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URINE ARSENIC CONCENTRATION AND OBSTRUCTIVE PULMONARY DISEASE IN THE U.S. POPULATION

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Abstract

Arsenic (As) is a known carcinogen commonly found in drinking water. An emerging body of evidence suggests that exposure to inorganic As may be associated with nonmalignant respiratory disease. The aim of this study was to determine whether there is an association between As exposure at levels seen in the United States and prevalence of asthma, emphysema, chronic bronchitis, and respiratory symptoms.Urinary As was collected from 5365 participants from the combined 2003–2006 National Health and Nutrition Examination Survey (NHANES) cohorts. Two methods to adjust for organic As component were incorporated into the statistical model. Linear and logistic regression models compared urinary As adjusted for organic As with diagnoses of obstructive pulmonary disease and respiratory symptoms. Geometric mean concentration of urinary As were not significantly different between participants with and those without asthma, chronic bronchitis, and emphysema. Odds of having asthma was 0.71 for participants with the highest quintile of urinary As (≥17.23 μg/dl) when compared to the lowest quintile (≤3.52 μg/dl). A significant association was found between increasing urinary As concentration and decreasing age, male gender, and non-“white” race. A significant association between urinary As and obstructive pulmonary disease and symptoms was not demonstrated in the U.S. population.

Arsenic (As) is a known lung, bladder, and skin carcinogen (IARC, 2004) and reproductive toxicant (Golub et al., 1998) that is found in drinking water throughout the world. Contaminated aquifers in parts of India, China, Taiwan, and Bangladesh resulted in the poisoning of hundreds of millions of people (Smedley & Kinniburgh, 2002; Lin et al., 1998). The U.S. Environmental Protection Agency (EPA) estimates that more than 13 million individuals in the United States reside in areas where water exceeds the 10-μg/L standard for inorganic As (U.S. EPA, 2001).

Inorganic As, the more toxic form, inhibits pyruvate dehydrogenase, consequently decreasing activity of the citric acid cycle and ultimately decreasing the production of cellular ATP (Bernstam & Nriagu, 2000). Through sulfhydryl group binding, inorganic As also inhibits a number of other cellular enzymes, resulting in inhibition of cellular glucose uptake, fatty acid oxidation, and production of glutathione. As toxicity results in cutaneous (hyperkeratosis), neurologic (peripheral neuropathy), gastrointestinal (noncirrhotic portal fibrosis), hematologic (anemia), vascular (blackfoot disease), metabolic (diabetes mellitus), reproductive, and pulmonary (lung cancer) manifestations (Golub et al., 1998; Tsai et al., 1998; Chiu et al., 2007).

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An emerging body of evidence suggests that exposure to inorganic As may lead to nonmalignant respiratory conditions such as chronic cough and bronchiectasis. The impact of As exposure on lung pathology was first suggested in the 1970s when autopsies from four out of five children with evidence of As-related keratosis were found to have interstitial fibrosis and bronchiectasis (Rosenberg, 1974). Nearly all of the epidemiological studies that followed were conducted without biomarker analysis and instead relied on surrogates for exposure such as dermatologic manifestations of As exposure or environmental sampling from local wells (Zaldiver & Ghai, 1980; Borgono et al., 1977; Mazumder et al., 2000).

The mechanism underlying As-induced damage to lung tissue remains disputed. Several autopsy studies have described large deposits of As in lung epithelium (Rosenberg, 1974; Saady et al., 1989). Oxidative stress from As exposure in the lungs is a hypothesized pathophysiological mechanism (Hays et al., 2006; Lantz & Hays, 2006; Bernstam & Nriagu, 2000). Previous studies investigating pulmonary effects from As exposure have been in populations with significant contamination of well water. Participants in these studies have relatively high body burdens with total urinary As concentration greater than 100 μg/L. Consequently, they are more likely to have As deposits in the lung with resultant oxidative damage than populations with lower level exposures. The pulmonary affects of low-level As exposure have not been described previously.

There is debate as to whether chronic low-level exposure to As, such as exposure common in the United States, might result in chronic disease. Navas-Acien et al. (2008) recently reported an increased risk of type 2 diabetes mellitus for individuals with urinary As concentration greater than the 80th percentile when compared to those below the 20th percentile. However, the validity of the findings has recently been called into question (Steinmaus et al., 2009a, 2009b; Longnecker, 2009). The crux of the debate is how to best quantify exposure to inorganic As, the more toxic As moiety, when complete As speciation is not available.

Our objective in this study was to investigate the association of urinary As concentration with the prevalence of asthma, chronic bronchitis, and emphysema diagnoses and respiratory symptoms. Several approaches to estimate exposure to inorganic As in the U.S. population were used.

MATERIALS AND METHODS

Study Population

The study population is from the National Health and Nutrition Examination Survey (NHANES) conducted by the U.S. National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC). Study protocols were approved by their institutional review board. Both oral and written informed consent was obtained from all participants. As biomarker data was available for a randomly selected subset of one-third of the NHANES 2003–2004 and NHANES 2005–2006 cohorts. The combined cohorts from 2003–2006 include 20,470 participants who were selected using a multistage probability sampling design (CDC, 2010). Urinary As concentrations were analyzed in 5365 participants aged 6 yr and older. Two hundred and thirty-six participants with missing As speciation data were excluded from the analysis (Figure 1).

Our study was restricted to participants 20 years and older, as pediatric asthma has different etiologies from chronic respiratory disease and children have less chronic exposures than adults. Recent seafood consumption as assessed by 24-h dietary recall was restricted to reduce the influence of organic As found in fish on measured total urine As concentration. Three hundred and sixty-nine participants were found to have had at least one serving of

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seafood or fish within the past 24 h. Two participants with measured total As concentration 10 times the 99th percentile were excluded as outliers, leaving 2687 participants in the final analysis.

Laboratory Analysis

Spot urine samples were obtained at the time of physical examinations and were collected in As-free containers. They were shipped to the Environmental Health Sciences Laboratory of the National Center for Environmental Health on dry ice where all samples were analyzed within 3 wk of collection. Total urine As levels were measured using inductively coupled plasma dynamic reaction cell-mass spectrometry on a PerkinElmerELAN 6100 DRC Plus or ELAN DRC II inductively coupled plasma- mass spectrometer (ICP-MS) (PerkinElmer SCIEX, Concord, ON, Canada). Speciated As was determined using liquid chromatography for separation and mass spectrometry for measurement. Interassay coefficient of variation for control samples was 9.2% for total As with mean concentration of 8.15 μg/L. Detection limits for 2003–2004 samples were 0.6 μg/L for total As, 0.4 μg/L for arsenobetaine, and 0.6 μg/L for arsenocholine. For 2005–2006 samples, detection limits were 0.74 μg/L for total As, 0.4 μg/L for arsenobetaine, and 0.6 μg/L for arsenocholine.

Urine creatinine concentration was measured by a Jaffe rate reaction and CX3 analyzer (Beckman Instiruments, Inc., Brea, CA) and was used to adjust for urine dilution in spot urine samples. Serum mercury (Hg) was used as a biomarker for recent seafood consumption. Concentrations were measured using multi-element quadrupole inductively coupled plasma–mass spectrometry (PerkinElmer Instruments, Shelton, CT).

Outcome and Covariates

The primary outcome of interest was self-report physician diagnosis of asthma, chronic bronchitis, and emphysema. An additional outcome of interest was response to the symptom questions, “Do you usually cough on most days for 3 consecutive months or more throughout the year,” “Do you bring up phlegm on most days for 3 consecutive months or more throughout the year,” and “In the past 12 months have you had wheezing or whistling in your chest?”

Information on demographics and other covariates was collected as part of the NHANES survey. Self-report of gender, age, race/ethnicity, and level of education was collected as part of the demographic questionnaire. A smoking history questionnaire asks whether participants have ever smoked greater than 100 cigarettes in their lifetime and whether they are currently smokers. Pack-years value was calculated for current smokers. Tobacco-smoke exposure was further assessed by serum continine, measured using isotopedilutionhigh-performance liquid chromatography. Information on body mass index (BMI) was collected by dividing the participants’ weight in kilograms by their height in meters squared as measured during the physical exam component of the survey. Information on seafood consumption was obtained from both 24-h dietary recall interview and from serum Hg concentrations. The dietary recall was based on U.S. Department of Agriculture food codes. The list of food codes for each survey year was screened for foods that contain a fish or seafood item.

Statistical Analysis

Statistical analysis was performed using SAS 9.1 (SAS Institute, Inc., Cary, NC). The study design was a cross-sectional survey of respiratory outcomes (dependent variable) and urinary concentrations of As (independent variable). Since most subjects in the study population had less than detectable levels of inorganic As and not all inorganic species were quantified, it was not possible to use direct measurement of total inorganic As. Instead, total

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As concentration was used as the exposure of interest and two different methods were employed to adjust for the presence of organic As. The first method was outlined by Navas-Acien et al. (2008): Tertile categories were included for urine aresenobetaine and blood Hg levels into our logistic regression model. This model controls for exposure to organic As by adjusting for arsenobetaine concentration, the majority component of organic As (Lai et al., 2004). The model further controls for fish exposure, the primary source of organic As, by adjusting for serum Hg concentration, an accepted biomarker for fish consumption. The second method for estimating inorganic As from total As concentrations is that proposed by Steinmaus et al. (2009a). The measured components of organic As, arsenobentaine and arsenocholine, were subtracted from total As concentration. Arsenocholine concentrations for all but the 43 participants with measurements above the limit of detection were computed as 0.

Median and interquartile ranges of total As and estimated inorganic As (total minus organic As) were compared for the outcomes of interest (diagnosis of asthma, emphysema, chronic bronchitis, and chronic cough) and a number of covariates (gender, age, body mass index, smoking status, serum cotinine, race/ethnicity, education, serum Hg). Linear regression was performed on log-transformed total and estimated inorganic As to determine the ratio of geometric mean As concentrations in participants with respiratory disease to participants without.

Using logistic regression, the odds ratio (OR) and 95% confidence intervals (CI) were calculated for diagnosis of asthma, chronic bronchitis, emphysema, and respiratory symptoms, comparing participants above the 80th percentile of total and estimated inorganic As concentrations with those below the 20th percentile. Urinary As concentrations were not log-transformed for the logistic regression, as independent variables do not require a normal distribution in logistic regression and logarithmic values can change dose-response relationships. Covariates believed to be associated both with exposure to As and with development of lung pathology were added to both logistic regression models. These included gender, age (20–39, 40–59, ≥60 yr), race/ethnicity (white, black, Mexican American, other), education (< high school, high school, < high school), BMI (<25, 25–29, ≥30 kg/m^2), smoking status (never, former, current), continuous serum Hg (μg/L), and serum cotinine category (<0.015, 0.015–9.9, ≥10 ng/ml). Continuous urinary creatinine (mg/dl) was added to all models to control for dilution of spot-urine samples.

Level of statistical significance was set at $\alpha = .05$ and all statistical analyses were two-sided. Analysis was performed with and without NHANES sample weights; however, incorporation of sample weights exerted little effect on outcomes. Unweighted outcomes are presented in our results, since the aim of our study was to assess associations and not to describe population estimates (National Center for Health Statistics, 2005).

RESULTS

Complete As biomarker data was available for 5129 participants in the 2003-2004 and 2005-2006 combined National Health and Nutrition Examination Survey (NHANES) cohorts. Data were analyzed on 2687 participants who met our inclusions criteria. Median urine concentration of total urine As was 8.9 μg/L with an interquartile range (IQR) of 4.3–15.6. Inorganic As concentrations were estimated by subtracting total As from measured organic As. Eleven participants had an estimated inorganic concentration less than 0 due to inaccuracies in the measurement of arsenobentaine, a major component of organic As. Of the 2676 participants with nonnegative estimates of inorganic As, median inorganic As was 5.8 μg/L (IQR 3.2–10.5) (Table 1). Using the Pearson correlation coefficient, total As concentrations correlated significantly with arsenobentaine ($r = .94$) and estimated

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concentrations of inorganic As (r = .72). Serum Hg was not highly correlated with total As (r = .20) or arsenobentaine (r = .18).

As concentrations were associated with race/ethnicity, age, and gender with statistical significance, but not with education, BMI, or smoking status. Total As for participants who self-identify as “black” was 37% higher than participants who self-identify as “white.” Younger age was associated with higher concentrations of estimated inorganic As but was not statistically associated with measured total As. Men had 27% higher total As and 34% higher estimated inorganic As than women. Total As concentration was also significantly associated with serum Hg and arsenobentaine concentrations.

As concentrations were not significantly different between participants with and without a diagnosis of asthma, emphysema, or chronic bronchitis. The 337 (12.6%) participants with a diagnosis of asthma had median total As of 7.3 μg/L, less than nonasthmatics with a median concentration of 8.3 μg/L. A similar trend was seen for the 51 (1.9%) participants with a diagnosis of emphysema and 173 (6.5%) participants with a diagnosis of chronic bronchitis. Median total As concentrations for the participants who report a chronic cough, phlegm, and wheezing were also lower than those with no respiratory symptoms, although not significantly for chronic cough and wheezing.

Linear regression (adjusting for gender, age, race/ethnicity, education, BMI, cotinine, and urinary creatinine) was performed on log-transformed total and estimated inorganic As to determine the ratio of geometric mean As concentrations in participants with respiratory disease compared to participants without. For asthmatics versus nonasthmatics, the ratio of total As geometric mean was 0.92 (0.82, 1.02). For chronic bronchitis the ratio was 1.06 (0.99, 1.12), and for emphysema it was 0.95 (0.89, 1.02). Comparison of geometric means for estimated inorganic As concentrations were similar (Table 2).

Participants with greater than the 80th(<17.23 μg/L) percentile total As had a crude odds ratio of 0.85 (95% CI: 0.59, 1.23) for having asthma when compared to participants with less than the 20th(<3.52 μg/L) percentile. After adding potential confounders into the model, the adjusted odds ratio was 0.71 (0.41, 1.24). Adjusting for organic As and fish consumption by adding arsenobentaine and Hg concentrations into the model increased the odds ratio to 1.27 (0.51, 3.12). The adjusted odds ratio for estimated inorganic As was 0.79 (0.43, 1.46). Similar trends were seen when assessing odds for having chronic bronchitis and emphysema comparing participants with the lowest quintile of exposure to those with the highest. Adjusted odds ratios for both total and estimated inorganic As were all below 1 although they did not reach statistical significance (Table 3). Adjusted odds ratios for having respiratory symptoms were assessed in an identical manner and were also below 1. Odds of having reported wheezing was 0.56 (0.33, 0.95) between the two groups. While this did reach statistical significance, models adjusting for organic As did not (Table 4).

DISCUSSION

Our results show no significant association between asthma, emphysema, chronic bronchitis, chronic cough, and phlegm with urinary As at levels found in the general U.S. population. Calculated odds ratios for asthma, chronic bronchitis, and emphysema by total As quintile were not statistically significant at $\alpha = .05$ level. Various attempts to control for the impact of organic As concentration were made in our analysis of measured total As; however, no statistically significant association was calculated. There did seem to be a significant negative association between total As exposure and wheezing; however, no significant association was seen when adjusting for organic As.

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Organic As originates primarily from seafood consumption. Seafood consumption has been associated with decreased prevalence of asthma, atopy, and wheezing (Miyake et al., 2009). Our analysis was modeled after two methods used in the diabetes literature to control for the portion of organic As included in total As measurements. Adding arsenobentaine and Hg (a biomarker for seafood consumption) into the model did demonstrate a quantitative increase in relative risk with asthma and emphysema; however, the association was not statistically significant. This method of controlling for the component of organic As in measured total As has been widely debated. Arsenobentaine is the majority component of total As; as such, the two are highly associated. In our study arsenobentaine and total As have a correlation coefficient of .94. Adding arsenobentaine into the model this essentially controlled for the exposure itself; placing two highly correlated variables into the same model can result in unstable results (Clayton & Hill, 1993).

A different method as proposed by Steinmaus et al. (2009b) is to estimate inorganic As concentrations by subtracting arsenobentaine and arsenocholine, two measured organic arsenicals, from total As. This approach has been criticized as being an inaccurate estimate of inorganic As as it does not factor in other unmeasured organic arsenicals and does not adequately control for seafood intake (Navas-Acien et al., 2009a). In our study both logistic and linear regressions of estimated inorganic As failed to show a statistically significant association between estimated inorganic As and respiratory disease.

There are several reasons why our findings do not agree with earlier studies that suggest an association between ingested As and chronic respiratory disease. The urinary As levels found in the NHANES cohort are substantially lower than those found in earlier studies. Mean urinary As of 241 participants from a large prospective cohort in Araihazar, Bangladesh, was 189 μg/L, more than 10-fold the level of the 80th percentile in the NHANES cohort (Parvez et al., 2008). Exposure to inorganic As in the United States in general is significantly lower than in other parts of the world. A study of 1774 patients with chronic As toxicity living in 627 villages in Inner Mongolia, China, found average water concentrations ranging from 5 to 182 μg/L (Guo et al., 1998), significantly elevated from drinking water in the United States, regulated to meet the U.S. EPA maximum contaminant level of 10 μg/L. It is possible that while As exposure at levels seen in endemic areas such as China and Bangladesh are associated with respiratory disease and symptoms, levels of exposure common to the United States are not.

Our study has the advantage of having biomarker data with speciation of arsenicals. Previous studies showing an association between respiratory disease and symptoms with As exposure relied on surrogates of exposure. For example, in multiple studies exposure status was based on concentrations from wells in the region, and not actual exposure or dose to the participant (Zaldiver & Ghen, 1980; Mazumder et al., 2000). Other studies relied on the presence of hyperkeratosis (a clinical finding of As toxicity) as a surrogate of As exposure (Borgono et al., 1977; Mazumder et al., 2005; Milton et al., 2003). These methods of exposure assessment do not reflect the quantity of biological dose received and are therefore fairly coarse indices of exposure, prone to exposure misclassification. Differential exposure misclassification is possible if the researcher who assigns exposure status by observation of hyperkeratosis is biased in the ascertainment of outcome status. In using the NHANES biomarker data in our analysis, it was possible to analyze a quantifiable measurement of dose and use speciation data to control for the influence of organic As exposure.

Nearly all previous epidemiological studies used symptom report as the primary outcome of interest, raising the concern of recall bias. Few studies examined outcomes beyond subjective symptom report. Studies from highly exposed villages in Bangladesh failed to show a statistically significant relationship between As exposure and diagnosis of chronic

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bronchitis (Milton & Rahman, 2002; Milton et al., 2003). A study of 38 participants from West Bengal had an adjusted odds ratio of 10 (95% CI: 2.7, 37) for evidence of bronchiectasis on high-resolution computed tomography (CT) for individuals with As-induced skin lesions compared to individuals with normal skin (Mazumder et al., 2005).

A major limitation of our study is that it relied upon questionnaire report of diagnosis and symptoms and not a more objective assessment of outcome status such as medical record review, physical exam, or pulmonary function testing. While there is bound to be some misclassification of outcome, there is little concern that outcome misclassification would be differential as exposure status (i.e., urinary As concentration) is unknown to the participant. Nondifferential misclassification would likely bias our results towards the null and partly explain our findings of no association. Pulmonary function tests (PFT) would provide a more reliable and objective assessment of respiratory disease; however, PFT data are not yet released for the NHANES cohort with biomarker data. While few studies examined PFT in participants with Asosis (De et al., 2004; von Ehrenstein et al., 2005), only one study was able to compare biomarker and PFT data. An inverse association between urinary As and predicted forced expiratory volume in 1 s (FEV_1) was observed in 31 participants with arsenicosis in Bangladesh (Parvez et al., 2008).

A further limitation of our study is the relatively short biological half-life of urine As and the small window of exposure that it provides. While As biomarkers of toenail, hair, and blood do exist, speciations of those samples are technically difficult and estimation of inorganic As is inaccurate (Navas-Acien & Guallar, 2008). Despite relatively small individual variability of urinary As (Navas-Acien et al., 2009b), it is unknown whether urinary arsenic reflects long-term exposure in the present study. Even though a single urine biomarker sample does not assess past exposure prior to the development of respiratory disease, it is an accepted indicator of recent As exposure.

Interesting associations between unadjusted As concentration and gender, age, and race/ethnicity were noted. The association remained significant after adjustment for other covariates (smoking, BMI, education, and creatinine). Similar findings were reported elsewhere. Navas-Acien et al. (2009a), using NHANES data, also found total As to be relatively elevated in men when compared to women, in younger age groups, and in non-“white” participants, although not significantly so for gender. In a case-control study of lung cancer, As concentrations from toenail clippings were quantified for 461 participants from two U.S. states (Heck et al., 2009). Arsenic concentrations followed a similar pattern in relation to age and race/ethnicity, although without statistical significance. It is unlikely that these associations are solely due to differences in fish consumption, since our findings were stronger for an association with estimated inorganic As concentrations where the organic component primarily from fish is subtracted. It is possible that relatively elevated levels in non-“white” participants might be related to contaminated drinking water or industrial occupational exposures. While occupation may be independently associated with both As exposure and obstructive pulmonary disease, access to data on occupation was not available and it was not possible to control for potential confounding.

In conclusion, our results do not show an association between urinary As concentration and prevalence of asthma, chronic bronchitis, or emphysema in the U.S. population. Additional analysis of chronic cough, phlegm production, and wheezing did not show consistently significant association after adjusting for organic As. This is the first study that assesses the relationship between nonmalignant respiratory disease and As exposure in the United States. While our findings are not consistent with earlier studies showing an association between As exposure and respiratory symptoms, our study uses speciated biomarker data and controls for the influence of organic As. While it is possible that elevated urinary As concentrations

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common in As endemic regions may influence development of pulmonary disease and respiratory symptoms, it is noteworthy that in a minimally exposed U.S. population no such association was seen.

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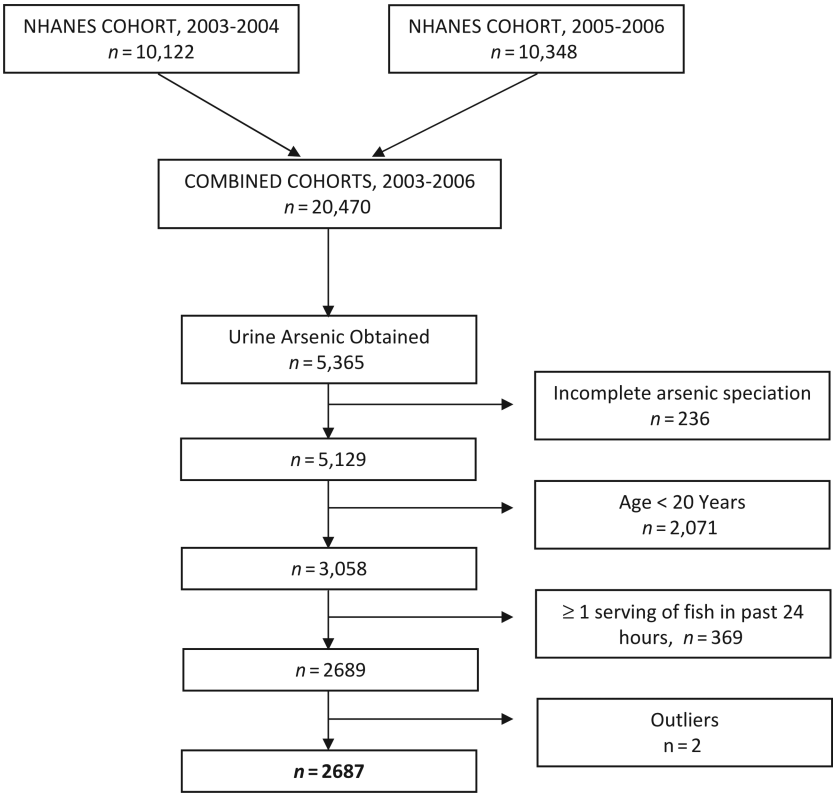

FIGURE 1.

Study population from the combined 2003–2004 and 2005–2006 NHANES cohorts. Of the 20,470 participants in the combined cohorts, 5365 gave urine samples for arsenic analysis; however, 236 participants had incomplete arsenic speciation data. After restricting 2071 participants under 20 yr of age, 369 participants who had consumed at least 1 serving of fish in the past 24 h, and removing 2 outliers, 2687 participants were included in the analysis.

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TABLE 1

Median Total and Estimated Inorganic Urinary Arsenic Concentration (μg/L) by Diagnoses and Sociodemographic Variables of the NHANES Cohort, 2003–2006

	Total arsenic			Estimated inorganic[a]		
Characteristics	**Number (%)**	**Median, (IQR)**	***p***	**Number (%)**	**Median, (IQR)**	***p***
Overall	2687 (100)	8.9 (4.3–15.6)		2676[b] (100)	5.8 (3.2–10.5)	
Asthma						
Yes	337 (12.6)	7.3 (4.3–12.6)	.22	334 (12.5)	5.4 (3.3–9.8)	.52
No	2346 (87.4)	8.3 (4.3–15.8)		2338 (87.5)	5.8 (3.1–10.6)	
Emphysema						
Yes	51 (1.9)	6.3 (3.2–14.7)	.81	173 (6.5)	5.3 (2.9–8.7)	.74
No	2629 (98.1)	8.1 (4.3–15.6)		2495 (93.5)	5.9(3.2–10.6)	
Chronic bronchitis						
Yes	173 (6.5)	6.8 (3.6–15.7)	.6	50 (1.9)	4.3 (2.9–7.9)	.87
No	2506 (93.5)	8.3 (4.4–15.6)		2619 (98.1)	5.8 (3.2–10.6)	
Chronic cough						
Yes	234 (10.7)	6.3 (3.1–13.3)	.56	233 (10.7)	4.6 (2.3–8.0)	.68
No	1958 (89.3)	8.5 (4.4–15.2)		1948 (89.3)	5.6 (3.2–10.9)	
Phlegm						
Yes	208 (9.4)	7.7 (3.6–14.4)	.02	207 (9.4)	5.3 (2.7–9.5)	.95
No	1985 (90.6)	8.3 (4.3–16.1)		1975 (90.6)	5.8 (3.1–10.7)	
Wheezing						
Yes	385 (14.3)	7.3 (3.9–13.9)	.64	385 (14.4)	5.6 (3.1–9.4)	.77
No	2301 (85.7)	8.3 (4.3–15.8)		2290 (85.6)	5.8 (3.2–10.7)	
Gender						
Male	1318 (49.1)	9.0 (4.9–16.6)	.07	1312 (49.0)	6.7 (3.7–11.4)	<.01
Female	1369 (50.9)	7.1 (3.6–13.9)		1364 (51.0)	5.0 (2.7–9.5)	
Age, yr						
20–39	977 (36.4)	8.2 (4.5–15.8)	.74	976 (36.4)	6.2 (3.3–11.1)	<.01
40–59	788 (29.3)	8.5 (4.6–15.7)		786 (29.4)	6.0 (3.3–10.0)	
≥60	922 (34.3)	7.7 (3.8–15.3)		914 (34.2)	5.2 (2.8–9.5)	

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	Total arsenic			Estimated inorganic[a]		
Characteristics	**Number (%)**	**Median, (IQR)**	***p***	**Number (%)**	**Median, (IQR)**	***p***
Race/ethnicity						
White	1410 (52.5)	7.0 (3.5–13.7)	.01	1401 (52.5)	5.0 (2.7–8.8)	<.01
Black	563 (20.9)	9.6 (5.3–19.6)		563 (21.0)	6.4 (3.8–11.5)	
Mexican American	551 (20.5)	8.9 (4.8–15.2)		550 (20.5)	6.9 (3.8–11.6)	
Other	163 (6.1)	12.8 (5.3–33.1)		162 (6.0)	8.9 (4.0–18.2)	
Education						
<High school	800 (29.8)	7.8 (4.4–15.1)	.84	796 (29.8)	6.0 (3.3–10.9)	.14
High school	669 (24.9)	8.4 (4.4–16.1)		666 (24.9)	5.9 (3.2–10.4)	
>High school	1219 (45.3)	8.1 (4.2–15.7)		1211 (45.3)	5.7 (3.1–10.2)	
BMI, kg/m^2						
<25	861 (32.1)	7.5 (3.8–14.5)	.88	854 (31.9)	5.4 (2.9–10.2)	.84
25–29	1062 (39.5)	8.3 (4.2–16.0)		1059 (39.6)	6.1 (3.1–10.6)	
≥30	764 (28.4)	8.4 (4.8–16.0)		763 (28.5)	5.9 (3.5–10.6)	
Smoker						
Never	1389 (51.7)	8.1 (4.3–15.7)	.23	1383 (51.7)	5.7 (3.1–10.9)	.33
Former	715 (26.6)	8.4 (4.3–16.0)		713 (26.6)	5.9 (3.2–10.4)	
Current	583 (21.7)	7.7 (4.2–15.1)		580 (21.7)	6.0 (3.1–10.0)	
Continine, ng/ml						
<0.015	478 (18.5)	7.4 (3.4–13.3)	.19	475 (18.5)	5.3 (2.6–9.6)	.1
0.015–9.9	1444 (56.0)	8.4 (4.5–16.2)		1439 (56.0)	5.8 (3.2–10.9)	
≥10	659 (25.5)	7.9 (4.4–15.5)		656 (25.5)	5.9 (3.3–10.0)	

Note. BMI, body mass index; IQR, interquartile range.

[a] Inorganic arsenic concentration is estimated by subtracting total urinary arsenic by organic arsenic (arsenobentaine and arsenocholine concentrations).

[b] Eleven participants with a negative estimated inorganic arsenic were excluded from the analysis.

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TABLE 2

Ratio of Measured Mean Total Arsenic Concentration and Estimated Inorganic Arsenic Concentration Comparing Participants With and Without Respiratory Disease

Diagnosis		Total arsenic	Estimated inorganic[a]
Asthma	Mean (μg/L)case/control	13.08/17.30	8.46/9.36
	Adjusted[b] (95% CI)	0.92 (0.82, 1.02)	0.92 (0.83, 1.02)
Chronic bronchitis	Mean (μg/L)case/control	15.57/16.88	7.74/9.37
	Adjusted (95% CI)	1.06 (0.99, 1.12)	1.10 (0.98, 1.19)
Emphysema	Mean (μg/L)case/control	11.24/16.88	6.51/9.30
	Adjusted (95% CI)	0.95 (0.89, 1.02)	0.93 (0.84, 1.05)
Chronic Cough	Mean (μg/L)case/control	17.98/17.09	8.26/9.39
	Adjusted (95% CI)	0.89 (0.82, 1.02)	0.85 (0.74, 0.99)
Phlegm	Mean (μg/L)case/control	23.42/16.52	9.32/9.26
	Adjusted (95% CI)	0.99 (0.89, 1.11)	1.02 (0.87, 1.23)
Wheeze	Mean (μg/L)case/control	15.22/17.02	8.88/9.30
	Adjusted (95% CI)	0.86 (0.79, 0.92)	0.93 (0.83, 1.05)

[a] Inorganic arsenic concentration is estimated by subtracting total urinary arsenic by organic arsenic (arsenobentaine and arsenocholine concentrations).

[b] Linear regression of log-transformed urinary arsenic concentrations were adjusted for gender, age (20–39, 40–59, ≥60 yr), race/ethnicity (white, black, Mexican American, other), education (<high school, high school, >high school), BMI (<25, 25–29, ≥30 kg/m^2), serum cotinine category (<0.015, 0.015–9.9, ≥10 ng/ml), and continuous urinary creatinine (mg/dl). Ratio of adjusted mean concentrations and 95% confidence intervals are presented for participants with/without respiratory diagnoses.

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TABLE 3

Odds Ratio and 95% Confidence Intervals of Having Respiratory Disease Comparing Lowest Quintile With Highest Quintile of Measured Total Urinary Arsenic and Estimated Inorganic Arsenic

Diagnosis	Numberwith	Numberwithout	Total arsenic		Estimated inorganic
			Adjusted[a] OR (95% CI)	Organic adjusted[b] OR (95% CI)	adjusted[a] OR (95% CI)
Asthma					
≤20th %	69	467	1.00	1.00	1.00
≥80th %	60	478	0.71 (0.41, 1.24)	1.27 (0.51, 3.12)	0.79 (0.43, 1.46)
	129	945	$p = .23$	$p = .60$	$p = .46$
Chronic Bronchitis					
≤20th %	40	494	1.00	1.00	1.00
≥80th %	35	503	0.83 (0.42, 1.62)	0.77 (0.24, 2.51)	0.76 (0.36, 1.61)
	75	997	$p = .58$	$p = .67$	$p = .47$
Emphysema					
≤20th %	15	520	1.00	1.00	1.00
≥80th %	7	466	0.77 (0.24, 2.49)	1.29 (0.17, 9.82)	0.72 (0.13, 3.81)
	22	986	$p = .66$	$p = .80$	$p = .70$

Note. CI, confidence interval; OR, odds ratio.

[a]Adjusted for gender, age (20–39, 40–59, ≥60 yr), race/ethnicity (white, black, Mexican American, other), education (<high school, high school, >high school), BMI (<25, 25–29, ≥30 kg/m^2), serum cotinine category (<0.015, 0.015–9.9, ≥10 ng/ml), and continuous urinary creatinine (mg/dl).

[b]Further adjustment of total arsenic for arsenobentaine concentration (μg/L), a major component of organic arsenic, and serum mercury (μg/L), a biomarker for fish consumption.

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TABLE 4

Odds Ratio and 95% Confidence Intervals of Having Respiratory Symptoms Comparing Lowest Quintile With Highest Quintile of Measured Total Urinary Arsenic and Estimated Inorganic Arsenic

Symptom	Numberwith	Numberwithout	Total arsenic		Estimated inorganic
			Adjusted[a] OR (95% CI)	Organic adjusted[b] OR (95% CI)	adjusted[a] OR (95% CI)
Chronic cough					
≤20th %	71	378	1.00	1.00	1.00
≥80th %	37	419	0.63 (0.34, 1.18)	0.49 (0.16, 1.50)	0.61 (0.30, 1.22)
	108	797	*p* = .15	*p* = .21	*p* =.16
Wheezing					
≤20th %	85	451	1.00	1.00	1.00
≥80th %	62	476	0.56 (0.33, 0.95)	0.85 (0.35, 2.07)	0.74 (0.43, 1.29)
	147	927	*p* = .03	*p* =.73	*p* =.29
Phlegm					
≤20th %	51	398	1.00	1.00	1.00
≥80th %	34	422	0.76 (0.39, 1.48)	0.66 (0.20, 2.20)	0.75 (0.36, 1.54)
	85	820	*p* = .42	*p* =.50	*p* =.44

Note. CI, confidence interval; OR, odds ratio.

[a]Adjusted for gender, age (20–39, 40–59, ≥60 yr), race/ethnicity (white, black, Mexican American, other), education (<high school, high school, >high school), BMI (<25, 25–29, ≥30 kg/m^2), serum cotinine category (<0.015, 0.015–9.9, ≥10 ng/ml), and continuous urinary creatinine (mg/dl).

[b]Further adjustment of total arsenic for arsenobentaine concentration (μg/L), a major component of organic arsenic, and serum mercury (μg/L), a biomarker for fish consumption.