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Prospective cohort study of respiratory effects at ages 14 to 26 following early life exposure to arsenic in drinking water

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Background: We previously reported chronic respiratory effects in children who were then 7–17 years of age in Matlab, Bangladesh. One group of children had been exposed to high concentrations of arsenic in drinking water in utero and early childhood (average 436 µg/L), and the other group of children were never known to have been exposed to >10 µg/L. The exposed children, both males and females, had marked increases in chronic respiratory symptoms.

Methods: The current study involves a further follow-up of these children now 14–26 years of age with 463 located and agreeing to participate. They were interviewed for respiratory symptoms and lung function was measured. Data were collected on smoking, body mass index (BMI), and number of rooms in the house as a measure of socioeconomic status.

Results: Respiratory effects were still present in males but not females. In the high exposure group (>400 µg/L in early life) the odds ratio (OR) among male participants for dry cough in the last 12 months was 2.36 (95% confidence interval [CI] = 1.21, 4.63, $P = 0.006$) and for asthma OR = 2.51 (95% CI = 1.19, 5.29, $P = 0.008$). Forced vital capacity (FVC) was reduced in males in the early life high-exposure group compared with those never exposed (–95ml, $P = 0.04$), but not in female participants.

Conclusions: By the age range 14–26, there was little remaining evidence of chronic respiratory effects in females but pronounced effects persisted in males. Mechanisms for the marked male female differences warrant further investigation along with further follow-up to see if respiratory effects continue in males.

Keywords: Arsenic; Lung function; Respiratory; Pulmonary; In utero; Children; Early life exposure

Introduction

Arsenic in drinking water has been linked to various nonmalignant respiratory illnesses. Several studies in adults have suggested an increased risk of respiratory symptoms and diseases including impairment of lung function following chronic

exposure to inorganic arsenic.^{1–6} Long-term exposure to inorganic arsenic has been found to be associated with increased risk of respiratory symptoms such as chronic cough, dyspnea and breathlessness and the relationships were dose-dependent.^{7–10} A cross-sectional study in Bangladesh found a greater risk of chronic bronchitis with added sounds in chest among people having arsenic-induced skin lesions compared with people without these lesions.¹¹ Excess mortality from nonmalignant lung disease has been reported recently for the same cohort with the highest exposure group having a 75% increased risk of mortality compared with the lowest exposure group.¹² Several studies have also observed declines in lung function following exposure to arsenic via drinking water.^{13–15}

There is growing evidence that early life arsenic exposure has profound health effects in later life. Arsenic readily crosses the placenta in human beings.¹⁶ Exposure to arsenic in utero and early childhood resulted in increased mortality among young adults 30–49 years of age from lung cancer and bronchiectasis in Chile. For those born during the high arsenic exposure period 1958–1970, the standardized mortality ratios (SMRs) for lung cancer and bronchiectasis were 6.1 (95% confidence interval [CI] = 3.5, 9.9; $P < 0.001$) and 46.2 (95% CI = 21.1,

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What this study adds

This prospective study involves children who had been exposed to high concentrations of inorganic arsenic in drinking water in utero and early life. We previously assessed them at 7–17 years of age and found increased chronic respiratory symptoms. In this article, we report our findings when they were 14–26 years of age in what is the first study to assess adolescents and young adults following early life exposure to arsenic. Pronounced respiratory effects were still present in males but had largely disappeared in females. Mechanisms for the marked male female differences warrant further investigation.

87.7; $P < 0.001$), respectively.¹⁷ A recent study in Chile revealed increased incidence of lung cancer following arsenic exposure and the association was strongest in younger adults exposed to arsenic in early life.¹⁸ Lung cancer is considered the major long-term cause of death following exposure to arsenic in drinking water.^{19,20} Exposure to arsenic in prenatal life and early childhood via drinking water in Chile was also found to be associated with reduced lung function in a study following early life arsenic exposure.²¹ A study following *in utero* arsenic exposure in Bangladesh found evidence of reduced lung function and airway inflammation at age 9, mainly in boys.²²

While there is considerable evidence that early life arsenic exposure increases lung disease in adults, only limited information is available on pulmonary effects in children themselves before adulthood. A study in Antofagasta, Chile, in the 1970s reported reduction in prevalence of respiratory symptoms in children after reduction in water arsenic concentrations.²³ *In utero* and early life exposure to arsenic has also been found to be associated with increased risk of respiratory infections in infants.^{24,25} Few studies have investigated arsenic exposure during fetal development and early life on respiratory consequences in infants and children. Evidence suggested that early life arsenic exposure resulted in long-term nonmalignant pulmonary diseases in adults²⁶ and much later in life²⁷ as indicated by increased mortality from bronchiectasis and lung cancer, in adults.¹⁷ So far, no study has followed children with well-documented early life arsenic exposure to assess long-term health consequences in the later part of childhood and as young adults. We were the first to follow a cohort with high arsenic exposure in early life and assess respiratory and other health effects in children, then 7–17 years of age.²⁸ We now further assess these same children at 14–26 years of age.

Methods

Since 1966, the International Centre for Diarrheal Disease Research, Bangladesh (icddr,b) has been maintaining an internationally recognized and unique Health and Demographic Surveillance System (HDSS) in 142 villages in Matlab, a Sub-district of Bangladesh. Vital events including birth, death, marriage, and in and out migration, are recorded by household visits every 2 months. In 2002–2003, icddr,b conducted a population-based survey of all 220,000 Matlab residents, documenting the residential tubewell history of each individual over the age of 5 at the time. Tubewells near residences were the main source of drinking water in these communities. Moreover, arsenic measurements were conducted in 2002–2003 for all 13,286 tubewells in operation in the Matlab area. In our first study of early life arsenic exposure in this population, 650 potential participants born between 1991 and 2002 were selected using the population survey database of 220,000 residents in the sub-district of Matlab. Half of them were selected because they had the highest recorded tubewell water arsenic concentrations in the homes where they were born, and the other half were selected because they had the lowest tubewell arsenic concentrations in the homes where they were born.²⁸

In the earlier study, we were able to locate and obtain maternal exposure data during pregnancy and assess respiratory symptoms for 571 of the 650 when they were in the age range 7–17,²⁸ and they constitute the target for this follow-up study. We visited the households of potential participants for the follow-up. We found that 27 were known to have moved out of the Matlab district, 17 declined to participate, and 64 could not be located and we have no information about them. In the end, in total 463 participants were included in the current follow-up study when they were in the age range of 14–26 (Figure 1). Of them, 235 and 228 children participated in the exposed and unexposed cohorts, respectively. Among the 235 exposed children, 135 were in the high exposure (400+ $\mu\text{g/L}$) group, and 100

in the medium exposure (10–400 $\mu\text{g/L}$) group. The questionnaires were revised to record information of the new houses, schools, and work places and their water sources, and also new water sources of the previous homes and the schools.

Assessment of respiratory and other medical illnesses

Detailed histories of respiratory symptoms and disorders including wheezing, asthma, pneumonia, and tuberculosis since our last visit between 2008 and 2010 were taken. Ever and current wheezing (i.e., wheezing in the last 12 months), and asthma were assessed based on the core questionnaire of the International Study of Asthma and Allergy in Childhood (ISAAC), a validated tool used for the assessment of asthma symptoms in children worldwide.^{29,30} Cough and phlegm, shortness of breath, and family history of asthma were obtained according to an ISAAC supplementary questionnaire³¹; <http://links.lww.com/EE/A76>. Two trained physicians asked the questions in a structured interview.

Anthropometric and lung function measurement

Height and weight were obtained for all participants before testing lung function. Standing height was measured to the nearest of 0.1 cm and weight was measured using a bathroom scale to the nearest of 100 gm. Lung function was measured with the EasyOne spirometer (NDD Medical Technologies) which has been used successfully in many studies^{13,21} including our previous one with the same children in Bangladesh.²⁸ It is a handy, portable spirometer that uses ultrasound to measure airflow. The measurement is independent of gas composition, pressure, temperature, and humidity, and eliminates errors due to those variables making it suitable for the hot and humid conditions in Matlab. After explaining the procedure and demonstrating it, subjects were asked to blow out forcibly as hard as possible through the disposable mouthpiece in the standing position without using a nose clip. The procedure was repeated on average four times in order to produce smooth, reproducible curves that meet American Thoracic Society criteria.³² Spirometry was conducted by a physician with extensive experience administering spirometry on children. Lung function parameters, primarily forced vital capacity (FVC), FEV1 (forced expiratory volume in first second), and FEV1/FVC ratio, were recorded. Spirometry measurements were obtained for 463 participants without use of bronchodilators. The quality was excellent with grade A being achieved for 95% (440 participants) and grade B for 5% (23 participants). No tests were graded C–F. All the spirometry results were used in the analysis. In addition, lung function data were reviewed by our pulmonologist co-investigator (Professor John Balmes).

Because of the gender differences we found with respiratory effects now confined to males, we identified gender difference reported in other studies of respiratory effects associated with exposure to inorganic arsenic in water above 50 $\mu\text{g/L}$. We also assessed gender differences in published studies of arsenic-caused skin lesions, since this is a useful marker of the effects of exposure to arsenic in drinking water. Finally, we identified studies of arsenic methylation as a potential explanation of the gender differences. Inorganic arsenic is first mono-methylated to monomethylarsonic acid (MMA) the trivalent form which is highly toxic, and one possibility was that the preponderance of some arsenic effects in males could be due to more arsenic remaining as MMA in males compared with females, and not being further methylated to less toxic dimethylarsinic acid (DMA).

Ethical considerations

The institutional review boards of the University of California, Berkeley and icddr,b approved the study. Informed consent was

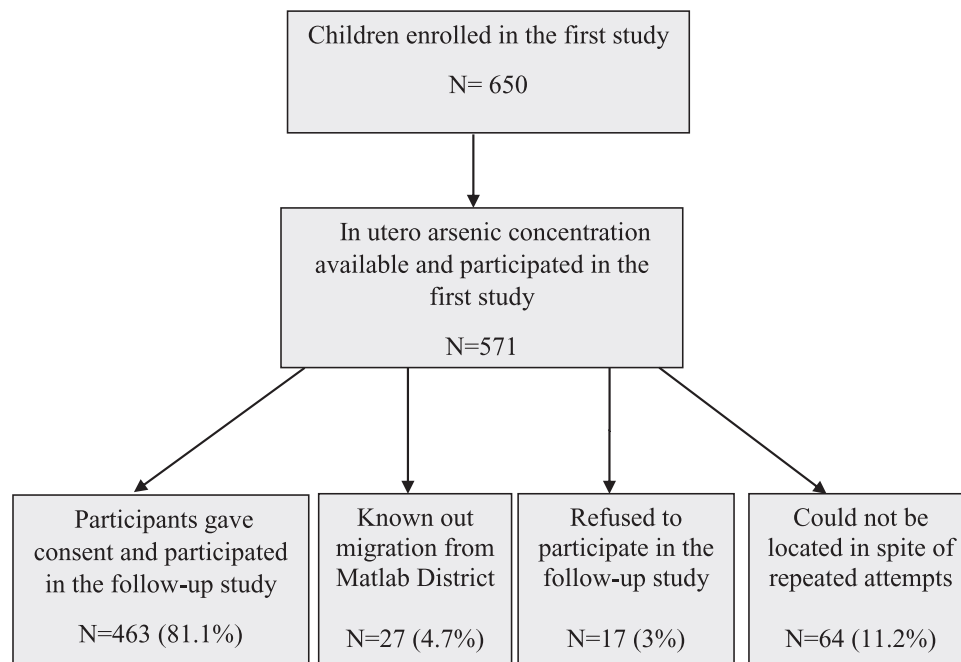


Figure 1. Flow chart of the study participation.

obtained from parents and young adults over 18 years of age and assent was obtained from children 14–17 of age.

Data analysis

Univariate analyses were conducted to evaluate the differences in general characteristics and socio-demographic factors between the low and high exposed cohorts. We performed Fisher's exact test to compare the dichotomous respiratory symptoms between the cohorts separated by sex. Logistic regression analysis was used to assess the relationship of each respiratory symptom with arsenic water concentrations initially adjusting for age and gender, and then for each gender separately. Children exposed to >400 $\mu\text{g/L}$ in early life (high exposure) and 10 – 400 $\mu\text{g/L}$ in early life (medium exposure) were compared with children exposed to <10 $\mu\text{g/L}$ in early life (low exposure). Because of the pronounced gender differences found, results are presented for each gender separately. Variables adjusted for were age, body mass index (BMI), smoking (self and father), and number of rooms in the house. No female participants or mothers reported smoking. Multiple linear regression analysis was used to assess the association of water arsenic concentration with FEV1 and FVC. First, age, sex, and height were included in the linear regression model. Then more analyses were conducted adjusted for age, height, weight, smoking (self and father), and number of rooms in the house. In view of the clear direction of the hypothesis that there might be increased risks of respiratory effects associated with exposure to arsenic in drinking water, *P*-values reported are one-tailed. All CIs are 95%.

Results

A total of 463 subjects 14–26 years of age participated in this study. The mean age was 18.1 years. Table 1 presents socio-demographic characteristics of the study subjects. Among the participants, 135 (29.2%) were exposed to high arsenic concentrations in early life (>400 $\mu\text{g/L}$), 100 (21.6%) were exposed to medium arsenic concentrations (10 – 400 $\mu\text{g/L}$) and 228 (48.2%) were exposed to low concentration of As (<10 $\mu\text{g/L}$). Of the total 463 subjects, 229 (49.5%) were males and 234 (50.5%) were

females. Participants below the age of 17 years were more likely to have been exposed to high arsenic concentration compared with the 22–26 years age group (46.7% vs. 14.1%). Participants with more educated fathers were found to have used lower arsenic concentration water in early life. The proportion of fathers who smoked was about the same in the low exposure participants compared with those highly exposed (61.8% compared with 62.2%). Respondents residing in higher quality type houses had similar exposure patterns as those in low quality mud houses. The number of rooms in the house as an indicator of socioeconomic status also had a little relationship with exposure. Other factors including BMI and respondent's educational status were similar across the exposure groups.

Odds ratios (ORs) for respiratory symptoms are shown in Table 2 for males and in Table 3 for females. After adjustment for age, BMI, self, and father's smoking status and rooms in the house, the OR for dry cough in the last 12 months in males in the high exposure cohort was increased (OR: 2.36, 95% CI = 1.21–4.63, *P* = 0.006). Other symptoms for highly exposed males were also markedly increased including woken up with shortness of breath (OR: 1.71, 95% CI = 0.90, 3.24, *P* = 0.05) and shortness of breath when walking on level ground (OR: 2.21, 95% CI = 0.86, 5.67, *P* = 0.05). Asthma was also markedly increased in highly exposed males (OR: 2.51, 95% CI = 1.19, 5.29, *P* = 0.008). There were 86 male participants who reported smoking, but the respiratory symptom findings were similar for smokers and nonsmokers (see Supplementary material; <http://links.lww.com/EE/A76>). Thus, there was no evidence of synergy of arsenic exposure with smoking.

However, increased respiratory symptoms with arsenic exposure were not found in females. and in fact for many respiratory symptoms the odds ratios among females were <1 in the highly exposed group (Table 3).

Table 4 presents lung function test results analyzed by multiple linear regression. It displays the differences in two major pulmonary function parameters, FEV1 and FVC between the highly exposed group (>400 $\mu\text{g/L}$) and the medium exposed group (10 – 400 $\mu\text{g/L}$), compared with the low exposure cohort with <10 $\mu\text{g/L}$ of arsenic in early life drinking water. We adjusted for age, height, weight, self and father's smoking status, and rooms in the house. The results showed decreased FEV1 in

Table 1.
Socio-demographic characteristics of study participants (total n = 463)

Characteristics	Total N (%)	<10 µg/L; N (%)	10–400 µg/L; N (%)	>400 µg/L; N (%)	P ^a
Sex					
Male	229 (49.5)	108 (47.4)	47 (47.0)	74 (54.8)	0.17
Female	234 (50.5)	120 (52.6)	53 (53.0)	61 (45.2)	
Age (years)					
14–17	224 (48.4)	118 (51.8)	43 (43.0)	63 (46.7)	0.39
18–21	163 (35.2)	74 (32.5)	36 (36.0)	53 (39.3)	
22–26	76 (16.4)	36 (15.8)	21 (21.0)	19 (14.1)	
BMI					
<18	150 (32.4)	76 (33.3)	29 (29.0)	45 (33.3)	0.71
≥18	313 (67.6)	152 (66.7)	71 (71.0)	90 (66.7)	
Education (years)					
No	3 (0.7)	2 (0.9)	1 (1.0)	0 (0.0)	0.24
1–5	54 (11.7)	20 (8.8)	9 (9.0)	25 (18.5)	
6–10	302 (65.2)	151 (66.2)	66 (66.0)	85 (63.0)	
11–15	100 (21.6)	53 (23.3)	23 (23.0)	24 (17.8)	
16+	4 (0.9)	2 (0.9)	1 (1.0)	1 (0.7)	
Smoking					
Yes	86 (18.6)	35 (15.4)	21 (21.0)	30 (22.2)	0.21
No	377 (81.4)	193 (84.7)	79 (79.0)	105 (77.8)	
No. of family members					
1–3	75 (16.2)	39 (17.1)	17 (17.0)	19 (14.1)	0.68
4–6	304 (65.7)	153 (67.1)	64 (64.0)	87 (64.4)	
7–9	62 (13.4)	27 (11.8)	12 (12.0)	23 (17.0)	
10+	22 (4.8)	9 (4.0)	7 (7.0)	6 (4.4)	
Mother's education					
No education	136 (29.4)	66 (29.0)	32 (32.0)	38 (28.2)	0.34
Primary	197 (42.6)	89 (39.0)	43 (43.0)	65 (48.2)	
Secondary and above	130 (28.1)	73 (32.0)	25 (25.0)	32 (23.7)	
Father's education					
No education	157 (33.9)	80 (35.1)	36 (36.0)	41 (30.4)	0.004
Primary	172 (37.2)	67 (29.4)	41 (41.0)	64 (47.4)	
Secondary and above	134 (28.9)	81 (35.5)	23 (23.0)	30 (22.2)	
Type of house					
Mud	313 (67.6)	155 (68.0)	66 (66.0)	92 (68.2)	0.50
Mixed	45 (9.7)	23 (10.1)	6 (6.0)	16 (11.9)	
Concrete	69 (14.9)	34 (14.9)	16 (16.0)	19 (14.1)	
Tin	36 (7.8)	16 (7.0)	12 (12.0)	8 (5.9)	
Rooms in the house					
1	57 (12.3)	21 (9.2)	14 (14.0)	22 (16.3)	0.15
2	133 (28.7)	62 (27.2)	36 (36.0)	35 (25.9)	
3	195 (42.1)	102 (44.7)	39 (39.0)	54 (40.0)	
4+	78 (16.9)	43 (18.9)	11 (11.0)	24 (17.8)	
Father smokes					
Yes	288 (62.2)	141 (61.8)	63 (63.0)	84 (62.2)	0.98
No	175 (37.8)	87 (38.2)	37 (37.0)	51 (37.8)	

^aTwo-tailed *P*-value.

males in the high exposure group compared with those exposed to <10 µg/L (−75 mL, 95% CI = −180.1, 30.2, *P* = 0.08) and FVC (−95 mL, 95% CI = −201.1, −11.0, *P* = 0.04). However, there was no reduction in the two lung function parameters in exposed females.

Table 5 presents key findings we identified in published studies giving gender specific data on arsenic effects. There were gender differences for all five studies of chronic respiratory effects and six studies of arsenic-cause skin lesions with males showing greater effects. Finally, many studies now show that men do not metabolize arsenic as well as women. This is reflected in higher concentrations of highly toxic MMA in men compared with women as seen in the studies listed in Table 5.

Discussion

To our knowledge, this is the first study that has followed a cohort exposed to arsenic in early life to investigate the effects of in utero and early childhood exposure on respiratory effects in adolescents and young adults. Males with early life arsenic exposure (>400 µg/L) were more likely to report various

respiratory symptoms including dry cough, woken up due to shortness of breath and asthma. Reductions in FEV1 and FVC were observed in male subjects with high arsenic exposure compared with low arsenic exposure. However, these effects were not evident in females.

Long-term exposure to arsenic via drinking water has been implicated with chronic respiratory illnesses in several studies in adults.^{7–10,17} A prospective study in Bangladesh showed an inverse dose–response relationship between arsenic and lung function parameters, FEV1, and FVC. Individuals in the highest baseline water arsenic category (>97 µg/L) had a significant reduction in FEV1 and FVC of 80.6 and 97.3 mL, respectively.¹³ A study in India reported increased respiratory symptoms including impairment in lung function among those with long-term exposure to arsenic in drinking water and the effects were more pronounced in males compared with females. Men with arsenic induced skin lesions had a 256 mL (95% CI = 114, 398.4; *P* < 0.001) and 288 mL (95% CI = 134.9, 440.8; *P* < 0.001) reduction in FEV1 and FVC, respectively.¹ Findings from a study in Chile suggested that prenatal exposure to arsenic increases the risk of respiratory illnesses later in life.²¹ A recent

Table 2. Results from multivariate logistic regression analysis of respiratory symptoms and arsenic exposure in early life (10–400 and >400 µg/L) compared with <10 µg/L in males (adjusted for more variables^a)

Respiratory symptoms	<10 µg/L		10–400 µg/L			>400 µg/L			
	N	N	OR	95% CI	P ^b	N	OR	95% CI	P ^b
Coughing									
When having a cold (last 12 months)	76	29	0.57	0.27, 1.22	0.93	48	0.70	0.36, 1.35	0.86
When not having a cold (last 12 months)	17	4	0.47	0.15, 1.50	0.90	11	0.90	0.39, 2.09	0.59
Dry cough (last 12 months)	24	14	1.49	0.67, 3.31	0.16	29	2.36	1.21, 4.63	0.006
Wheezing									
Ever	37	20	1.33	0.65, 2.72	0.22	34	1.60	0.86, 2.95	0.07
Last 12 months	9	4	0.73	0.17, 3.03	0.67	14	2.31	0.80, 6.63	0.06
Number of wheezing attacks (1–3 times)	6	4	1.40	0.37, 5.32	0.31	8	2.07	0.67, 6.37	0.10
Number of wheezing attacks (4+ times)	3	0				4	1.89	0.40, 9.00	0.21
Number of nights sleep disturbed (<1/week)	1	1	2.28	0.14, 38.6	0.28	6	11.6	1.30, 103	0.01
Number of nights sleep disturbed (1 or more/week)	3	1	0.56	0.05, 6.01	0.68	2	0.80	0.12, 5.37	0.59
Severe enough to affect speech	3	1	0.69	0.07, 7.02	0.62	4	1.87	0.40, 8.88	0.21
After exercise	6	3	1.07	0.25, 4.60	0.46	8	1.99	0.65, 6.14	0.12
Without exercise	1	1	2.78	0.16, 48.7	0.24	3	4.32	0.43, 43.9	0.11
When having a cold	7	2	0.60	0.12, 3.05	0.73	9	1.96	0.68, 5.65	0.11
When not having a cold	3	2	1.37	0.22, 8.66	0.37	5	2.28	0.52, 10.0	0.14
Shortness of breath									
Woken up with shortness of breath	31	17	1.25	0.59, 2.63	0.28	31	1.71	0.90, 3.24	0.05
Woken up with tightness of chest	12	8	1.39	0.51, 3.78	0.26	12	1.38	0.57, 3.36	0.24
When walking fast or climbing	26	9	0.64	0.27, 1.53	0.84	26	1.58	0.81, 3.07	0.09
When walking on level ground	9	6	1.61	0.53, 4.93	0.20	12	2.21	0.86, 5.67	0.05
Asthma	16	12	1.80	0.75, 4.27	0.09	23	2.51	1.19, 5.29	0.008

^aAdjusted for age, BMI, smoking (self and father), and number of rooms in house.

^bOne-tailed *P*-value.

study in Mexico has reported reduction in FVC in children following exposure to arsenic in utero and early childhood.⁴⁹ Actually, we do not know of any study with enough participants having arsenic water concentrations above 50 µg/L that has not found chronic respiratory effects.

In our previous study of the same cohorts in Bangladesh at 7–17 years of age, we found strong associations between chronic respiratory symptoms, especially wheezing when not

having a cold (OR = 8.41, 95% CI = 1.66, 42.6), and shortness of breath when walking fast or climbing (OR = 3.19, 95% CI = 1.22, 8.32), with prenatal exposure to arsenic of >500 µg/L in drinking water, but there was little effect on lung function.²⁸ Respiratory symptom effects at that time were evident for both boys and girls.

However, the present study found elevated risks of respiratory symptoms only among males while there was now no

Table 3. Results from multivariate logistic regression analysis of respiratory symptoms and arsenic exposure in early life (10–400 and >400 µg/L) compared with <10 µg/L never exposed in females (adjusted for more variables^a)

Respiratory symptoms	<10 µg/L		10–400 µg/L			>400 µg/L			
	N	N	OR	95% CI	P ^b	N	OR	95% CI	P ^b
Coughing									
When having a cold (last 12 months)	71	34	1.37	0.69, 2.74	0.19	33	0.83	0.45, 1.59	0.72
When not having a cold (last 12 months)	15	5	0.74	0.25, 2.22	0.70	7	0.91	0.35, 2.39	0.57
Dry cough (last 12 months)	63	30	1.13	0.57, 2.22	0.36	31	0.96	0.51, 1.79	0.56
Wheezing									
Ever	28	18	1.57	0.74, 3.33	0.12	19	1.44	0.70, 2.93	0.16
Last 12 months	13	5	0.45	0.12, 1.67	0.88	4	0.29	0.08, 1.13	0.96
Number of wheezing attacks (1–3 times)	10	4	0.87	0.25, 3.07	0.58	2	0.35	0.07, 1.69	0.90
Number of wheezing attacks (4+ times)	3	1	0.69	0.06, 8.27	0.61	1	0.55	0.05, 5.79	0.69
Number of nights sleep disturbed (<1/week)	2	3	3.64	0.54, 24.6	0.09	0			
Number of nights sleep disturbed (1 or more/week)	7	1	0.29	0.03, 2.51	0.87	4	1.04	0.29, 3.76	0.48
Severe enough to affect speech	6	3	1.05	0.24, 4.63	0.47	3	0.94	0.23, 3.95	0.53
After exercise	12	5	0.93	0.30, 2.94	0.55	4	0.60	0.18, 1.98	0.80
Without exercise	3	1	0.32	0.03, 3.68	0.82	1	0.43	0.04, 4.75	0.75
When having a cold	10	5	1.14	0.35, 3.70	0.41	4	0.74	0.22, 2.50	0.69
When not having a cold	1	0				3	7.44	0.63, 88.1	0.06
Shortness of breath									
Woken up with shortness of breath	18	14	2.18	0.94, 5.05	0.04	13	1.49	0.66, 3.37	0.17
Woken up with tightness of chest	12	11	2.05	0.78, 5.37	0.07	10	1.75	0.69, 4.44	0.12
When walking fast or climbing	49	24	1.04	0.53, 2.06	0.45	26	1.04	0.55, 1.95	0.46
When walking on level ground	22	11	1.23	0.53, 2.85	0.32	11	0.99	0.44, 2.22	0.51
Asthma	22	11	1.07	0.45, 2.52	0.44	12	1.04	0.46, 2.33	0.46

^aAdjusted for age, BMI, smoking (self and father), and number of rooms in house.

^bOne-tailed *P*-value.

Table 4.

Results from multivariate linear regression analysis of lung function and arsenic exposure in early life (10–400 and >400 µg/L) compared with <10 µg/L

	10–400 µg/L			<i>P</i> ^b	>400 µg/L		
	FEV1 (mL)	95% CI			FEV1 (mL)	95% CI	<i>P</i> ^b
All	29.5	–45.1, 104.1		0.78	–15.0	–82.2, 52.2	0.33
Male	57.0	–64.1, 178.1		0.82	–75.0	–180.1, 30.2	0.08
Female	20.4	–65.9, 106.6		0.68	52.7	–27.6, 133.1	0.90
	FVC (mL)				FVC (mL)		
All	21.3	–54.0, 96.6		0.71	–34.8	–102.6, 33.1	0.16
Male	19.8	–102.4, 142.1		0.63	–95.0	–201.1, 11.0	0.04
Female	45.7	–40.4, 131.9		0.85	38.0	–42.2, 118.3	0.82

^aAdjusted for age, height, weight, smoking (self and father), and number of rooms in house.

^bOne-tailed *P*-value.

effect of early life arsenic exposure among females. Interestingly, we observed reduced lung function among the male participants which was absent in the cohort study when they were younger. Although these sex specific findings are somewhat surprising, many studies have reported gender differences in arsenic effects.⁵⁰ Key studies and findings we identified concerning gender differences are presented in Table 5. Pesola et al⁸ found the risk for dyspnea was greater among males compared with females. Parvez et al¹³ observed that arsenic exposure affected FEV1 only in men and the risk for reduced FVC was greater among males. Similarly, von Ehrenstein et al¹ found increased

respiratory symptoms in India and a marked decline in both FVC and FEV1 in arsenic exposed males, but not in females. Dauphine et al showed that early life arsenic exposure in Chile had a detrimental effect on lung function, especially FVC in adult males.²¹ Raqib et al found that the correlation between prenatal inorganic arsenic and acute respiratory infections was stronger in boys in comparison to girls.²⁵

Gender variation has also been observed in arsenic-induced skin lesions with higher risks among males (Table 5).^{1, 33–37} A study in Mexico reported that boys living in an arsenic-contaminated area scored poorly on various cognitive tests in

Table 5.

Findings from previously published studies with gender data on arsenic exposure and respiratory effects, skin lesions, and methylation efficiency of inorganic arsenic into MMA

Study	Health effect	Population studied	Key finding regarding gender differences
	Respiratory		
Parvez et al, 2013 ¹³		Bangladesh	Greater reduction in FEV1 (male = –66.6; female = –29.3) and FVC (male = –63.9; female = –46.0) in males
Pesola et al, 2012 ⁸		Bangladesh	Dyspnea crude OR male = 2.01 (1.15, 3.52; <i>P</i> = 0.015); female = 1.51 (1.24, 1.85; <i>P</i> < 0.001)
Dauphiné et al, 2011 ²¹		Chile	Much greater reductions in FEV1 (male = –440; female = –17) and FVC (male = –673; female = –27) in males
Raqib et al, 2009 ²⁵		Bangladesh	Acute respiratory infections in boys 6–12 months: <i>r</i> = 0.57, <i>P</i> = 0.02; girls: <i>r</i> = 0.07, <i>P</i> = 0.86 (at gestation weeks 6–10)
von Ehrenstein et al, 2005 ¹		India	Shortness of breath OR for male nonsmokers with no skin lesions = 3.8 (95% CI = 0.7, 20.6), for female nonsmokers with no skin lesions = 1.6 (0.6, 4.2)
	Skin lesions		
Lindberg et al, 2008 ³³		Bangladesh	Male OR for skin lesions compared with females 1.3 (95% CI = 1.0, 1.7)
Ahsan et al, 2006 ³⁴		Bangladesh	Males adjusted 1.8 (<i>P</i> = 0.03) prevalence odds ratio 4.15 (95% CI = 3.27, 5.26) compared with females
Rahman et al, 2006 ³⁵		Bangladesh	Males had a higher risk of obtaining skin lesions than females (odds ratio 10.9 vs. 5.78) in the highest average exposure quintile (<i>P</i> = 0.005).
von Ehrenstein et al, 2005 ¹		India	50.4% of study source population was female, but skin lesions male: <i>n</i> = 93; female: <i>n</i> = 39
Kadono et al, 2002 ³⁶		Bangladesh	Skin lesions overall more severe in males (<i>P</i> < 0.001); each type also more severe in males (keratosis on soles <i>P</i> < 0.001; keratosis on palms <i>P</i> < 0.05; melanosis and hypopigmentation on trunk <i>P</i> < 0.05)
Guha Mazumder et al, 1998 ³⁷		India	Keratosis prevalence per 100: male = 3.0; female = 1.2. Hyperpigmentation prevalence per 100: male = 6.4; female = 3.1
	MMA		
Wei et al, 2016 ³⁸		China	Male %MMA = 15.92 (SD 4.71); female %MMA = 13.62 (SD 4.16)
Lindberg et al, 2008 ³⁹		Bangladesh	Males over 20 associated with higher %MMA (Beta coefficient –0.36, <i>P</i> < 0.01) in multiple regression
Lindberg et al, 2007 ⁴⁰		Hungary, Romania, Slovakia	Males correlated with higher %MMA (Beta coefficient –0.14, <i>P</i> < 0.01) in multiple regression analysis
Steinmaus et al, 2006 ⁴¹		Argentina and USA	Women had lower %MMA in both Argentina and US (Women: Argentina = 13.4%; US = 10.4%. Men: Argentina 14.8%; US = 13.9%)
Gamble et al, 2005 ⁴²		Bangladesh	Women %MMA at 11.5 ± 4.8 vs 15.5 ± 5.2 in men
Hsueh et al, 2003 ⁴³		Taiwan	Males %MMA = 16.5 ± 1.1; females = 13.6 ± 0.8; <i>P</i> < 0.05
Chen et al, 2003 ⁴⁴		Taiwan	Men had lower methylation efficiency in both steps of methylation. For the secondary step DMA(V) / MMA(V), men = 10.02 (SD13.66); women = 11.71 (SD 12.85); <i>P</i> = 0.32
Loffredo et al, 2003 ⁴⁵		Chile, China, Mexico	In the Mexico, high exposure group MMA concentrations were higher in men (158.4) than women (133.7). Numbers of participants from the other countries were too few to assess
Hsueh et al, 1998 ⁴⁶		Taiwan	Males %MMA = 20.23 ± 1.13; females = 13.89 ± 0.88; <i>P</i> < 0.05
Hopenhayn-Rich et al, 1996 ⁴⁷		Chile	Women had lower %MMA. At about 600 µg/L, women = 12.8 (3.7–25.7) and men = 16.5 (7.0–26.8)
Hopenhayn-Rich et al, 1996 ⁴⁸		Chile	For subjects exposed to either about 15 µg/L or about 600 µg/L (low and high exposure groups combined), mean %MMA for women = 11.5 (SD 4.3) and men = 14.4 (SD5.9)

comparison to girls living in the same area.⁵¹ Differences in arsenic effects between males and females may be due to sex differences in arsenic metabolism (Table 5). Males are reported to have lower methylation capacity than females, so more arsenic is present in inorganic form or as MMA3, both of which are highly toxic.^{52,39,40} Although one might expect stronger findings in males than in females, we have no explanation for the sex-specific findings in this follow-up compared with our first study. It seems that the respiratory symptom effects in girls have largely disappeared, while boys continue to have symptoms and now also have evidence of reduced lung function. Further follow-up of these children, including urinary arsenic speciation, may help elucidate these puzzling observations.

The mechanisms by which arsenic causes chronic respiratory illness via drinking water are not well understood. Immune suppression is considered one of the possible ways. A review of published reports suggests that arsenic causes immune suppression by inducing apoptosis,^{53,54} oxidative stress,^{55,56} and inflammation.^{56,57} Early life arsenic exposure through drinking water has been found to be associated with reduced size and function of the thymus leading to immune suppression and increase susceptibility to infection.^{25,58} In vitro evidence suggests that arsenic alters the respiratory epithelial barrier and impairs wound repair through the upregulation of MMP-9 by pulmonary epithelial cells.⁵⁹

One of the strengths of the current study is the individual assessment of drinking water arsenic exposure levels during prenatal life, and individual arsenic exposure assessment in childhood. A limitation of the study was that we did not take water samples from tube well sources that were used for <6 months; which might affect exposure status to some extent. A more important limitation was that we are not able to separate effects of exposure in utero from exposure in early childhood. The reason for this is that the drinking water the mother used during pregnancy was mostly the same water as used by the child after birth. We therefore refer to “early life exposure” and not to “in utero” exposure in the title and elsewhere in the article. Another limitation was not having urine concentrations during pregnancy in addition to the water arsenic concentrations. However, with the wide distribution of water arsenic concentrations with a major contrast between high and low exposure, not having urine concentrations is not important. In addition, urine concentrations only measure arsenic exposure spanning a few days.

We were surprised that there is now no evidence of respiratory effects in girls. This suggests that with reductions in arsenic exposure, girls may recover from respiratory effects more rapidly than boys. Further follow-up of our cohort will show if respiratory effects persist in males and if females have permanently recovered from chronic respiratory effects resulting from early life exposure. We conclude by noting that there is extensive evidence that there are long-term effects resulting from early life exposure to arsenic so every effort should be made to reduce exposure especially in early life.

Conflicts of interest

The authors declare that they have no conflicts of interest with regard to the content of this report.

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