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Decrements in Lung Function Related to Arsenic in Drinking Water in West Bengal, India

Ondine S. von Ehrenstein[1], D. N. Guha Mazumder[2], Yan Yuan[1], Sambit Samanta[2], John Balmes[1,3], Arabinda Sil[2], Nilima Ghosh[2], Meera Hira-Smith[1], Reina Haque[4], Radhika Purushothamam[1], Sarbari Lahiri[2], Subhankar Das[2], and Allan H. Smith[1]

[1] Arsenic Health Effects Research Program, School of Public Health, University of California, Berkeley, CA.
[2] Institute of Post Graduate Medical Education and Research, Kolkata, India.
[3] Division of Occupational and Environmental Medicine, University of California, San Francisco, CA.
[4] Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA.

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During 1998–2000, the authors investigated relations between lung function, respiratory symptoms, and arsenic in drinking water among 287 study participants, including 132 with arsenic-caused skin lesions, in West Bengal, India. The source population involved 7,683 participants who had been surveyed for arsenic-related skin lesions in 1995–1996. Respiratory symptoms were increased among men with arsenic-caused skin lesions (versus those without lesions), particularly "shortness of breath at night" (odds ratio (OR) = 2.8, 95% confidence interval (CI): 1.1, 7.6) and "morning cough" (OR = 2.8, 95% CI: 1.2, 6.6) in smokers and "shortness of breath ever" (OR = 3.8, 95% CI: 0.7, 20.6) in nonsmokers. Among men with skin lesions, the average adjusted forced expiratory volume in 1 second (FEV_1) was reduced by 256.2 ml (95% CI: 113.9, 398.4; $p < 0.001$) and the average adjusted forced vital capacity (FVC) was reduced by 287.8 ml (95% CI: 134.9, 440.8; $p < 0.001$). In men, a 100-μg/liter increase in arsenic level was associated with a 45.0-ml decrease (95% CI: 6.2, 83.9) in FEV_1 ($p = 0.02$) and a 41.4-ml decrease (95% CI: −0.7, 83.5) in FVC ($p = 0.054$). Women had lower risks than men of developing skin lesions and showed little evidence of respiratory effects. In this study, consumption of arsenic-contaminated water was associated with respiratory symptoms and reduced lung function in men, especially among those with arsenic-related skin lesions.

arsenic; India; respiratory function tests; signs and symptoms, respiratory; water; water pollutants

Abbreviations: CI, confidence interval; $FEF_{25–75}$, forced expiratory flow between 25 and 75 percent of forced vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; OR, odds ratio; SMR, standardized mortality ratio.

Worldwide, populations have been identified that consume drinking water with arsenic concentrations above the World Health Organization's guideline value and the US Environmental Protection Agency's maximum contaminant level of 10 μg/liter (1–4). Widespread arsenic poisoning from drinking water is present in West Bengal, India (5), and neighboring Bangladesh (6, 7). Millions of people are exposed, and more contaminated areas along the Ganges River delta were recently identified (8). Naturally occurring arsenic that contaminates drinking water is the source of this ongoing global public health problem.

Arsenic in drinking water has been linked to lung cancer (9–14) and several other diseases, including cardiovascular disease, peripheral neuropathy, skin lesions, skin cancer, and bladder cancer (15). The International Agency for Research on Cancer recently classified arsenic in drinking water as a "Group I" human carcinogen based on evidence of increased risks of skin cancer, bladder cancer, and lung cancer (16). Most lung carcinogens also cause chronic respiratory disease, but very few studies have assessed nonmalignant respiratory effects in arsenic-exposed populations, although some limited evidence supports increased risks (14, 17–19).

Reprint requests to Dr. Allan H. Smith, Arsenic Health Effects Research Program, School of Public Health, 140 Warren Hall, University of California, Berkeley, CA 94720-7360 (e-mail: ahsmith@berkeley.edu).

In our study region in West Bengal, India, and in neighboring Bangladesh, increased respiratory symptoms were found in arsenic-exposed populations studied during the 1990s (20–22), and reduced lung function was reported in a small case series involving 17 patients (23). However, epidemiologic studies to date have been based on symptoms, and there has been no systematic population-based study with objective measures of lung function.

We previously reported dose-response data for skin lesions and arsenic concentrations in drinking water in a case-control study in West Bengal (24). In this paper, we report findings concerning respiratory symptoms and lung function from a study conducted under the a priori hypothesis (formulated before funding was obtained and the study was conducted) that symptoms would be increased and lung function reduced with arsenic exposure.

MATERIALS AND METHODS

Study design and population

This study involved participants in a case-control study of arsenic-related skin lesions who were selected from the source population of 7,683 people, as described in detail previously (24). In brief, in the population-based case-control study, investigators selected 265 persons identified as having skin lesions among survey participants living in 21 West Bengal villages whose primary drinking water sources contained less than 500 μg/liter of inorganic arsenic in 1995–1996. Controls were selected from all survey participants who did not have arsenic-related skin lesions when seen during the 1995–1996 survey and whose main tube well-water source, like the cases', had an arsenic concentration of less than 500 μg /liter. For each case, one control matched on age (within 5 years) and sex was randomly identified from all eligible noncases. Response rates among persons who were located and invited to participate were 88 percent in cases and 94 percent in controls. Cases ($n = 192$) and controls ($n = 213$) were investigated concurrently, so a few ''extra'' controls remained in the study after it was found that the skin lesion case they were matched with from the 1995–1996 survey could not be located, refused to participate, or had died.

The current study of respiratory outcomes was designed as a cross-sectional investigation of both the cases with skin lesions in the case-control study and the controls without skin lesions in that same study. The study was confined to participants at least 20 years of age ($n = 355$) who had completed lung function testing and for whom information on smoking was available ($n = 342$). Furthermore, those participants with possible skin lesions that were not confirmed to be ''definite or probable'' arsenic-related skin lesions were excluded from the analysis ($n = 55$). With these exclusions, 287 participants remained, 132 classified as having arsenic-related skin lesions and 155 classified as not having such lesions. The study protocol was approved by the institutional review boards of both the Institute of Post Graduate Medical Education and Research (Kolkata, India) and the University of California, Berkeley (Berkeley, California). Informed consent was obtained before the questionnaire was administered.

Interviews

Between April 1998 and January 2000, a physician interviewer who was blind to original case/control status administered a structured questionnaire in Bengali in the homes of participants. The questionnaire assessed the following information: lifetime residential history, current and past water sources at home and at work sites, current and past (5 years prior) fluid consumption patterns, smoking habits, sociodemographic characteristics such as type of dwelling (concrete or brick, mixed materials, mud or thatched natural fibers), and education. Detailed information on current and lifetime smoking was obtained, including number of cigarettes smoked per day, type of cigarette smoked (manufactured cigarettes, ''bidis'' (small, locally made cigarettes), other), and years of starting and quitting smoking. Respiratory symptoms, including cough, phlegm, shortness of breath, and wheeze, were assessed by means of a structured interview based on the Medical Research Council questionnaire (25).

Lung function measurement

Lung function was measured with a portable spirometer (MicroLab ML 3500; Micro Medical Ltd., Kent, United Kingdom). The field physician demonstrated the procedure to the participants, and the participants practiced the use of the mouthpiece with the spirometer until they felt comfortable. In general, results of three acceptable readings were recorded, and the analysis involved the best of the three readings. Separate analyses were carried out using the highest reading of two reproducible measurements of forced expiratory volume in 1 second (FEV_1) (less than 10 percent variation between the two best readings). Spirometry was done by two trained physicians, the second replacing the first about halfway through the study. In each period, exposed and unexposed participants were assessed concurrently. Height and weight were measured by a trained field research assistant.

Physical examination of skin

Participants underwent a full medical examination conducted according to a written protocol (24). A careful examination of the skin was conducted in a well-lit area outdoors under natural light. Visible or palpable dermal lesions were documented, and notation was made of the location and appearance of the lesions and whether the patterns were characteristic of arsenic-induced skin toxicity. Any dermal change ''definitely or probably'' induced by arsenic was classified as a ''current skin lesion.'' This was determined through joint review of photographs of lesions by four physicians or, if photographs were not available, by the physician interviewer who recorded on the questionnaire that the dermal changes were or were not of a type related to arsenic. In the analyses presented in this paper, the presence of skin lesions was classified on the basis of this current assessment rather than on the initial brief assessment made at the time of the original population survey of 7,683 persons. Arsenic-induced skin lesions have distinct

characteristics, and in this study they served as a biologic marker of exposure. They result from many years of arsenic exposure, usually with a latency of more than 10 years from first exposure (24). It is very difficult to assess arsenic exposure from all water sources over many years in exposure assessment, so arsenic skin lesions are an excellent marker for identifying persons with prolonged exposure.

Arsenic exposure assessment

The field team collected water samples from all functioning tube wells that had been used by participants for at least 6 months in the last 20 years, as reported previously (24). Water samples from approximately 800 functioning tube wells in the 21 villages combined were collected. The water samples were transported on dry ice to the laboratory in Kolkata on the same day; they were then kept frozen at −20°C until they were transported on dry ice to the University of Washington (Seattle, Washington) for arsenic analysis. Total water arsenic was measured by flow injection analysis using atomic fluorescence detection with in-line photooxidation and continuous hydride generation (26). The lower limit of quantification was 0.2 μg/liter. Each sample was assayed twice (mean percent relative standard deviation = 2.3 percent) (24).

Information about tube well usage at each residence and work site and the results of the arsenic measurements were used to construct arsenic exposure histories. Annual average water arsenic concentrations were first calculated for participants for each calendar year on the basis of measured water arsenic concentrations in each tube well used during that year and the fraction of drinking water the participant had obtained from that source during that year. Peak water arsenic concentration (μg/liter) was defined as the highest known annual average water concentration of arsenic ingested by a participant. The peak concentration was estimated for the period from the year in which the participant had first started using tube wells to 1998–1999 (24).

Statistical methods

Frequency distributions of characteristics such as age, smoking, and arsenic exposure were calculated according to sex and skin lesion classification. Female smokers were excluded from further analyses because of small numbers in this subgroup ($n = 6$). Using logistic regression analysis, we calculated age-adjusted odds ratios for dichotomous respiratory symptoms according to skin lesion status in male nonsmokers, male smokers, and female nonsmokers. Self-reported history of physician-diagnosed respiratory disease was not included as an outcome in the analyses, since there were very few such reports; this probably reflects difficulty in obtaining access to health care in rural areas in West Bengal, limited information given to patients, and difficulty in recall more than actual disease history.

Residuals of the spirometric parameters (observed values minus expected values) based on the total sample were derived from linear regression models with linear terms for age and height, stratified by sex and smoking status. The residuals were grouped into three participant categories—male nonsmokers, male smokers, and female nonsmokers—according to skin lesion status and into three arsenic exposure categories (<100 μg/liter, 100–399 μg/liter, ≥400 μg/liter); mean values with standard errors and differences between mean values were calculated in the different categories and visually assessed. Multivariate linear regression analyses using the original spirometric parameters (not the residuals) were conducted separately for men and women, with terms for either skin lesions (dichotomized) or water arsenic level (continuous variable) and age, height, and smoking. Other potential confounders such as weight, occupation (service, farmer, other), education (no formal education, primary, secondary or higher), and type of house (mud, mixed materials, brick) were assessed in the linear regression models. Two-sided p values were calculated. All data analyses were carried out using the SAS statistical software package (version 8.0e; SAS Institute, Inc., Cary, North Carolina).

RESULTS

General characteristics of the study population and their arsenic exposure are presented according to skin lesion classification and sex in table 1. Although half of the source population was female (50.4 percent), skin lesions were over two times more common in men ($n = 93$) than in women ($n = 39$). Among persons with skin lesions, 90 percent of men and 97 percent of women had peak water arsenic concentrations of 100 μg/liter or more. Distributions of other characteristics were similar in participants with and without skin lesions (table 1). Among men, approximately 70 percent reported ever smoking, whereas less than 6 percent ($n = 6$) of women had ever smoked. Most male smokers (78.2 percent) reported smoking exclusively or primarily the small, locally hand-made Indian cigarettes called ''bidis.'' The majority of men were either farmers or field laborers. (There are no major industries in this rural, agriculture-based subsistence economy.) Women rarely worked outside the home.

Risks for respiratory symptoms associated with arsenic-related skin lesions were generally elevated in men, with odds ratios between 1.3 and 2.8 in smokers and between 1.3 and 3.8 in nonsmokers (table 2). The strongest findings among men were related to breathlessness (''walking uphill'': odds ratio (OR) = 2.1, 95 percent confidence interval (CI): 1.0, 4.6; ''walking at a group pace'': OR = 2.4, 95 percent CI: 1.1, 5.5; ''shortness of breath at night'': OR = 2.8, 95 percent CI: 1.1, 7.6) and ''morning cough'' (OR = 2.8, 95 percent CI: 1.2, 6.6) in smokers and to ''shortness of breath ever'' (OR = 3.8, 95 percent CI: 0.7, 20.6) in nonsmokers. Among women, the highest odds ratios were similarly related to breathlessness (''walking at a group pace'': OR = 1.9, 95 percent CI: 0.8, 4.6) and cough (''morning cough'': OR = 2.6, 95 percent CI: 0.9, 7.5), but the increases were generally smaller than those in men and the confidence intervals included unity (table 2).

Pronounced decrements in lung function were observed in men with skin lesions, both nonsmokers and smokers, as compared with those without skin lesions (figure 1). Male

TABLE 1. Characteristics of study participants according to sex and the presence or absence of arsenic-related skin lesions, West Bengal, India, 1998–2000

	Men ($n = 178$)				Women ($n = 109$)			
	Skin lesion ($n = 93$)		No skin lesion ($n = 85$)		Skin lesion ($n = 39$)		No skin lesion ($n = 70$)	
	No.	%	No.	%	No.	%	No.	%
Age (years)								
20–29	13	14.0	16	18.8	4	10.3	11	15.7
30–39	23	24.7	22	25.9	9	23.1	20	28.6
40–49	17	18.3	26	30.6	10	25.6	16	22.9
50–59	16	17.2	11	12.9	10	25.6	10	14.3
≥60	24	25.8	10	11.8	6	15.4	13	18.6
Smoking history								
Never smoker	29	31.2	25	29.4	37	94.9	66	94.3
Ever smoker	64	68.8	60	70.6	2	5.1	4	5.7
Current no. of cigarettes smoked per day								
1–10	24	50	28	51.8	1	50	1	100
>10	24	50	26	48.2	1	50	0	
Type of cigarette (ever smokers)								
Bidis*	53	82.8	44	73.3	1	50	3	75
Manufactured cigarettes	9	14.1	15	25	1	50	0	
Missing data	2	3.1	1	1.7	0		1	25
Type of dwelling								
Concrete/brick	21	22.6	9	10.6	4	10.3	12	17.1
Mixed-quality materials	26	28	28	32.9	14	35.9	25	35.7
Mud/thatched	45	48.4	48	56.5	21	53.9	31	44.3
Missing data	1	1.1	0		0		2	2.9
Education								
Secondary or higher	25	26.9	21	24.7	5	12.8	13	18.6
Primary	41	44.1	50	58.8	16	41	20	28.6
No formal education	25	26.9	14	16.5	18	46.2	35	50
Missing data	2	2.2	0		0		2	2.9
Occupation								
Farmer	38	40.9	37	43.5	2	5.1	2	2.9
Service (laborer, vendor)	41	44.1	38	44.7	2	5.1	3	4.3
Worked at home (homemaker)	3	3.2	2	2.4	33	84.6	60	85.7
Unemployed	11	11.8	8	9.4	2	5.1	5	7.1
Peak† arsenic exposure (μg/liter)								
0–99	9	9.7	36	42.4	1	2.6	18	25.7
100–399	66	71	34	40.0	25	64.1	40	57.1
≥400	18	19.4	15	17.7‡	13	33.3	12	17.1

* Small, locally hand-made Indian cigarettes.

† Highest known 12-month average arsenic concentration in drinking water.

‡ $p < 0.001$ (chi-squared test) for difference between subjects with and without skin lesions. Chi-squared tests were conducted separately for males and females.

smokers had, on average, lower mean residual values for spirometric parameters than male nonsmokers. The decreases in FEV_1 and forced vital capacity (FVC) in male nonsmokers with skin lesions as compared with nonsmoking men without skin lesions were 157.3 ml (95 percent CI: −24.7, 339.2) for FEV_1 and 188.5 ml (95 percent CI: 0.6, 376.3) for FVC. In male smokers, the decreases were 271.1 ml (95 percent CI: 158.0, 384.2) for FEV_1 and 304.1 ml (95 percent CI: 180.1, 428.1) for FVC. Among women, the respective reductions were 63.2 ml (95 percent CI: −31.8, 158.2) for

TABLE 2. Age-adjusted odds ratios for respiratory symptoms according to sex, smoking status, and the presence or absence of arsenic-related skin lesions, West Bengal, India, 1998–2000

	Male nonsmokers						Male smokers						Female nonsmokers					
	Skin lesion ($n = 29$)		No skin lesion ($n = 25$)				Skin lesion ($n = 64$)		No skin lesion ($n = 60$)				Skin lesion ($n = 37$)		No skin lesion ($n = 66$)			
	No.	%	No.	%	OR*	95% CI*	No.	%	No.	%	OR	95% CI	No.	%	No.	%	OR	95% CI
Wheeze (past 12 months)†	13	44.8	8	32	1.7	0.6, 5.3	36	56.3	25	41.7	1.6	0.8, 3.4	14	37.8	18	27.3	1.5	0.6, 3.7
Shortness of breath																		
Ever	8	27.6	2	8	3.8	0.7, 20.6	23	35.9	15	25	1.3	0.6, 3.0	11	29.7	13	19.7	1.6	0.6, 4.2
At night (past 12 months)	2	6.9	1	4	1.7	0.1, 20.9	21	32.8	7	11.7	2.8	1.1, 7.6	4	10.8	11	16.7	0.6	0.2, 1.9
Morning cough (ever)	3	10.3	2	8	1.3	0.2, 8.7	28	43.8	11	18.3	2.8	1.2, 6.6	10	27	8	12.1	2.6	0.9, 7.5
Chronic cough‡	4	13.8	2	8	1.9	0.3, 11.4	24	37.5	14	23.3	1.6	0.7, 3.7	10	27	9	13.6	2.2	0.8, 6.2
Chronic phlegm‡	1	3.5	0				17	26.6	7	11.7	2.5	0.9, 6.6	1	2.7	6	9.1	0.2	0.03, 2.2
Chronic bronchitis§	0		0				12	18.8	6	10	2.0	0.7, 5.8	1	2.7	5	7.6	0.3	0.03, 2.7
Breathlessness while walking																		
Uphill or fast¶	13	44.8	6	24	2.3	0.7, 7.6	35	54.7	19	31.7	2.1	1.0, 4.6	21	56.8	32	48.5	1.2	0.5, 2.9
At a group pace#	8	27.6	2	8	3.6	0.7, 20	26	40.6	12	20	2.4	1.1, 5.5	16	43.2	18	27.3	1.9	0.8, 4.6

* OR, odds ratio; CI, confidence interval.
† Question asked: "Have you had attacks of wheezing or whistling in your chest at any time in the last 12 months?"
‡ At least 3 out of 12 months, ever.
§ Cough and phlegm for at least 12 months, ever.
¶ Question asked: "Do you get short of breath walking fast or climbing up?"
# Question asked: "Do you get short of breath walking with other people of your own age on level ground?"

FEV_1 and 101.5 ml (95 percent CI: −8.8, 211.8) for FVC. Decreases in FEV_1 and FVC related to increased water arsenic concentration were observed among men; reductions in mean values from low exposure (arsenic level <100 μg/liter) to high exposure (arsenic level ≥400 μg/liter) were 194.7 ml (95 percent CI: 35.5, 353.9) for FEV_1 and 83.8 ml (95 percent CI: −93.8, 261.5) for FVC in nonsmokers and 226.1 ml (95 percent CI: 45.2, 407.0) for FEV_1 and 247.6 ml (95 percent CI: 58.3, 436.9) for FVC in smokers. Among women, the respective reductions were 28.5 ml (95 percent CI: −71.3, 128.2) for FEV_1 and 7.5 ml (95 percent CI: −122.4, 137.5) for FVC.

In the multivariate linear regression analyses stratified by sex and adjusted for age, height, and smoking, lung function was significantly decreased for signs of arsenic-related skin lesions among men, with a reduction in FEV_1 of 256.2 ml (95 percent CI: 113.9, 398.4; $p < 0.001$) and a reduction in FVC of 287.8 ml (95 percent CI: 134.9, 440.8; $p < 0.001$) (table 3). To further investigate the effects of ingested arsenic on respiratory flows, we investigated the FEV_1:FVC ratio and forced expiratory flow between 25 and 75 percent of forced vital capacity ($FEF_{25–75}$). We found significant reductions related to the presence of skin lesions that were consistent with the findings for FEV_1 and FVC in men. Reductions in FEV_1 (156.4 ml; 95 percent CI: −3.2, 316.0; $p = 0.055$) and FVC (119.7 ml; 95 percent CI: −52.0, 291.4; $p = 0.2$) were also observed in relation to smoking, but the effect size was smaller than that for the presence of skin lesions. Using arsenic levels in water as a measure of exposure instead of skin lesions, we found decreases of 45.0 ml (95 percent CI: 6.2, 83.9; $p = 0.02$) for FEV_1 and 41.4 ml (95 percent CI: −0.7, 83.5; $p = 0.054$) for FVC per 100-μg/liter increase in arsenic among men.

Potential confounders such as weight, type of house, education, and occupation were assessed in the multivariate models but did not change the estimates for skin lesions or arsenic in water. In addition, we considered different smoking variables, including indicator variables for current, ex-, and never smoking and a variable for pack-years of smoking. No combination of smoking variables had any effect on the arsenic findings. For example, the estimate for reduction in FEV_1, which was −256 ml in table 3, changed to −252 ml with a separate indicator variable for ex-smoking and to −254 ml when pack-years were included in the model. Interestingly, among women, estimates for skin lesions (table 4) or arsenic in water did not indicate a strong relation with lung function.

The findings did not change when we carried out the analyses either including all subjects with spirometric measurements or excluding those for whom two FEV_1 measurements with a variance of 10 percent or less between two repeated measurements could be not obtained (7.3 percent of all who participated in lung function measurement).

DISCUSSION

To our knowledge, this is the first population-based investigation of the effects of arsenic in drinking water on lung function. We found pronounced, significant reductions

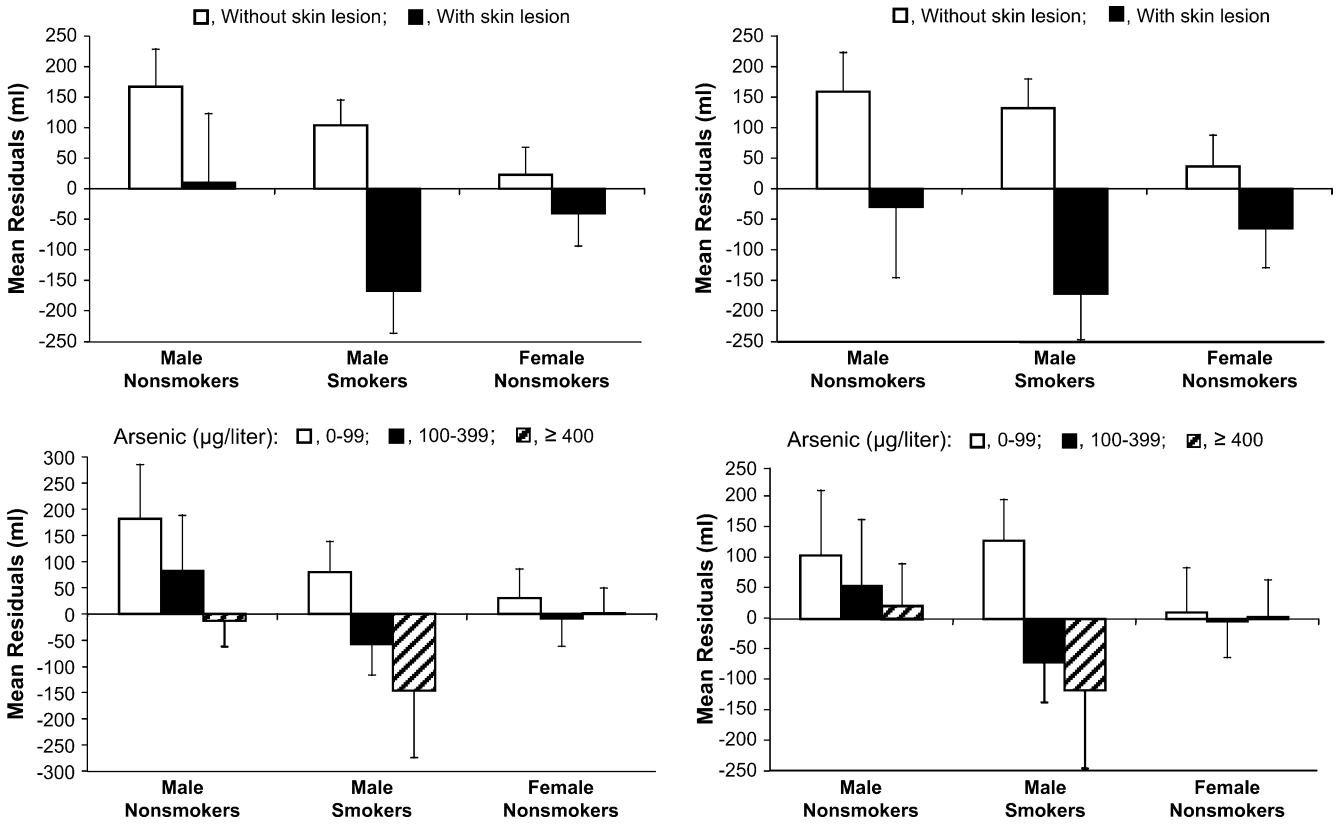

FIGURE 1. Age- and height-adjusted mean residuals (ml) for forced expiratory volume in 1 second (left panels) and forced vital capacity (right panels), according to the presence or absence of arsenic-related skin lesions (upper panels) and highest known 12-month average arsenic concentration (lower panels) in drinking water (μg/liter), West Bengal, India, 1998–2000. Bars, standard error.

in FEV_1, FVC, and $FEF_{25–75}$, as well as a small decrease in the FEV_1:FVC ratio, related to long-term consumption of contaminated drinking water in men. Men with arsenic-induced skin lesions had FEV_1 and FVC values approximately 250 ml and 280 ml lower, respectively, than men without skin lesions. Respiratory symptoms were also increased in relation to skin lesions in men. In women, findings indicated a markedly weaker impact of ingested arsenic on lung function or respiratory symptoms.

Only a few previous studies considered the relation of nonmalignant respiratory diseases to arsenic in drinking water or arsenic-induced skin lesions, and these were mainly based on mortality or symptom data. In Taiwan, increased standardized mortality ratios (SMRs) for bronchitis in men (SMR = 1.48, 95 percent CI: 1.25, 1.73) and women (SMR = 1.53, 95 percent CI: 1.30, 1.80) were found in an area where ''blackfoot'' disease was prevalent because of consumption of artesian well water containing arsenic (median arsenic level = 780 μg/liter) (19). In region II (the arsenic-affected area) in Chile, where the drinking water was contaminated with high levels of arsenic, an increased SMR for chronic obstructive pulmonary disease was found in young adults aged 30–39 years who were exposed to arsenic early in life (10 cases observed, 0.9 expected; SMR = 11.1; $p < 0.001$) (14). An earlier case series report from the same area in Chile suggested that children exposed to arsenic developed recurrent bronchitis, pneumonia, and bronchiectasis at a higher rate than the population average (18). Two studies to date have considered the relation of respiratory symptoms to arsenic exposure in West Bengal (21) and Bangladesh (22). Both studies found an increase in reported symptoms that was consistent with chronic respiratory conditions in persons with higher arsenic exposure.

Although previous studies on nonmalignant respiratory effects of ingested arsenic are limited, convincing evidence that ingested arsenic may indeed cause lung disease comes from cancer studies conducted in Latin America and Asia (12–14, 27, 28). A clear trend for lung cancer risk to be associated with arsenic concentration in drinking water was shown by Ferreccio et al. (13) in Chile, with odds ratios increasing to 7.1 (95 percent CI: 3.4, 14.8) for arsenic concentrations ranging from less than 10 μg/liter to 800 μg/liter. With such high lung cancer risks, it is reasonable to anticipate that nonmalignant respiratory effects might occur as well. For example, smoking, asbestos, and silica each have both malignant and nonmalignant effects in the lungs.

TABLE 3. Results from multivariate linear regression analysis of lung function and arsenic-related skin lesions in men ($n = 178$), with adjustment* for age, height, and smoking, West Bengal, India, 1998–2000

Variable	FEV_1† (ml)	95% CI†	*p* value‡	FVC† (ml)	95% CI	*p* value‡	FEV_1:FVC ratio	95% CI	*p* value‡	$FEF_{25–75}$† (ml/second)	95% CI	*p* value‡
Skin lesion	−256.2	−398.4, −113.9	<0.001	−287.8	−440.8, −134.9	<0.001	−0.025	−0.05, −0.002	0.03	−259.1	−510.6, −7.6	0.04
Age§ (years)	−23.6	−28.8, −18.5	<0.001	−21.3	−26.9, −15.8	<0.001	−0.003	−0.004, −0.002	<0.001	−40.4	−49.7, −31.2	<0.001
Height (cm)	34.4	23.6, 45.2	<0.001	43.3	31.7, 54.9	<0.001	0.09	−0.09, 0.26	0.3	24.6	5.5, 43.7	0.012
Smoking¶	−156.4	−316.0, 3.2	0.055	−119.7	−291.4, 52.0	0.2	−0.026	−0.05, −0.0006	0.045	−231.2	−513.2, 50.9	0.12

* The following variables were added to the model one by one and were not found to confound the association with skin lesions: weight, occupation (service, farmer, other), education (no formal education, primary, secondary or higher), and type of house (mud, mixed materials, brick).

† FEV_1, forced expiratory volume in 1 second; CI, confidence interval; FVC, forced vital capacity; $FEF_{25–75}$, forced expiratory flow between 25% and 75% of forced vital capacity.

‡ Two-tailed.

§ Continuous variable.

¶ Smoking was defined as ever smoking versus never smoking. Different smoking variables, including pack-years of smoking, were also incorporated into the models but had no effect on the skin lesion results.

TABLE 4. Results from multivariate linear regression analysis of lung function and arsenic-related skin lesions in women* ($n = 103$), with adjustment† for age and height, West Bengal, India, 1998–2000

Variable	FEV_1‡ (ml)	95% CI‡	*p* value§	FVC‡ (ml)	95% CI	*p* value§	FEV_1:FVC ratio	95% CI	*p* value§	$FEF_{25–75}$‡ (ml/second)	95% CI	*p* value§
Skin lesion	−63.8	−210.5, 83.0	0.4	−102.5	−270.9, 66.0	0.2	0.008	−0.02, 0.04	0.6	−61.8	−330.3, 206.8	0.6
Age¶ (years)	−21.2	−26.6, −15.8	<0.001	−20.6	−26.8, −14.4	<0.001	−0.003	−0.004, −0.002	<0.001	−33.1	−42.9, −23.2	<0.001
Height (cm)	22.1	7.7, 36.5	0.003	30.6	14.0, 47.1	<0.001	−0.07	−0.4, 0.2	0.6	−1.5	−27.8, 24.9	0.9

* Female nonsmokers only.

† The following variables were added to the model one by one and were not found to confound the association with skin lesions: weight, occupation (service, farmer, other), education (no formal education, primary, secondary or higher), and type of house (mud, mixed materials, brick).

‡ FEV_1, forced expiratory volume in 1 second; CI, confidence interval; FVC, forced vital capacity; $FEF_{25–75}$, forced expiratory flow between 25% and 75% of forced vital capacity.

§ Two-tailed.

¶ Continuous variable.

The results of lung function testing in this study are unlikely to be due to differential misclassification, because exposure assessment and spirometry are both objective measures. The sizes of the decrements in FEV_1 and FVC in men and their associated tests of significance, as well as the consistency between findings for lung function and respiratory symptoms among men and women, suggest that the findings are unlikely to be due to chance. There is also no reason to expect the results in men to be due to confounding. The reason is that arsenic levels in tube wells vary widely within villages and from house to house. When people in the area built their houses and villages or started to smoke, they did not know that arsenic was present in some locations and not others. Major determinants of lung function, such as age, smoking, height, and socioeconomic status, were considered in the analysis but were not actually confounding factors, and there is no reason to expect other or unknown factors to have caused major confounding.

The smoking-related reduction in FEV_1 among men—156 ml (table 3)—is approximately 60 percent of the reduction found for skin lesions in this population (256 ml). The average number of pack-years of smoking by men in this study was 22.7. On the basis of an estimate for the US population of a decrease in FEV_1 of 7.4 ml per pack-year (29), men with 22.7 pack-years would be expected to have an average decrement in FEV_1 of 168 ml. Interestingly, this is close to our observed average reduction in smokers of 156 ml (table 3). The findings suggest that consumption of high concentrations of arsenic in drinking water is a stronger determinant of lung function decrements among men in this population than smoking, although these smokers smoked considerably less than their US counterparts.

It is unclear why strong pulmonary effects were found in men but not in women in this population. One possibility relates to study power, as manifest by the fairly wide confidence intervals in tables 2 and 4. However, one explanation may be an underlying biologic difference in susceptibility between males and females, which has also been suggested for the much greater frequency of skin lesions in males than in females (24, 30) and may be related to sex differences in human arsenic metabolism (31). In one study from Chile (14), male sex was associated with higher risks attributable to arsenic for lung cancer (excess deaths: men, 401; women, 105). Two studies from Asia suggested higher lung cancer risks among men than among women (27, 28).

The pathophysiologic mechanism by which ingested arsenic leads to impairments in lung function and increased respiratory symptoms is yet to be understood, and further investigation is needed. The decreases in FEV_1 and FVC that we observed in men were of similar magnitudes, suggesting a restrictive (e.g., lung fibrotic or neuromuscular) process. From a public health perspective, our findings are particularly important given the millions of people exposed to arsenic in drinking water globally and the relevance of reductions in lung function as risk factors for and markers of pulmonary disease (32, 33) and overall population morbidity and mortality (34–36), with early life exposures being potentially particularly harmful (37, 38). Arsenic in drinking water should be considered a risk factor for chronic pulmonary disease.

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