.14, 21.09	0.6570

Odds ratios which are bolded are statistically different from one at the $\alpha = 0.05$ level. Adjusted for gender, race/ethnicity, education level, marital status, age, FIPR, BMI, and alcohol consumption in the multifactor logit regression

Specific to the non-smoker group, some quantiles of tin were associated with increased odds of self-reported emphysema, while some quantiles of manganese, lead, antimony, thallium, and tungsten were associated with an inverse relationship with self-reported emphysema. Heavy metals have commonly been linked to lung diseases such as lung cancer through smoking. The protective factor seen with several metals in non-smokers suggests that the smoking itself, rather than the metal may be causing the emphysema in these patients [84].

Among demographic data, participants with self-reported emphysema were more likely to be separated, ages 45–60 or 60 years and older, and have a serum cotinine above the LLOD. Buendia-Roldan et al. [85] determined that those with subclinical pulmonary emphysema were older, smoker males, and had a low BMI. Those with emphysema also had a higher mean age. There was no association with male gender, and underweight BMI (< 18.5) was determined to be a protective factor. Buendia-Roldan et al. [85] found that the average BMI of the emphysema group was 24, which is considered normal, and 27 in the control group, which we classified as overweight. Among protective factors, Non-Hispanic Black, some college, FIPR > 3.5, and birth outside the US were protective factors. Non-Hispanic Black was also found to be a protective factor for self-reported emphysema. African Americans had a higher odds ($P \leq 0.0001$) of not having a prior COPD diagnosis despite having airflow obstruction consistent with COPD compared to Non-Hispanic White participants. This suggests that African Americans may be at higher risk to getting forms COPD, such as emphysema, at a younger age and with fewer pack years, and are more likely to be undiagnosed [86].

Limitations

This study was conducted using three NHANES datasets. The data collection was conducted by the Centers for

Table 7 Urinary speciated arsenic adjusted odds ratios and their 95% confidence intervals (CI), and associated *P* values related to self-reported emphysema in non-smokers

Urinary arsenic compound	Quantile	Odds ratio	95% CI	*P* value
Arsenous acid	2nd	4.08	0.63, 26.39	0.1252
	3rd	2.03	0.14, 29.57	0.5856
	4th	1.89	0.13, 27.46	0.6232
Arsenic acid	2nd	0.50	0.02, 14.23	0.6702
	3rd	1.43	0.09, 23.74	0.7935
	4th	2.12	0.20, 22.21	0.5110
Arsenobetaine	2nd	2.60	0.16, 43.08	0.4838
	3rd	9.87	0.60, 162.03	0.0964
	4th	0.61	0.03, 13.04	0.7418
Arsenocholine	2nd	$\mathbf{1.34\times10^{9}}$	$\mathbf{2.17\times10^{8}, 8.30\times10^{9}}$	**0.0000**
	3rd	$\mathbf{4.10\times10^{8}}$	$\mathbf{4.76\times10^{7}, 3.53\times10^{9}}$	**0.0000**
	4th	$\mathbf{7.64\times10^{7}}$	$\mathbf{6.31\times10^{6}, 9.26\times10^{8}}$	**0.0000**
Dimethylarsinic acid (DMA)	2nd	0.09	0.00, 3.41	0.1740
	3rd	2.21	0.14, 34.60	0.5514
	4th	1.14	0.08, 16.47	0.9205
Monomethylarsonic acid (MMA)	2nd	4.79	0.44, 52.44	0.1811
	3rd	0.65	0.07, 6.16	0.6889
	4th	0.89	0.07, 11.75	0.9243
Total urinary arsenic	2nd	$\mathbf{1.51\times10^{9}}$	$\mathbf{2.66\times10^{7}, 8.59\times10^{10}}$	**0.0000**
	3rd	$\mathbf{3.42\times10^{8}}$	$\mathbf{1.16\times10^{7}, 1.01\times10^{10}}$	**0.0000**
	4th	$\mathbf{7.23\times10^{7}}$	$\mathbf{7.22\times10^{6}, 7.23\times10^{8}}$	**0.0000**

Odds ratios which are bolded are statistically different at the $\alpha = 0.05$ level. Adjusted for gender, race/ethnicity, education level, marital status, age, FIPR, BMI, and alcohol consumption in the multifactor logit regression

Disease Control and Prevention (CDC) and the methods and datapoints could not be changed. Therefore, the diagnosis of emphysema was self-reported, through a questionnaire asking participants if they had been diagnosed with emphysema, rather than through spirometry or more definitive diagnostic modalities. In addition, urinary PAH, arsenic, and metal concentrations were used to assess the association with self-reported emphysema as this was included in the NHANES datasets, rather than blood samples. No data on individual participants' exposures to PAHs or urinary metals was included in the NHANES dataset. Therefore, this study was unable to link potential sources of exposure that could have resulted in increased concentrations of certain PAHs or metals. Furthermore, this is a cross-sectional study, and causality cannot be determined.

Conclusion

Six forms of urinary PAHs including 1-hydroxynaphthalene, 2-hydroxynaphthalene, 3-hydroxyfluorene, 2-hydroxyfluorene, 1-hydroxypyrene, and 2 & 3-hydroxyphenanthrene and two forms of urinary metals, cadmium and cesium, were linked to an increased odds of self-reported emphysema in the US adult population. Urinary arsenobetaine and total urinary arsenic were found to be inversely associated with self-reported emphysema. Among non-smokers, quantiles of 2-hydroxynaphthalene, arsenocholine, total urinary arsenic, cesium, and tin were associated with increased odds of self-reported emphysema. Quantiles of 1-hydroxyphenanthrene, cadmium, manganese, lead, antimony, thallium, and tungsten were associated with protective factors for self-reported emphysema in

Table 8 Urinary metals adjusted odds ratios and their 95% confidence intervals (CI), and associated *P* values related to self-reported emphysema in non-smokers

Urinary metal compound	Quantile	Odds ratio	95% CI	*P* value
Barium	2nd	0.6044	−2.0842, 3.2930	0.6432
	3rd	0.5099	−1.5994, 2.6191	0.6185
	4th	0.4205	−2.1042, 2.9452	0.7313
Cadmium	2nd	**−1.9030**	**−3.7251, −0.0808**	**0.0354**
	3rd	−3.6018	−7.9872, 0.7836	0.0951
	4th	**−2.7914**	**−5.1833, −0.3995**	**0.0194**
Cobalt	2nd	−2.0070	−5.6726, 1.6586	0.2619
	3rd	0.8083	−2.3831, 3.9997	0.6019
	4th	0.8265	−1.6376, 3.2906	0.4901
Cesium	2nd	**17.2636**	**15.5607, 18.9665**	**0.0000**
	3rd	**17.3201**	**14.9887, 19.6514**	**0.0000**
	4th	**18.3938**	**16.3860, 20.4016**	**0.0000**
Molybdenum	2nd	−0.9380	−3.1272, 1.2512	0.3788
	3rd	−3.0152	−6.5729, 0.5425	0.0853
	4th	−0.0115	−2.7437, 2.7207	0.9931
Manganese	2nd	1.9969	−0.3136, 4.3073	0.0795
	3rd	**−17.9040**	**−20.7405, −15.0676**	**0.0000**
	4th	1.2320	−1.0301, 3.4941	0.2644
Lead	2nd	**−3.1348**	**−5.6592, −0.6104**	**0.0132**
	3rd	−1.3532	−3.4696, 0.7633	0.1913
	4th	−1.4695	−4.4172, 1.4781	0.3065
Antimony	2nd	**−17.2520**	**−19.5662, −14.9378**	**0.0000**
	3rd	0.0216	−3.2226, 3.2658	0.9890
	4th	1.5005	−0.6321, 3.6331	0.1512
Tin	2nd	−0.9605	−3.2937, 1.3727	0.3976
	3rd	**19.0696**	**16.7682, 21.3710**	**0.0000**
	4th	**19.0489**	**16.9892, 21.1087**	**0.0000**
Strontium	2nd	−0.8497	−3.5555, 1.8561	0.5181
	3rd	−0.6697	−3.3098, 1.9703	0.6013
	4th	−0.4839	−2.5171, 1.5493	0.6239
Thallium	2nd	**−17.1372**	**−19.3024, −14.9719**	**0.0000**
	3rd	1.7230	−1.0411, 4.4870	0.2024
	4th	1.5814	−1.2104, 4.3731	0.2460
Tungsten	2nd	**−18.8402**	**−22.2743, −15.4060**	**0.0000**
	3rd	0.3131	−2.6107, 3.2370	0.8252
	4th	2.3977	−1.9757, 6.7711	0.2613
Uranium	2nd	1.3097	−1.5171, 4.1366	0.3415
	3rd	0.4883	−2.9551, 3.9317	0.7700
	4th	0.7103	−2.3097, 3.7302	0.6280
Mercury	2nd	0.9631	−2.2328, 4.1591	0.5350
	3rd	−0.5402	−2.9095, 1.8291	0.6385
	4th	−1.1014	−3.6273, 1.4244	0.3704

Odds ratios which are bolded are statistically different from one at the $\alpha = 0.05$ level. Adjusted for gender, race/ethnicity, education level, marital status, age, FIPR, BMI, and alcohol consumption in the multifactor logit regression

non-smokers. Further studies are needed to determine the causation for this link between urinary PAHs, arsenic, and metals and their contribution to lung dysfunction in emphysema.

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Data Availability The datasets analyzed during the current study are available in the NHANES repository provided by the CDC to the public.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical Approval 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.

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