Arsenic Exposure and Impaired Lung Function

Findings from a Large Population-based Prospective Cohort Study

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Rationale: Exposure to arsenic through drinking water has been linked to respiratory symptoms, obstructive lung diseases, and mortality from respiratory diseases. Limited evidence for the deleterious effects on lung function exists among individuals exposed to a high dose of arsenic.

Objectives: To determine the deleterious effects on lung function that exist among individuals exposed to a high dose of arsenic.

Methods: In 950 individuals who presented with any respiratory symptom among a population-based cohort of 20,033 adults, we evaluated the association between arsenic exposure, measured by well water and urinary arsenic concentrations measured at baseline, and post-bronchodilator-administered pulmonary function assessed during follow-up.

Measurements and Main Results: For every one SD increase in baseline water arsenic exposure, we observed a lower level of FEV₁ (−46.5 ml; $P < 0.0005$) and FVC (−53.1 ml; $P < 0.01$) in regression models adjusted for age, sex, body mass index, smoking, socioeconomic status, betel nut use, and arsenical skin lesions status. Similar inverse relationships were observed between baseline urinary arsenic and FEV₁ (−48.3 ml; $P < 0.005$) and FVC (−55.2 ml; $P < 0.01$) in adjusted models. Our analyses also demonstrated a dose-related decrease in lung function with increasing levels of baseline water and urinary arsenic. This association remained significant in never-smokers and individuals without skin lesions, and was stronger in male smokers. Among male smokers and individuals with skin lesions, every one SD increase in water arsenic was related to a significant reduction of FEV₁ (−74.4 ml, $P < 0.01$; and −116.1 ml, $P < 0.05$) and FVC (−72.8 ml, $P = 0.02$; and −146.9 ml, $P = 0.004$), respectively.

Conclusions: This large population-based study confirms that arsenic exposure is associated with impaired lung function and the deleterious effect is evident at low- to moderate-dose range.

Keywords: arsenic exposure; lung function; Bangladesh

Arsenic from drinking water has been linked with cancers, dermatologic, cardiovascular, reproductive, and neurotoxic outcomes among adults and children (1–8). Chronic exposure to arsenic

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Nonmalignant respiratory effects of low- to moderate-dose arsenic exposure are currently unknown.

What This Study Adds to the Field

This study documents, for the first time, that low- to moderate-dose arsenic exposure may have deleterious nonmalignant respiratory effects.

has also been linked to nonmalignant respiratory effects including respiratory symptoms, chronic obstructive pulmonary disease, and respiratory disease mortality (9–12). However, the evidence of the effect of arsenic exposure on lung function is limited, especially at the low- to moderate-dose ranges. Several studies from arsenic-endemic areas of South Asia reported lower FEV₁ and FVC among individuals with arsenical skin lesions or drinking water with very high levels of arsenic ($>250 \mu\text{g/L}$) (13–15). Interestingly, a recent retrospective study from Chile identified that those exposed to arsenic either *in utero* or early life had a lower FEV₁ (11.5%; $P = 0.04$) and FVC (12.2%; $P = 0.04$) in adulthood compared with those unexposed (16).

The published studies measuring pulmonary function involved small sample sizes and most lacked individual-level exposure data or measured arsenic exposure ecologically (13–16). Little is known of the relationship between arsenic exposures and lung function in populations exposed to low-to-moderate levels of arsenic or among individuals without skin lesions.

To evaluate the effects of arsenic exposure on lung function, we conducted analyses using data from the Health Effects of Arsenic Longitudinal Study (HEALS), a prospective cohort of 20,033 individuals in Araihaazar, Bangladesh (17). HEALS participants have been exposed to a wide range (0.1–790 $\mu\text{g/L}$) of water arsenic thus providing a unique opportunity to prospectively examine the relationship of low-to-moderate levels of arsenic exposure (measured in drinking water and urine) with lung function impairment based on both prebronchodilator and post-bronchodilator-administered pulmonary function tests (PFTs). Some of the initial results of these studies have been previously reported in the form of an abstract (18).

METHODS

Study Population and Recruitment

The description of HEALS study methodologies has been presented elsewhere (17, 19). Briefly, using a population-based sampling scheme,

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we recruited a total of 20,033 adults (11,746 during 2000–2002 and 8,287 during 2006–2008) with an overall response rate of 97%. At baseline, in addition to drinking water (tube-well), urine and blood samples, detailed arsenic exposure history, and smoking and demographic data were collected by trained interviewers. This study was approved by the Institutional Review Boards of Columbia University, University of Chicago, and Bangladesh Medical Research Council.

Measurements of Arsenic Exposure

Water arsenic. Field sample collection and laboratory analyses procedures are described elsewhere in detail (20–22). Briefly, the water samples, collected in 20-ml polyethylene scintillation vials, were acidified to 1% with high-purity Optima HCl (Fisher Scientific, Pittsburgh, PA) at least 48 hours before analysis (21). The water samples were analyzed by high-resolution inductively coupled plasma mass spectrometry for multielements (including arsenic) as previously described (21). The detection limit for arsenic of this method is 0.1 $\mu\text{g/L}$; the SD of a single measurement is conservatively estimated at 4 $\mu\text{g/L}$ (22). Arsenic concentration in well water has been relatively stable and does not change over time under normal conditions, especially in our study area (23, 24).

Urinary arsenic and creatinine assays. Urinary arsenic (UA) was measured at baseline and biannually thereafter in spot urine samples, which were collected in 50-ml acid-washed tubes and carried in portable coolers with ice-packs until storage at -20°C within 6 hours. UA assays were performed with graphite furnace atomic-absorption using a Perkin-Elmer Analyst 600 graphite furnace system (Branford, CT) as described (25). The detection limit for UA was 2 $\mu\text{g/L}$. Urinary creatinine was analyzed by a colorimetric method based on the Jaffe reaction. At follow-up visits, we collected information on the status of well and water consumption behavior and pattern from the study participants, and measured UA as a biomarker for exposure to track potential changes in exposure.

Follow-up and Outcome Assessment

Follow-up. Since recruitment, the cohort has been undergoing active and passive follow-up through several complementary approaches. First, trained physicians visited all participants biannually at their homes to assess health status information, to update demographic and lifestyle data, and to collect urine samples. Second, trained health assistants visited study participants semiannually at their homes to gather information on health outcomes including clinical symptoms, major illnesses, or death. Finally, in addition to active follow-up through scheduled home visits, we established a dedicated clinic in the study area to provide routine primary health care exclusively to all study participants through trained primary care physicians, which also provides a supplementary method for follow-up. Study participants with suggestive signs or symptoms of any major chronic diseases ascertained through the active or supplemental follow-up mechanisms are invited to the chronic disease unit of our clinic for a comprehensive clinical assessment, and biochemical, radiologic, and other diagnostic investigations.

Outcome assessment. For this analysis we included individuals with any self-reported respiratory symptoms because they were at a higher risk of suffering from a chronic lung disease. This approach is consistent with our interest in early detection and diagnosis of respiratory outcomes, which is also one of the aims of the HEALS study. We identified a total of 1,485 study participants with self-report of symptoms of respiratory disease including chronic cough, shortness of breath, or blood in the sputum during follow-up between 2005 and 2010. These individuals were invited to the chronic disease unit of our clinic to undergo further evaluation and diagnostic confirmation, which included a PFT, followed by appropriate treatment and referral to the only local hospital in the study area. Of 1,485 individuals invited, 182 did not come to the appointment. Because of our comprehensive follow-up mechanism in which we systematically identified and invited all individuals with any self-report of symptoms of respiratory disease, PFT measures in this study include a wide range of values representing full spectrum of risk in the population. As a consequence a large number of study participants had PFT measures within normal range.

Pulmonary function test. Of 1,303 who came to the appointment, we first evaluated each participant for active communicable infection or symptoms suggestive of a malignancy by clinical examination. A chest radiograph (posterior anterior and lateral views) was performed to carefully examine for presence of parenchymal, bony, or cardiac abnormalities. If

an infection, such as tuberculosis, was suspected, lung function testing was deferred until such an infection was confirmed and treated. We could not perform PFT on participants who were too ill ($n = 18$); had confirmed diagnosis of tuberculosis or lung malignancy ($n = 44$); or who were unwilling to take the test ($n = 109$).

Between March 2008 and November 2011, PFT was performed on 1,132 individuals with a portable, battery-operated, ultrasound transit-time–based spirometer (EasyOne; NDD Medical Technologies, Chelmsford, MA, and Zurich, Switzerland), which has been used successfully for PFT in previous studies (18, 24, 26) and in the same population in Bangladesh (27). All tests were performed in accordance with the American Thoracic Society recommendations (28). Lung function parameters, such as FVC, FEV₁, peak expiratory flow rate, and FEV₁/FVC ratio, were obtained and recorded. All PFTs were performed at roughly similar times of the day (9 AM to noon) to minimize diurnal variation. Adult spirometry was interpreted using the Global Initiative for Chronic Obstructive Lung Disease criteria (29).

On the day of the PFT, height and weight were measured and smoking history was assessed from the study participants included in this analysis. After explaining the purpose of the study and the procedure, individuals while in a seated position were asked to exhale forcibly as hard and as fast as possible through the disposable mouthpiece. The procedure was repeated up to six times until three reproducible reports were generated. A minimum of three and a maximum of six efforts were attempted.

Post-bronchodilator PFT. We conducted prebronchodilator and post-bronchodilator–administered PFT on all participants as part of our clinical assessment to identify chronic lung diseases including asthma, obstructive, and restrictive pulmonary diseases in our cohort. All pre-bronchodilator and post-bronchodilator–administered PFTs were performed by a single trained physician at our clinic who was masked to the arsenic exposure status of the participants.

During scheduling of PFT appointment, participants were asked to avoid taking any kind of bronchodilator for 12–24 hours before coming to clinic. After baseline (prebronchodilator) PFT, 400 μg salbutamol was administered by a spacer. Spirometry was repeated after 15 minutes. A positive response was recorded with an increase of 12% and 200 ml in the FEV₁ or FVC from baseline values after inhalation of the bronchodilator drug.

Quality control and calibration. Because the EasyOne spirometer is a handheld device, we compared its readings among several patients and healthy volunteers with a standard spirometer clinically used at the Dhaka Chest Institute hospital, Bangladesh, in collaboration with expert pulmonologists. The agreement between the spirometry used at Dhaka Chest Institute hospital and EasyOne was excellent (27).

The EasyOne spirometer determines the quality grade of the PFT from A to F. We considered the best three comparable readings with grades A or B (with the three readings within 5% variation or 100 ml) for analysis. We ensured that expiration time was maintained for at least 6 seconds. On the graph, we checked for smoothness and rapid start of the blow without any broken or double lines that may occur because of cough or hesitation. A single trained physician checked each selected reading. In addition, 5% of the randomly selected PFT data were reevaluated by one of the coauthors (C.O.), a board-certified pulmonologist at the University of Chicago, to ensure quality of the test results. We calibrated the devices every morning following the EasyOne manual guideline, using a known 3-L syringe. We started the calibration by nulling the spirantes. We ensured that during the procedure there was no air flow through it. A successful calibration was determined by an accuracy message displayed by the device.

Of 1,132 individuals who underwent PFT, 118 were excluded because of poor quality data based on the protocol developed by our pulmonologists, resulting in data on 950 participants available for analyses in the present study.

Statistical Analyses

Descriptive statistics were conducted first to evaluate differences in demographic and lifestyle variables between the study population and the overall cohort, and to assess whether arsenic exposure variables (water and urinary arsenic) and PFT measures (FEV₁ and FVC) differed by demographic and lifestyle variables using *t* tests and analysis of variance. We assessed associations between water arsenic and UA with FEV₁ and FVC in separate multivariate linear regression models, with and without

adjustment for potential confounders including age, sex, body mass index (BMI; kilogram per square meter), educational attainment, betel nut use, skin lesion and smoking status. Arsenic exposure variables were grouped into tertiles to assess the dose–response relationship. We examined the assumption of nonlinear effects of arsenic exposure by including higher-order polynomial terms for arsenic exposure variables in the models, and there was no indication of any nonlinear relation. Therefore, we also estimated differences in PFT measures for one SD increase in arsenic exposure variables for better interpretation of the results. In addition, we conducted stratified analyses to evaluate the associations between baseline arsenic exposure and lung function by sex and baseline smoking and arsenical skin lesion status. Sensitivity analyses were conducted using smoking status at the follow-up visit closest to the PFT and to additionally control for other indicators of socioeconomic status including television ownership and land ownership; however, results were similar and therefore they are not shown. The prevalence of restriction pattern was uncommon in the study population. Nevertheless, sensitivity analyses were also conducted to evaluate associations between arsenic exposure and restricted pattern using FEV₁ and FVC ratio. All statistical analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

The study population represents a set of individuals who are at higher risk of respiratory disease screened from our total population-based cohort. Compared with cohort participants who were not included in the present study, subjects included

were older, thinner, of lower educational attainment, and more likely to have smoked or used betel nut. They were also more likely to have respiratory symptoms, as expected (*see the Appendix, Table A1*).

Distributions of arsenic exposure variables and pulmonary function measures by baseline demographic and lifestyle variables are shown in Table 1. As expected, lung function declined with increasing age. The average age of the study participants was 42 years at baseline. Male sex and higher BMI were associated with better lung function. Betel nut users had poorer lung function measures. Ever-smokers had higher levels of FVC compared with never-smokers, probably because of the fact that most smokers were men. There were only 83 participants with skin lesions in this study and their level of FEV₁ was significantly lower than those without skin lesions. Individuals with higher educational attainment had better lung function measures.

Table 2 shows the association between arsenic exposure at baseline and lung function measures adjusted for demographic and lifestyle factors including age, sex, BMI, length of education, smoking status, betel nut use, and presence of arsenical skin lesions. There was an inverse dose–response relationship between baseline arsenic exposure levels, measured using either WA or UA, and both FEV₁ and FVC values. Individuals in the highest tertile of baseline well WA concentration (>97 µg/L) had a significantly lower FEV₁ (−80.6 ml; *P* < 0.01) and FVC

TABLE 1. DISTRIBUTION OF LUNG FUNCTION MEASURES AND BASELINE ARSENIC EXPOSURE BY BASELINE DEMOGRAPHIC AND LIFESTYLE CHARACTERISTICS

Baseline Demographic and Lifestyle Characteristics	% (n)	Baseline Water Arsenic (µg/L)	Baseline Urinary Arsenic (µg/g Creatinine)	FEV ₁ (L)	FVC (L)
Age					
<37	32.3 (307)	92.37	279.41	1.85	2.46
37–47	33.3 (317)	92.02	285.64	1.48	2.16
>47	34.3 (326)	85.41	264.13	1.30	2.09
<i>P</i> value		0.65	0.65	<0.01	<0.01
Sex					
Male	47.5 (417)	95.15	258.1	1.63	2.48
Female	52.5 (499)	83.99	296.5	1.44	1.96
<i>P</i> value		0.11	0.03	<0.01	<0.01
Body mass index					
<18	29.2 (275)	85.12	297.3	1.41	2.16
18–20.5	45.2 (425)	93.10	265.7	1.63	2.33
>20.5	25.5 (240)	89.42	250.5	1.66	2.25
<i>P</i> value		0.63	0.08	<0.01	<0.01
Smoking status					
Never	44.0 (417)	91.89	301.8	1.56	2.10
Ever	56.0 (533)	88.29	256.5	1.52	2.34
<i>P</i> value		0.60	0.01	0.33	<0.01
Betel nut use					
Never	45.0 (428)	97.19	276.4	1.75	2.41
Ever	55.0 (522)	83.85	276.0	1.36	2.09
<i>P</i> value		0.05	0.98	<0.01	<0.01
Skin lesion status					
No	84.2 (853)	86.51	264.9	1.55	2.24
Yes	8.4 (83)	125.08	396.7	1.39	2.16
<i>P</i> value		<0.01	<0.01	0.02	0.27
Education					
No education	55.0 (523)	83.78	286.5	1.46	2.16
1–5 yr	31.5 (300)	96.94	263.9	1.63	2.32
>5 yr	13.3 (127)	98.13	262.2	1.67	2.34
<i>P</i> value		0.45	<0.01	<0.01	<0.01
Land ownership					
No	54.0 (512)	93.21	310.8	1.62	2.31
Yes	46.0 (437)	107.10	290.6	1.58	2.27
<i>P</i> value		0.09	0.36	0.38	0.29
Television at home					
No	63.7 (605)	102.90	309.7	1.56	2.28
Yes	36.3 (345)	92.73	286.3	1.65	2.32
<i>P</i> value		0.09	0.13	0.10	0.61

TABLE 2. ASSOCIATION BETWEEN ARSENIC EXPOSURE AND LUNG FUNCTION MEASURES BASED ON MULTIVARIATE LINEAR REGRESSION MODELS

	n	FEV ₁ (ml)		FVC (ml)	
		b (95% CI)*	P Value	b (95% CI)*	P Value
Water arsenic concentration, µg/L					
<19	312	Ref		Ref	
>19–97	315	–33.1 (–114.6 to 48.4)	0.42	–13.2 (–97.3 to 71.0)	0.75
>97	315	–80.6 (–181.4 to –17.5)	0.01	–97.3 (–181.8 to –12.7)	0.02
Water arsenic concentration†	942	–46.5 (–83.0 to –10.0)	0.01	–53.1 (–90.7 to –15.4)	0.005
Urinary arsenic concentration, µg/g creatinine					
<125	298	Ref		Ref	
>125–285	321	–67.0 (–148.3 to 14.1)	0.10	–36.4 (–120.4 to 47.0)	0.39
>285	305	–90.5 (–173.6 to –7.4)	0.03	–81.0 (–166.7 to 4.8)	0.06
Urinary arsenic concentration†	924	–48.3 (–82.5 to –14.1)	0.005	–55.2 (–90.5 to –19.9)	0.02

Definition of abbreviation: CI = confidence interval.

*Effect estimates were adjusted for age, sex, body mass index, smoking, betel nut use, educational attainment, and skin lesion.

†One standard deviation of baseline water (118.1 µg/L) and urinary arsenic (277.2 µg/g creatinine).

(–97.3 ml; $P = 0.02$) compared with individuals with baseline well arsenic less than 19 µg/L. For every one SD increase in well arsenic concentration (118.1 µg/L), we observed that FEV₁ and FVC were lowered by 46.5 ml and 53.1 ml, respectively. Similar associations were observed using baseline UA as the exposure variable. Individuals in the highest tertile of baseline UA (>285 µg/g creatinine) had significantly lower FEV₁ (–90.5 ml; $P = 0.03$) and marginally significantly lower FEV₁ (–81 ml; $P = 0.06$) compared with individuals with UA less than 125 µg/g creatinine. For every one SD increase in baseline UA, we observed that FEV₁ and FVC were lower by 48.3 ml and 55.2 ml, respectively. These associations remained similar after excluding subjects with skin lesions. Each one SD increase in well WA was associated with a reduction of 49 ml ($P < 0.01$) and 55.8 ml ($P = 0.008$) in FEV₁ and FVC, respectively, among those without skin lesions. Each SD increase in UA was associated with a reduction of 48.6 ml ($P < 0.01$) and 54.9 ml ($P = 0.006$) in FEV₁ and FVC among those without skin lesions. Sensitivity analyses were also conducted using the FEV₁/FVC

ratio as the endpoint. The FEV₁/FVC ratio decreased with increasing age, decreasing BMI, and in men, among smokers, or those with skin lesions. The associations between arsenic exposures measured in urine or water and FEV₁/FVC ratio were inverse; however, they were not statistically significant (data not shown).

In fully adjusted separate multivariate linear regression models, we assessed associations between arsenic exposure and lung function stratified by sex and smoking status (Table 3). Because there was no evidence of a nonlinear relationship between arsenic exposure and lung function, arsenic exposure variables were treated as continuous variables, and we estimated differences in lung function in relation to a one SD increase in arsenic exposures in stratified analyses. The association of arsenic exposure, measured either using well WA or UA, with FVC was significant in men and in women separately. The association between arsenic exposure and FEV₁ was significant in men only ($P = 0.03$ for WA and 0.02 for UA). In women, the direction of the association was consistent although not statistically significant ($P = 0.09$ for WA and 0.13 for UA). The association remained significant among individuals

TABLE 3. ASSOCIATION BETWEEN ARSENIC EXPOSURE AND LUNG FUNCTION MEASURES BASED ON MULTIVARIATE LINEAR REGRESSION MODELS BY SEX AND SMOKING STATUS

	N	FEV ₁ (ml)		FVC (ml)	
		b (95% CI)*	P Value	b (95% CI)*	P Value
Men					
Water arsenic conc.†	496	–58.7 (–101.5 to –15.9)	0.03	–60.2 (–118.2 to –2.2)	0.04
Urinary arsenic conc.†	488	–66.6 (–126.4 to –6.8)	0.02	–63.9 (–126.8 to –0.9)	0.04
Women					
Water arsenic conc.†	446	–41.5 (–89.4 to 6.4)	0.09	–54.9 (–10.04 to –6.8)	0.02
Urinary arsenic conc.†	436	–29.3 (–410.3 to 351.7)	0.13	–46.0 (–84.2 to –7.9)	0.02
Ever-smokers					
Water arsenic conc.†	529	–51.1 (–102.8 to 0.4)	0.05	–52.7 (–108.1 to 2.7)	0.06
Urinary arsenic conc.†	523	–45.4 (–100.2 to 9.4)	0.10	–46.8 (–634.0 to 540.4)	0.11
Never-smokers					
Water arsenic conc.†	413	–40.6 (–91.4 to 10.2)	0.11	–53.9 (–103.1 to –4.6)	0.03
Urinary arsenic conc.†	401	–37.4 (–80.0 to 5.1)	0.08	–50.53 (–91.8 to –9.1)	<0.01
Ever-smoking men					
Water arsenic conc.†	447	–74.4 (–132.8 to –16.0)	0.01	–72.8 (–135.2 to –10.5)	0.02
Urinary arsenic conc.†	447	–65.0 (–128.0 to –1.7)	0.04	–60.6 (–128.0 to 6.8)	0.07
Never-smoking men					
Water arsenic conc.†	52	–18.3 (–200.8 to 164.1)	0.84	–24.2 (–196.1 to 147.7)	0.78
Urinary arsenic conc.†	52	–55.6 (–264.2 to 153.0)	0.60	–62.7 (–259.1 to 133.6)	0.53

Definition of abbreviations: CI = confidence interval; conc. = concentration.

*Effect estimates were adjusted for age, sex, body mass index, betel nut use, educational attainment, and skin lesion status. Stratified analyses by smoking status in overall were adjusted for sex and vice versa.

†One standard deviation of baseline water (118.1 µg/L) and urinary arsenic (277.2 µg/g creatinine).

without skin lesions and was particularly strong among male smokers. However, the effect of arsenic exposure on FEV₁ was similar by smoking status, with a weaker and nonsignificant association between arsenic exposure and FEV₁ in never-smokers. Given that 90% of the smokers were men, we conducted stratified analyses by smoking status in men. Among ever-smoking men, for each SD increase in well WA concentration, we observed a reduction of 72.8 ml ($P = 0.02$) in FVC and a reduction of 74.4 ml ($P = 0.01$) in FEV₁. Similar associations were observed using UA as the exposure variable. This association remained significant among individuals without skin lesions and was particularly strong among male smokers. With respect to skin lesion status, each one SD increase in well WA was associated with a reduction of 116 ml ($P < 0.05$) and 146.9 ml ($P = 0.004$) in FEV₁ and FVC, respectively, among participants with skin lesions ($n = 83$), compared with a reduction of 49 ml ($P < 0.01$) and 55.8 ml ($P = 0.008$) in FEV₁ and FVC, respectively, among those without skin lesions ($n = 553$). Each SD increase in UA was associated with a reduction of FEV₁ and FVC by 57 ml ($P = 0.14$) and 75.1 ml ($P = 0.06$), respectively, among participants with skin lesions, compared with a reduction of 48.6 ml ($P < 0.01$) and 54.9 ml ($P = 0.006$) in FEV₁ and FVC, respectively, among those without skin lesions.

DISCUSSION

To our knowledge, this is the first large population-based study that systematically evaluated the relationship between arsenic exposure and lung function at the individual level. Overall, we found a significant inverse relationship between past arsenic exposure assessed at baseline and post-bronchodilator FEV₁ and FVC during follow-up. This association remained significant in individuals without skin lesions, and was stronger in male smokers.

Our findings clearly demonstrate a significant impairment of lung function associated with arsenic exposure at lower levels of WA concentration than previous reports. We also made novel observations that betel nut use and low BMI seem to adversely impact lung function in arsenic-exposed population. Consistently, three earlier studies from India and Pakistan observed that high levels of WA were associated with impaired lung function in populations that rely on groundwater (13–15). A few past studies also reported adverse respiratory outcomes (10, 11, 15, 30) in persons with skin lesion from arsenic-affected areas of Bangladesh and India. However, these studies had included relatively small sample size ($n = 87$ –287).

The loss of lung function or adverse respiratory outcomes among individuals with skin lesions compared with those without lesions may not be directly attributable to arsenic exposure and its specific levels. However, in our study, the skin lesion cases were exposed to higher WA concentration (125 vs. 87 $\mu\text{g/L}$; $P = 0.008$), were slightly older (47 vs. 42 yr; $P < 0.0001$), and were more likely to be smokers (11% vs. 4%; $P < 0.0001$) compared with those without skin lesions. It is possible that these factors may have contributed to a greater loss of lung function among individuals with skin lesions in our study. Importantly, however, the inverse association between arsenic exposure and lung function in the present study remained similar in subjects without skin lesions, excluding the possibility that the association may be a result of pathogenesis or other extraneous correlates of skin lesions.

The literature on whether the association between arsenic exposure and lung function differs by smoking status is somewhat inconsistent. For instance, a study from India reported decreased FEV₁ (271 ml) and FVC (304 ml) among male smokers compared with nonsmokers (15). A retrospective study from Chile also found a strong effect of arsenic exposure on lung function impairment among nonsmokers who were exposed to arsenic early in life (16). By contrast, a study from Pakistan did not report

additional risk for impaired lung function among smokers exposed to arsenic in water (14). In the present study, we observed a clear decline in FVC among never-smokers exposed to arsenic. The association between arsenic exposure and FVC was also stronger in ever-smokers compared with never-smokers among men, supporting a possible synergy between arsenic exposure and smoking, which has been documented in studies on cancer and cardiovascular disease (2, 8).

We observed a decline of FVC, an early indication of restrictive type of lung impairment, associated with arsenic exposure across sex and smoking status. This is consistent with earlier findings where greater declines of FVC were reported (14, 15). The present study also observed a dose–response increase of restrictive changes among men. Restrictive lung defects are usually progressive and irreversible and may lead to serious lung disease including interstitial lung disease, which was reported anecdotally in the arsenic-exposed population in Chile. Effects of arsenic on permanent fibrotic changes of the lung have also been reported in animal studies (31, 32).

The mechanism by which WA leads to a decline in lung function remains unclear; however, earlier human and animal studies indicate deposition and permanent structural changes in the lung epithelium as a result of arsenic exposure (33, 34). Animal studies showed tissue inflammation and increased morphologic changes in the lung with increasing arsenic exposure (31, 35). Impaired repair mechanisms in the human epithelium of the airway have also been demonstrated by the up-regulation of metalloproteinase-9 in extracellular matrix in arsenic-exposed subjects (36). Clara cell 16 protein, which is known to play an important role in protecting the alveolar epithelium of the lung in chronic inflammation (37, 38), has also been impacted by arsenic exposure (27).

The present study has several strengths including a large sample size with population-based ascertainment, availability of individual-level measures of multiple arsenic exposure constructs, and standardized post-bronchodilator–administered spirometry variables. UA has strengths that it is a biomarker for internal dose from all sources of exposure and may capture more variation in exposure. However, arsenic concentrations measured in spot urine samples may be affected by the variation in dilution caused by variation in the state of hydration. Water arsenic exposure data can be interpreted easily for practical and policy issues. It is critical to assess exposure disease association using both WA and UA, because in a well-characterized population exposed to arsenic largely through drinking water the associations should be consistent. The study also has several limitations. Although systematically ascertained from an underlying population-based cohort, because the PFTs were conducted among individuals who reported having at least one self-report respiratory symptom, the study findings do not generalize directly to the general population. In addition, our findings may not be readily used for clinical evaluation because the standards are based on mostly Western populations.

In summary, we found that arsenic exposure at low-to-moderate levels impairs lung function in Bangladesh population. The inverse association between arsenic exposure and FVC was consistent across sexes, remained significant in never-smokers, and was strongest in male smokers. This suggests that a large proportion of the country's population are at an increased risk of developing serious respiratory diseases, including chronic obstructive pulmonary disease, bronchitis, and interstitial lung disease in the future (10, 12, 13). Although future research needs to evaluate the association among healthy individuals without any respiratory symptoms, the robust findings from the present population-based study warrant the need for appropriate mitigation and policy efforts not only for the reduction of arsenic

exposure but also on other cofactors including cessation of smoking to reduce the mortality and morbidity caused by arsenic-related respiratory diseases.

Author disclosures are available with the text of this article at www.atsjournals.org.

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APPENDIX

TABLE A1. DISTRIBUTION OF DEMOGRAPHIC AND LIFESTYLE CHARACTERISTICS OF THE OVERALL COHORT AND LUNG FUNCTION-TESTED STUDY PARTICIPANTS

	Subjects Not Included for Lung Function Test % (n) (N = 19,083)	Lung Function Performed Cases % (n) (N = 950)	P Value
Age			
<37	56 (10,614)	32 (307)	<0.0001
37–47	26 (5,054)	34 (317)	
>47	18 (3,350)	34 (326)	
Unknown	74		
Sex			
Male	41 (8,163)	53 (499)	<0.0001
Female	59 (11,870)	47 (451)	
Unknown	74		
Body mass index			
<18	31 (6,506)	45 (425)	<0.0001
18–20.5	35 (6,467)	29 (275)	
>20.5	34 (5,769)	26 (240)	
Unknown	351		
Smoking status			
Never	69 (13,049)	44 (417)	<0.0001
Ever	31 (5,952)	56 (533)	
Unknown	82		
Betel nut use			
Never	66 (12,555)	45 (428)	<0.0001
Ever	34 (6,449)	55 (522)	
Unknown	79		
Skin lesion status			
No	95 (18,150)	92 (859)	<0.0001
Yes	5 (873)	8 (77)	
Unknown	60	14	
Education			
No education	43 (8,168)	55 (523)	<0.0001
1–6 yr	34 (6,446)	32 (300)	
≥6 yr	23 (4,384)	13 (127)	
Unknown	85		
Baseline arsenic measure	Mean (SD)	Mean (SD)	
Water arsenic, µg/L	81.23 (105.8)	89.87 (107.2)	<0.01
Urinary arsenic, µg/g creatinine	257.7 (269.2)	276.2 (277.2)	<0.05