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RESEARCH ARTICLE

Association between environmental toxic metals, arsenic and polycyclic aromatic hydrocarbons and chronic obstructive pulmonary disease in the US adult population

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Abstract

Associations between environmental metals and chemicals and adverse human health effects have emerged recently, but the links among environmental metals and respiratory diseases are less studied. The aim of this study was to assess 14 urinary metals (cadmium, barium, cobalt, molybdenum, mercury, cesium, manganese, antimony, lead, tin, strontium, tungsten, thallium, and uranium), seven species of arsenic (arsenous acid, arsenic acid, arsenobetaine, arsenocholine, dimethylarsinic acid, monomethylarsonic acid, and total arsenic) and seven polycyclic aromatic hydrocarbon (PAH) (1-hydroxynaphthalene, 2-hydroxynaphthalene, 3-hydroxyfluorene, 2-hydroxyfluorene, 1-hydroxyphenanthrene, 1-hydroxypyrene, 2 & 3-hydroxyphenanthrene) compounds' concentrations in urine and the correlation with chronic obstructive pulmonary disease (COPD) in the adult US population. A cross-sectional analysis using the 2013–2014 and 2015–2016 National Health and Nutrition Examination Survey (NHANES) dataset was conducted. Self-questionnaires related to COPD criteria were used to identify the COPD cases. The correlation between urinary metals and PAH compounds and COPD was calculated. The total study population analyzed included 2885 adults aged 20 years and older. Seven types of urinary PAHs including 1-hydroxynaphthalene [odds ratio (OR): 1.832, 95% confidence interval (CI): 1.210, 2.775], 2-hydroxynaphthalene [OR: 3.361, 95% CI: 1.519, 7.440], 3-hydroxyfluorene [OR: 2.641, 95% CI: 1.381, 5.053], 2-hydroxyfluorene [OR: 3.628, 95% CI: 1.754, 7.506], 1-hydroxyphenanthrene [OR: 2.864, 95% CI: 1.307, 6.277], 1-hydroxypyrene [OR: 4.949, 95% CI: 2.540, 9.643] and 2 & 3-hydroxyphenanthrene [OR: 3.487, 95% CI: 1.382, 8.795] were positively associated with COPD. Urinary cadmium [OR: 12.382, 95% CI: 4.459, 34.383] and tin [OR: 1.743, 95% CI: 1.189, 2.555] showed positive associations with increased odds of COPD. The other types of urinary metals were not associated with COPD. The study observed that urinary PAHs, cadmium, and tin are significantly associated with COPD.

Keywords Polycyclic aromatic hydrocarbons · Cadmium · Tin · COPD · NHANES

Introduction

Exposure to environmental chemicals and metals causing adverse health effects is a major concern leading to numerous conditions including hypertension, cardiovascular disease, sleep disorders, decrease in cognitive function, and allergies (Shiue 2013a, b, c, 2014a, b, 2015a, b, c, d, 2017; Rahman et al. 2020a, b, 2021a, b, c, d). Exposure to heavy metals has been associated with chronic diseases likely due to oxidative stress and inflammation in the lungs causing tissue destruction (Rokadia and Agarwal 2013). Among occupational respiratory diseases, there has been a shift from exposure to mineral dust such as coal and silica in the twentieth century to low-dose allergens and irritants. This has led to a change in respiratory diseases from pneumonoconiosis to occupational asthma. Approximately 15% of all chronic obstructive pulmonary disease (COPD) cases in western societies have been attributed to dust, fumes, vapor, or gas (De Matteis et al. 2017).

The incomplete combustion of coal, gas, and oil, which contain carbon, are sources of polycyclic aromatic

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hydrocarbons (PAHs). PAHs, composed of primarily hydrogen and carbon atoms, contain two or more aromatic rings and are categorized as environmentally harmful pollutants (Honda and Suzuki 2020; Kataria et al. 2015). Industrial activity and engine-driven vehicles on the roads are significant sources causing PAH emissions to contaminate the air. Exposure to polluted air containing PAHs can cause various diseases in humans (Błaszczyk et al. 2017; Liu et al. 2015). The major route of exposure to PAHs is via the respiratory system; therefore, the risk of developing diseases such as respiratory and cardiovascular diseases is common (Perez-Padilla et al. 2010; World Health Organization (WHO) 2018).

Cadmium is considered one of the toxic non-essential metals that can cause adverse effects due to exposure in humans and other living species. Cadmium is a naturally occurring pollutant in the environment resulting from industrial and agricultural procedures. Primary cadmium exposure routes include consumption of contaminated food and water, and inhalation from smoking. Studies show that exposure to cadmium has been linked with kidney, lung, breast, pancreas, prostate, and nasopharynx cancers (Genchi et al. 2020; McElroy et al. 2006; Elghany et al. 1990). Furthermore, tin is a naturally occurring metal. The primary exposure of tin comes from the burning of fossil fuels, waste incineration, and production of tin, organotins, iron, steel, and non-ferrous metals. Inorganic tin accumulates in the lungs because of a lack of absorption and insolubility, leading to the lungs being the target organ (Cima 2011). Tin has been linked to several adverse health effects including interstitial pneumonia, neurotoxicity, nausea, vomiting, diarrhea, abdominal pain, headaches, skin rashes, high blood pressure, palpitations, fatigue, shortness of breath, asthma, and insomnia (Homma et al. 2003; Nath 2008; Shiue 2014b, 2015d; Cima 2011).

COPD is a preventable disease characterized by persistent respiratory symptoms and airflow limitation due to airway and alveolar abnormalities. This is caused by both small airway disease and parenchymal destruction (emphysema). Chronic inflammation leads to narrowing of small airways and the destruction of lung parenchyma which decreases elastic recoil and causes the airways to not stay patent on exhalation. The terms emphysema and chronic bronchitis are no longer used in the definition of COPD; however, emphysema refers to the destruction of lung alveoli, and chronic bronchitis is the presence of cough or sputum for at least 3 consecutive months over the period of 2 years (Global Initiative for Chronic Obstructive Lung Disease 2020). Asthma, rhinitis, COPD, bronchiectasis, occupational lung disease, pulmonary hypertension, pulmonary interstitial diseases, and sleep disordered breathing are considered major chronic respiratory diseases (Bousquet and Kaltaev 2007). COPD is considered the most common respiratory disease. Approximately 10% of the population 40 years and older suffer from COPD worldwide (Bousquet et al. 2010). Globally, COPD is one of the leading causes of morbidity and mortality. Respiratory symptoms, persistent limitations in airflow, and frequent exacerbation symptoms are key features of COPD in addition to shortness of breath, wheezing, and cough (Lozano et al. 2012; Asia Pacific COPD Roundtable Group 2005; Donaldson et al. 2002; Seemungal et al. 1998). Intermittent exacerbations of COPD modify the disease trajectory leading to a decreased quality of life by reducing lung function and functional capacity (Donaldson et al. 2002; Seemungal et al. 1998).

Smoking is considered one of the primary risk factors for COPD; however, environmental factors and occupational exposure increase the risk of COPD (Eisner et al. 2010; Blanc and Torén 2007). Smoking cessation and supplemental oxygen are the only two available treatments for patients with COPD to improve mortality (Mannino et al. 2002; Halbert et al. 2003; Murray and Lopez 1997; Anthonisen et al. 1994). Currently, there are no studies showing that existing medications for COPD, including long-acting bronchodilators and inhaled corticosteroids, modify the long-term degradation of lung function (Burge et al. 2000; Anthonisen et al. 1994; Pauwels et al. 1999; Vestbo et al. 1999; Tashkin et al. 2008; Decramer et al. 2009; Celli et al. 2008; Global Initiative for Chronic Obstructive Lung Diseases 2020). Other contributing factors associated with COPD, such as environmental exposure and occupational exposure, should be reduced.

The purpose of this study is to analyze the effects of 14 forms of urinary metals including barium, cadmium, cobalt, cesium, molybdenum, manganese, lead, antimony, tin, strontium, thallium, tungsten, uranium, and mercury, seven forms of urinary speciated arsenic, and seven types of urinary PAHs, and the association with the risk of COPD in the adult United States (US) population.

Methods

Study population

Data for this study was taken from the National Health and Nutrition Examination Survey (NHANES), a long-standing study using physical exams and interviews to determine the health and nutritional status of adults and children in the USA. The survey sample is designed to represent the US population of all ages; with selected subgroups (e.g. people over 60 and certain race/ethnicities) oversampled to ensure reliable statistics. The survey examines a nationally representative sample of about 5000 people each year located in counties across the country, 15 of which are visited each year. Only adults aged ≥ 20 years were included in our analysis below (National Center for Health Statistics [NCHS] 2017a, b).

Metals, arsenic, and PAH assessment

As in Shiue (2015d), several urinary metals, arsenic, and PAHs were included in the same study in order to compare and contrast the effect of each potential exposure with depression. The metals, arsenic species, and PAHs were selected according to what was provided in the NHANES datasets. The 2013–2014 and 2015–2016 NHANES datasets: Polycyclic Aromatic Hydrocarbons (PAH) — Urine (PAH_I), Metals — Urine (UM_I), Mercury — Urine (UHG_I), Arsenic — Total — Urine (UTAS_I), and Speciated Arsenics — Urine (UAS_I) were used for data covering urinary barium, cadmium, cesium, cobalt, manganese, molybdenum, lead, antimony, strontium, thallium, tin, tungsten, uranium, mercury, total arsenic, arsenous acid, arsenic acid, arsenobetaine, arsenocholine, dimethylarsinic acid (DMA), monomethylarsonic acid (MMA), 1-hydroxynapthalene, 2-hydroxynapthalene, 3-hydroxyfluorene, 2-hydroxyfluorene, 1-hydroxyphenanthrene, 1-hydroxypyrene, 2-hydroxyphenanthrene & 3-hydroxyphenanthrene concentrations (CDC 2020b, 2018a, b, c, d). The urinary species were normalized with the creatinine concentration using the dataset Albumin & Creatinine — Urine (ALB_CR_J) (CDC 2017a). Details of the analytical methods and detection limits for the various compounds are provided in the CDC references. Metals, arsenic, and PAHs were all included in this analysis to evaluate the effect of each form while comparing the effects as in previous literature (Shiue 2015b, d; 2016).

COPD assessment

COPD was determined using variable MCQ160o in the 2013–2014 and 2015–2016 Medical Conditions (MCQ_I) datasets. Questions were asked via questionnaires using a Computer-Assisted Personal Interview (CAPI) system in the home. The questionnaire asked participants "Has a doctor or other health professional ever told you that you had COPD?" (CDC 2017b). This response was used to define which patients had COPD in our study.

Covariates

Datasets for covariates came from the NHANES data files ALQ_I — Alcohol consumption, BMX_I — Body mass index, and DEMO_I — Demographic data, and COT_I — Serum cotinine (CDC 2018e, 2017c, d, 2019). Among demographic categories, the following variables were included: 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 educational level achieved (no high school, some high school, high school graduate, some college, college graduate), age (20–44 years, 45–60 years, 60 years and older), family income to poverty ratio (FIPR) (less than 1.5, 1.5–3.5, over 3.5), BMI was converted into a four-level categorical variable with underweight, BMI < 18.5; normal weight, BMI $\geq 18.5, < 24.9$; overweight, BMI $\geq 24.9, < 30.0$; and obese, BMI ≥ 30.0 per the CDC definitions, serum cotinine (below lower limit of detection, above lower limit of detection), alcoholic drink last 12 months (no, yes), and country of birth (USA, other) (CDC 2020a; Rahman et al. 2021a, e). NHANES was approved by the Research Ethics Review Board of the NCHS. This study was exempt from additional review by an institutional review board, as this is public-use data.

Statistical analysis

Data was first cleaned by removing missing responses, categorizing the continuous covariate variables, normalizing the concentrations of metals and PAHs with the creatinine concentration, and creating the binary categorical variable for COPD based on the binary NHANES variable M160o. The missing values for demographic categories, BMI, serum cotinine, alcohol use, and country of birth were removed, and the resulting data was used for all modeling. Missing responses for PAH and urinary metals were removed from the dataset before creation of the logit regression model. Values provided in NHANES data were used directly; the concentrations were normalized using the urinary creatinine concentration and then $\log_{10}$ transformed.

R version 3.6.3 was used for the statistical analysis with programs from the *survey* package and 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 (R Core Team 2020; Lumley 2004, 2010, 2020). Other 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 and store as *.csv files (Susmann 2016).

The assessment of correlation between COPD and the environmental chemicals was conducted using a multi-factor, weighted logit regression model. Logit regression was selected as the appropriate statistical modeling tool since the response factor (absence/presence of COPD) was a binary, categorical variable. The model included one of the environmental chemicals and selected demographic and lifestyle covariates (see Table 2 for the covariates and the categories used in the

analysis). This resulted in a regression model with 26 model parameters in which the absence/presence of COPD was modeled. The weighting factors for the model were taken from the NHANES dataset directly. The modeling results are given only for the environmental chemicals.

The COPD — covariate correlation summary given in Table 2 was done for the responses used in the COPD — PAH correlation summary considered later. Similar covariate correlation summaries were done (but not reported) for in the other environmental chemicals. There were slight differences in the numerical results but none that was significant.

Results

A total of N = 2885 participants were included in the study, 49.6% male and 50.4% female. About 4.0% of males and 2.9% of females were determined to have COPD in our sample (Table 1). Among race/ethnicity, non-Hispanic White had the highest percent with COPD at 6.2%; most participants with COPD were categorized as widowed, divorced, or separated, and were in the age group of 60 years and older. Higher percentages of participants with COPD had lower FIPR, and serum cotinine above the lower limit of detection and consumed alcohol. The factors determined significant for an increased odds of COPD were participants who were non-Hispanic White, ages 45–60 and 60 years and older, and a serum cotinine above the lower limit of detection. Factors that were significant for reducing the odds of COPD included living with a partner, and a FIPR of 1.5–3.5 and over 3.5 (Table 2).

Figure 1 reveals a visibly higher concentration of both 2-hydroxynaphthalene and 1-hydroxynaphthalene in those with COPD compared to those who did not have COPD. Among arsenic species, Fig. 2 shows total arsenic, MMA, DMA, arsenobetaine, and arsenous acid which has concentrations that are lower in those with COPD. Among the metals, Fig. 3 shows strontium and cesium have higher concentrations in those with COPD, while molybdenum has a lower concentration in those with COPD.

Several significant associations were found among PAH and metals and COPD (Table 3). All forms of PAHs studied, including 1-hydroxynaphthalene, 2-hydroxynaphthalene, 3-hydroxyfluorene, 2-hydroxyfluorene, 1-hydroxyphenanthrene, 1-hydroxypyrene, and 2 & 3-hydroxyphenanthrene were found to have significant associations with COPD. Among metals, cadmium (OR = 12.382, 95% CI = 4.459, 34.383, $p = 0.000$) and tin (OR = 1.743, 95% CI = 1.189, 2.555, $p = 0.008$) had significant associations with COPD. No other metals had a significant association with arsenic (Tables 4–5).

Discussion

Worldwide, mortality from COPD ranked third, leading to COPD being considered a significant public health issue (Vestbo et al. 2013). Deaths due to COPD are ranked fourth in the USA but are expected to rise due to exposures from environmental and occupational pollutants (CDC 2017e; Ford et al. 2013a, b; World Health Organization (WHO) 2000, 2002). This study analyzed the association among COPD and 14 metals, seven arsenic species, and seven PAH compounds.

PAHs have commonly been studied among populations with COPD exposed to air pollution. Numerous studies have found a positive association between PAH exposure and asthma; however, other obstructive lung diseases have been less studied (Nwaozuzu et al. 2021). Shiue (2016) found a positive association using 2011–2012 NHANES data between 2-hydroxyfluorene and emphysema (OR: 1.60, 95% Cl: 1.26, 2.03) and chronic bronchitis (OR: 1.42, 95% CI: 1.04, 1.94), in 3-hydroxyfluorene with emphysema (OR: 1.42, 95% CI: 1.15, 1.77) and chronic bronchitis (OR: 1.40, 95% CI: 1.03, 1.91), and in 2-hydroxynaphthalene for chronic bronchitis (OR: 1.32, 95% CI: 1.02, 1.72). 9-hydroxyfluorene, 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, 3-hydroxyphenanthrene, 1-hydroxypyrene, 1-hydroxynaphthalene, 4-hydroxyphenanthrene were not significant for emphysema or chronic bronchitis. In our study, we found 1-hydroxyphenanthrene, 1-hydroxypyrene, 2 & 3-hydroxyphenanthrene significant for COPD in addition to those that Shiue found significant associations for. Although similar questionnaires were used in our NHANES dataset, the 2011–2012 dataset did not include questionnaires on COPD but only for emphysema and chronic bronchitis. The 2015–2016 dataset used in our study specifically asked about COPD. Kilpatrick (2019) found a positive association between 1-napthol (OR: 1.150, 95% CI: 1.043, 1.268), 2-fluorene (OR: 1.257, 95% CI: 1.059, 1.492), and 2-phenanthrene (OR: 1.196, 95% CI: 1.025, 1.396) using NHANES 2007–2012 data.

Exposure to PAHs has been linked to DNA nucleotides, causing the production of DNA adducts that can cause mutations in DNA replication (Wogan et al. 2004; Sato and Aoki 2002; Pauk et al. 2013). In addition, PAHs can cause oxidative damage to DNA and participate in changes in oncogenes and tumor suppressor genes causing chromosomal aberrations (Farmer et al. 2003; Pauk et al. 2013). Those with large PAH exposures can be found to have anti-PAH antibodies. An increase in DNA adducts has been seen in patients with COPD who smoke and those with cancerous lung disease, suggesting that PAH exposure from smoking led to increased DNA changes (Pauk et al. 2013). Yang et al. (2017) determined that PAHs with

Table 1 Summary statistics for demographics related to COPD

Category	Variable	Sample					Population	
		N total	% total	N with COPD	% with COPD		% with COPD	
Gender	Male	1432	49.6%	57	4.0%	a	3.9%	a
	Female	1453	50.4%	42	2.9%	a	3.0%	a
Race/ethnicity	Mexican American	441	15.3%	8	1.8%	a	1.2%	a
	Other Hispanic	310	10.7%	2	0.6%	a	0.2%	a
	Non-Hispanic White	1186	41.1%	74	6.2%	b	4.6%	b
	Non-Hispanic Black	545	18.9%	10	1.8%	a	1.3%	a
	Non-Hispanic Asian	309	10.7%	2	0.6%	a	0.4%	a
	Other race multi-racial	94	3.3%	3	3.2%	ab	2.1%	ab
Marital status	Married	1460	50.6%	49	3.4%	bd	3.9%	b
	Widowed	193	6.7%	17	8.8%	a	9.7%	a
	Divorced	327	11.3%	21	6.4%	ab	5.3%	ab
	Separated	84	2.9%	7	8.3%	ab	6.0%	abc
	Never married	555	19.2%	3	0.5%	c	0.6%	c
	Living with partner	266	9.2%	2	0.8%	cd	0.3%	c
Highest education level achieved	No high school	266	9.2%	13	4.9%	a	7.4%	b
	Some high school	332	11.5%	15	4.5%	a	6.5%	ab
	High school graduate	641	22.2%	25	3.9%	a	3.9%	abc
	Some college	887	30.7%	32	3.6%	a	3.7%	ac
	College graduate	759	26.3%	14	1.8%	a	1.5%	c
Age	20–44	1269	44.0%	6	0.5%	c	0.4%	c
	45–60	689	23.9%	24	3.5%	a	3.6%	a
	60 and older	927	32.1%	69	7.4%	b	8.4%	b
Family income to poverty ratio (FIPR)	Less than 1.5	916	31.8%	46	5.0%	a	5.8%	a
	1.5–3.5	1090	37.8%	39	3.6%	a	4.2%	a
	Over 3.5	879	30.5%	14	1.6%	b	1.5%	b
Body mass index (BMI)	Normal weight	767	26.6%	22	2.9%	a	2.9%	a
	Underweight	36	1.2%	1	2.8%	a	5.7%	a
	Overweight	946	32.8%	37	3.9%	a	3.8%	a
	Obese	1136	39.4%	39	3.4%	a	3.4%	a
Serum cotinine	Below LLoD*	923	32.0%	15	1.6%	a	1.3%	a
	Above LLoD*	1962	68.0%	84	4.3%	b	4.6%	b
Alcoholic drink last 12 months	No	806	27.9%	16	2.0%	a	2.7%	a
	Yes	2079	72.1%	83	4.0%	b	3.6%	a
Country of birth	USA	2069	71.7%	91	4.4%	a	3.9%	a
	Other	816	28.3%	8	1.0%	b	0.9%	b

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

**LLoD* lower limit of detection

high benzo(a)pyrene (BaP)-equivalent concentrations, rather than the major PAH components, have caused the increased risk of COPD. Therefore, determining the BaP toxic equivalency factors of PAH can determine risk for COPD (Yang et al. 2017).

Among metals, the study found a significant association between tin and cadmium and COPD. Feng et al. (2015) analyzed 23 urinary metals and their association with obstructive and restrictive lung disease measured with spirometry. Iron was found to have a dose–response association with a decreased risk of COPD, while lead had an increased risk of COPD (Feng et al. 2015). Mutti et al. (2006) studied the exhaled breath condensate of COPD patients and found that those with COPD had higher levels of lead, cadmium, and aluminum, and lower levels of iron and copper compared to the non-smoking

Table 2 Demographic odds ratios (OR) and their 95% confidence intervals (CI) related to COPD

Category	Variable	Odds ratio	LCI	UCI	*p*-value
Gender	Male				
	Female	0.810	0.403	1.626	0.5571
Race/ethnicity	Mexican American				
	Other Hispanic	0.203	0.031	1.348	0.1093
	Non-Hispanic White	**4.144**	**1.246**	**13.783**	**0.0274**
	Non-Hispanic Black	0.863	0.217	3.427	0.8357
	Non-Hispanic Asian	0.649	0.090	4.689	0.6712
	Other race multi-racial	2.010	0.463	8.719	0.3585
Marital status	Married				
	Widowed	1.022	0.537	1.944	0.9477
	Divorced	0.676	0.314	1.455	0.3248
	Separated	1.762	0.464	6.687	0.4115
	Never married	0.303	0.071	1.285	0.1156
	Living with partner	**0.109**	**0.014**	**0.834**	**0.0411**
Highest education level achieved	No high school				
	Some high school	0.704	0.159	3.122	0.6475
	High school graduate	0.406	0.092	1.783	0.2416
	Some college	0.541	0.131	2.235	0.4031
	College graduate	0.276	0.055	1.391	0.1291
Age	20–44				
	45–60	**8.497**	**3.471**	**20.800**	**0.0001**
	60 and older	**19.667**	**7.994**	**48.384**	**0.0000**
Family income to poverty ratio (FIPR)	Less than 1.5				
	1.5–3.5	**0.454**	**0.239**	**0.862**	**0.0220**
	Over 3.5	**0.182**	**0.060**	**0.553**	**0.0053**
Body Mass Index (BMI)	Normal weight				
	Underweight	1.552	0.123	19.646	0.7368
	Overweight	0.958	0.496	1.851	0.8997
	Obese	0.825	0.390	1.742	0.6170
Serum cotinine	Below LLoD*				
	Above LLoD*	**4.039**	**1.861**	**8.764**	**0.0014**
Alcoholic drink last 12 months	No				
	Yes	1.632	0.531	5.013	0.3992
Country of birth	USA				
	Other	0.507	0.138	1.866	0.3153

Odds ratios which are presented in bold are statistically different from one at $\alpha = 0.05$ level

LCI lower confidence interval, *UCI* upper confidence interval

*LLoD lower limit of detection

controls (Mutti et al. 2006). Cadmium, a component of cigarette smoke, has been negatively correlated to forced expiratory volume in 1 s (FEV_1) in current (− 2.06%, 95% CI: − 2.86, − 1.26 per 1 log increase in urinary cadmium) and former smokers (− 1.95%, 95% CI − 2.87, − 1.03), but not in never smokers. Higher levels of urinary cadmium were also associated with a significantly lower FEV_1/FVC (forced vital capacity) ratio (Mannino et al. 2004). Among occupational studies, exposure to cadmium alloy has been linked to emphysema (Davison et al. 1988).

Tin has rarely been studied in the literature with its connection to COPD. Indium tin oxide (ITO) is a mixture of indium oxide and tin oxide and is commonly used in LCD displays (Liu et al. 2012). The increasing use has led to an increase in exposure of ITO resulting in interstitial pneumonia and pulmonary fibrosis (Liu et al. 2012; Homma et al. 2003; 2005). Liu et al. (2012) found significantly increased levels of SP-A and SP-D levels in ITO-manufacturing workers, which are markers of interstitial lung disease. In addition to interstitial lung diseases, Nakano et al. (2016) published

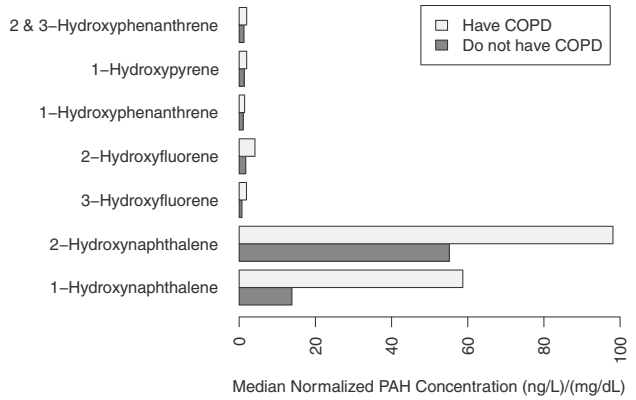

Fig. 1 Dose–response plots of participants with COPD for seven forms of PAH

a case report of an ITO worker who developed progressive lung destruction with accompanying severe centrilobular emphysema, with a FEV_1/FVC of 76.5%. Nakano et al. (2016) suggests ITO exposure is a risk factor for emphysema. Among children with asthma, tin was not found to have a significant association with ln(FEV_1), ln(FVC), or ln(FEV_1/FVC) (Madrigal et al. 2021). However, other metals have been linked to COPD in the past. Feng et al. (2015) found significant dose–response associations between lead and iron and COPD. Among children, urinary manganese was inversely associated with FEV_1/FVC and $FEF_{25–75}$ forced expiratory flow between 25 and 75% of vital capacity) (Madrigal et al. 2018). Jones et al. (2007) conducted an occupational study investigating lung cancer among former employees at a tin smelter. Among cumulative exposures of arsenic, cadmium, lead, antimony, and polonium-210, significant associations were found between lung cancer mortality and exposures to arsenic, lead, and antimony. In our study, tin and cadmium were found to have a significant association with COPD; however, no other metals were significant.

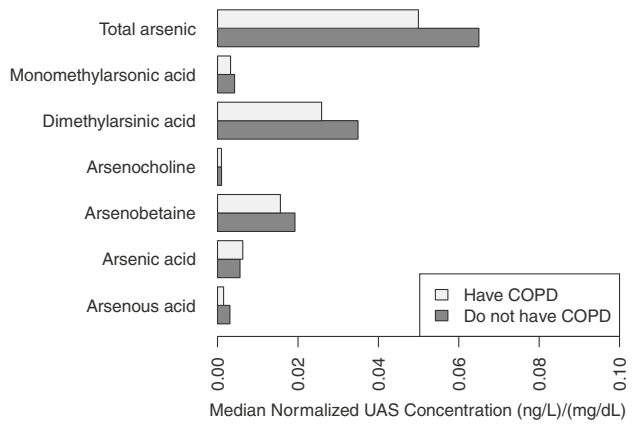

Fig. 2 Dose–response plots of participants with COPD for seven forms of speciated arsenic

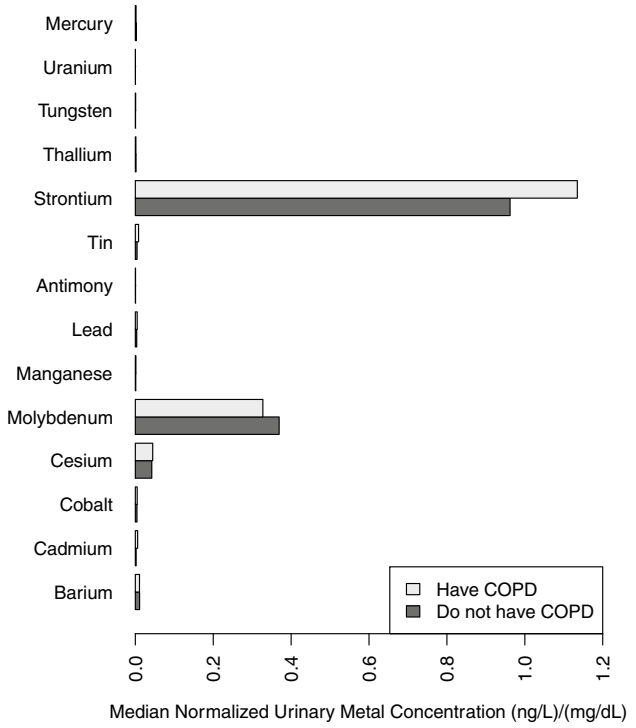

Fig. 3 Dose–response plots of participants with COPD for 14 urinary metals

Among arsenic's effect on lung function, Wei et al. (2021) determined a positive linear dose–response association between urinary arsenic and increased annual declines in FEV_1, predicted percent (pp)FEV_1, FVC, and ppFVC in coke oven workers. No significant effects of urinary arsenic on annual changes in FEV_1/FVC and $FEF_{25–75}$ were found (Wei et al. 2021). Furthermore, in a meta-analysis of nine studies, Sanchez et al. (2018) found that arsenic exposure was associated with lower FEV_1 and FVC but not with FEV_1/FVC, suggesting that arsenic exposure leads to restrictive lung disease rather than obstructive lung diseases such as COPD. Our study also found no significant

Table 3 PAH compounds odds ratios and their 95% confidence intervals (CI) related to COPD

Urinary PAH compounds	Odds ratio	LCI	UCI	*p*-value
1-Hydroxynaphthalene	**1.832**	**1.210**	**2.775**	**0.008**
2-Hydroxynaphthalene	**3.361**	**1.519**	**7.440**	**0.006**
3-Hydroxyfluorene	**2.641**	**1.381**	**5.053**	**0.006**
2-Hydroxyfluorene	**3.628**	**1.754**	**7.506**	**0.002**
1-Hydroxyphenanthrene	**2.864**	**1.307**	**6.277**	**0.013**
1-Hydroxypyrene	**4.949**	**2.540**	**9.643**	**0.000**
2 & 3-Hydroxyphenanthrene	**3.487**	**1.382**	**8.795**	**0.013**

Odds ratios which are written in bold are statistically different from one at $\alpha = 0.05$ level

LCI lower confidence interval. *UCI* upper confidence interval

Table 4 Urinary speciated arsenic odds ratios and their 95% confidence intervals related to COPD

Urinary arsenic compounds	Odds ratio	LCI	UCI	*p*-value
Arsenous acid	0.845	0.396	1.803	0.666
Arsenic acid	1.442	0.582	3.574	0.436
Arsenobetaine	0.642	0.376	1.099	0.117
Arsenocholine	1.350	0.649	2.806	0.428
Dimethylarsinic acid (DMA)	0.956	0.295	3.093	0.940
Monomethylarsonic acid (MMA)	0.945	0.289	3.091	0.926
Arsenic, total	0.656	0.279	1.542	0.342

Odds ratios presented at $\alpha = 0.05$ level. No odds ratios for speciated and total arsenic showed statistically significant asscoiation with COPD

LCI lower confidence interval, *UCI* upper confidence interval

associations between any form of urinary speciated arsenic and COPD.

Among demographic factors, Parulekar et al. (2017) determined that COPD patients ≥ 65 years were more likely to require long-term oxygen therapy, had worse lung function measured by FEV_1, and had worse exercise tolerance as measured by a 6-min walk distance. Older participants had higher percentages of emphysema (14% vs 8%, $p < 0.001$) and more gas trapping on CT (47% vs 36%, $p < 0.001$) compared to those < 65 years. Tilert et al. (2018) found a significant increase in the odds of participants with COPD > 60 years compared to 40–59 years (OR: 1.65, 95% CI: 1.07, 2.53). We found a significant increase in odds of COPD among ages 45–60 years and 60 years and older. Those with COPD also had a significantly higher percentage who were current (OR: 1.70, 95% CI: 1.17, 2.48) or former smokers (OR: 1.75, 95% CI: 1.23, 2.48) using NHANES data from 2007 to 2012. Our study using NHANES 2013–2016 data found increased odds when the cotinine level was above the LLoD, suggesting the participant was a smoker. When compared to non-Hispanic White, Tilert et al. (2018) determined that non-Hispanic Black and Hispanic had protective odds of COPD. Our data showed similar results in that non-Hispanic White had higher odds of COPD. Decreased odds for COPD were determined in those living with partner, and the participants with an FIPR of 1.5–3.5 or over 3.5. Eisner et al. (2011) found increased odds of COPD severity among those with low and medium incomes as compared to high.

Table 5 Urinary metal compound odds ratios and their 95% confidence intervals (CI) related to COPD

Urinary metal compound	Odds ratio	LCI	UCI	*p*-value
Barium	0.841	0.517	1.368	0.491
Cadmium	**12.382**	**4.459**	**34.383**	**0.000**
Cobalt	1.665	0.608	4.562	0.329
Cesium	1.942	0.575	6.553	0.294
Molybdenum	0.819	0.336	1.998	0.664
Manganese	0.879	0.437	1.772	0.722
Lead	0.585	0.258	1.326	0.209
Antimony	0.922	0.386	2.204	0.856
Tin	**1.743**	**1.189**	**2.555**	**0.008**
Strontium	1.278	0.729	2.238	0.398
Thallium	1.041	0.292	3.714	0.951
Tungsten	1.006	0.422	2.394	0.990
Uranium	1.616	0.907	2.880	0.114
Mercury	0.698	0.415	1.176	0.187

Odds ratios which are presented in bold are statistically different from one at $\alpha = 0.05$ level

LCI lower confidence interval, *UCI* upper confidence interval

Limitations

Data used in this study was obtained by NHANES and, therefore, we were limited by the method of COPD data collection. The dataset included COPD data by questionnaire from the participants but was not confirmed with pulmonary function testing with laboratory spirometry. In addition, the specific type of obstructive lung disease was not included, such as chronic bronchitis or emphysema. The question regarding the patients' history of COPD was used and, therefore, we do not know the cause or severity of the participants' COPD nor its timing relative to the urinalysis. Further clinical studies are needed to confirm the diagnosis of COPD among participants and understand the cause and management.

Conclusion

Our study found a positive association among urinary tin, cadmium, and seven forms of PAHs (1-hydroxynaphthalene, 2-hydroxynaphthalene, 3-hydroxyfluorene, 2-hydroxyfluorene, 1-hydroxyphenanthrene, 1-hydroxypyrene, 2 & 3-hydroxyphenanthrene) with COPD among US adults. No other metals or the arsenic compounds studied were found to be associated with COPD.

Author contribution Humairat H. Rahman conceptualized the study and contributed to the introduction and discussion. Stuart Munson-McGee conducted the data analysis and contributed to the drafting of the paper. Danielle Niemann contributed to the drafting of the paper. All the authors read and approved the final manuscript.

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.

Declarations

Ethics 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.

Consent to participate Consent was given by all the authors.

Consent for publication Consent was given by all the authors.

Competing interests The authors declare no competing interests.

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