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Arsenic exposure from drinking water and dyspnoea risk in Araihazar, Bangladesh: a population-based study

Gene R. Pesola*,#, Faruque Parvez¶,+, Yu Chen§, Alauddin Ahmed+, Rabiul Hasan+ and Habibul Ahsan#,+,f

ABSTRACT: Bangladesh has high well water arsenic exposure. Chronic arsenic ingestion may result in diseases that manifest as dyspnoea, although information is sparse.

Baseline values were obtained from an arsenic study. Trained physicians ascertained data on dyspnoea among 11,746 subjects. Data were collected on demographic factors, including smoking, blood pressure and arsenic exposure. Logistic regression models estimated odds ratios and confidence intervals for the association between arsenic exposure and dyspnoea.

The adjusted odds of having dyspnoea was 1.32-fold (95% CI 1.15–1.52) greater in those exposed to high well water arsenic concentrations ($\geqslant$50 $\mu g \cdot L^{-1}$) compared with low-arsenic-exposed nonsmokers ($p<0.01$). A significant dose–response relationship was found for arsenic (as well as smoking) in relation to dyspnoea. In nonsmokers, the adjusted odds of having dyspnoea were 1.36, 1.96, 2.34 and 1.80-fold greater for arsenic concentrations of 7–38, 39–90, 91–178 and 179–864 $\mu g \cdot L^{-1}$, respectively, compared with the reference arsenic concentration of <7 $\mu g \cdot L^{-1}$ ($p<0.01$; Chi-squared test for trend).

Arsenic exposure through well water is associated with dyspnoea, independently of smoking status. This study suggests that mandated well water testing for arsenic with reduction in exposure may significantly reduce diseases that manifest as dyspnoea, usually cardiac or pulmonary.

KEYWORDS: Arsenicosis, dyspnoea dose–response, environmental dyspnoea

Bangladesh is exposed to high well water concentrations of inorganic arsenic due to natural deposits underground [1, 2]. The current World Health Organization (WHO) and US standards for acceptable arsenic content of drinking water is <10 $\mu g \cdot L^{-1}$ [2]. The Bangladesh standard is <50 $\mu g \cdot L^{-1}$ and it has been estimated that about one out of 100 subjects exposed to this elevated level in drinking water could die of liver, lung, kidney or bladder cancer over a lifetime [2]. A positive association between well water arsenic exposure and dyspnoea has been suggested in cross-sectional studies [3, 4]. One large study compared the effects of arsenic levels in well water at $\geqslant$500 $\mu g \cdot L^{-1}$ with <50 $\mu g \cdot L^{-1}$ and found age-adjusted prevalence odds ratios (PORs) of 23.2 (95% CI 5.8–92.8) and 3.7 (1.3–10.6) for nonsmoking females and males, respectively, for presence of dyspnoea [3]. These high PORs occurred only in those with arsenic skin lesions [3]. A second study found nonsignificant PORs of 1.6 (0.6–4.2) and 3.8 (0.7–20.6) in subjects with arsenic-associated skin lesions *versus* no skin lesions for female and males, respectively, in nonsmoking subgroups [4]. The well water arsenic concentrations were described as $\geqslant$100 $\mu g \cdot L^{-1}$ in $\geqslant$90% of those with skin lesions [4].

Bangladesh is eighth in the world in terms of total number of smokers [5, 6]. Of the world's eight leading causes of death (heart disease, cerebrovascular disease, lower respiratory infections, chronic obstructive pulmonary disease (COPD), HIV/AIDS, diarrhoeal disease, tuberculosis, and cancers of the trachea, bronchus and lung), smoking is a risk factor for all but HIV/AIDS and diarrhoeal diseases [5, 6]. Most of these smoking-related diseases can also present with dyspnoea.

The purpose of this investigation was to determine whether elevated well water arsenic exposure was associated with chronic dyspnoea, independently of smoking. This is a rare opportunity to determine whether or not chronic arsenic exposure causes dyspnoea. Detection of an arsenic–dyspnoea relationship would serve as further incentive to completely eliminate arsenic from well

AFFILIATIONS
*Division of Pulmonary and Critical Care Medicine, Dept of Medicine, Harlem Hospital, Columbia University,
#Depts of Epidemiology,
¶Environmental Health Sciences, Mailman School of Public Health, Columbia University,
§Dept of Environmental Medicine, NYU Langone Medical Center, New York, NY,
fDept of Health Studies, Medicine, and Human Genetics and Cancer Research Center, University of Chicago, Chicago, IL, USA.
+Columbia University Arsenic and Health Research Office in Bangladesh, Dhaka, Bangladesh.

CORRESPONDENCE
G.R. Pesola
Harlem Hospital/Columbia University
Dept of Medicine
Section of Pulmonary Disease
MLK 12106
506 Lenox Ave
New York
NY 10037
USA
E-mail: grp4@columbia.edu

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water and reduce the Bangladesh arsenic water standard to that of the WHO.

MATERIALS AND METHODS

Data source and approvals

Study subject baseline data were obtained from the cohort study ''Health Effects of Arsenic Longitudinal Study'' (HEALS) [7]. Study procedures were approved by the ethical committee of the Bangladesh Medical Research Council (Dhaka, Bangladesh) and institutional review boards of Columbia University (New York, NY, USA) and University of Chicago (Chicago, IL, USA).

Subjects and demographics

Baseline data were collected as previously described [7]. In brief, eligibility for HEALS included being aged $\geqslant$18 yrs, being married (stability of residence), and having resided in Araihazar, Bangladesh for $\geqslant$5 yrs.

After obtaining consent, a 45-min interview collected demographics including age, sex, body mass index (BMI), educational attainment (0–16 yrs), occupational history and smoking (past, present or never). Vital signs, including blood pressure, were measured, as were height and weight. A spot urine sample was collected and stored as described [7]. The baseline clinical examination included an assessment of arsenic-related skin lesions [7].

The outcome variable dyspnoea was determined by trained physicians asking the question ''During the last 6 months, have you had dyspnoea?'' Elicitation of the presence or absence of dyspnoea in this patient population has a reliability >90% [8].

Laboratory analysis

Well water arsenic concentrations were analysed at the Geochemistry Research Laboratory of Columbia University [9] by graphite furnace atomic absorption (GFAA). The detection limit for GFAA was 5 $\mu g \cdot L^{-1}$. Water samples with concentrations at the detection limit were re-analysed by inductively coupled plasma-mass spectrometry with a detection limit of 0.1 $\mu g \cdot L^{-1}$ [10].

The urinary arsenic concentration was measured by GFAA spectrometry [11]. Urinary creatinine was measured by a colorimetric diagnostics kit (Sigma, St Louis, MO, USA) and the total arsenic in urine (in $\mu g \cdot L^{-1}$) was divided by the urinary concentration of creatinine (in $g \cdot L^{-1}$) to obtain an adjusted concentration of arsenic (in $\mu g \cdot g^{-1}$ creatinine) [12].

Statistical analysis

The Pearson Chi-squared test was used to compare categorical data between sexes for BMI, smoking and arsenic concentrations, and for calculating well water arsenic concentrations by five groups from high to low, with dyspnoea as the outcome. The Chi-squared test for trend (linear-by-linear association) was used to determine whether increasing cigarette consumption or increasing well water or urinary arsenic concentrations resulted in a significant increase in prevalence of dyspnoea. An unpaired t-test was conducted to compare ages between females and males. The Pearson correlation coefficient determined the correlation between water arsenic concentration and urinary arsenic excretion.

Unconditional logistic regression was used to estimate the odds ratio for dyspnoea. BMI was categorised into three groups (normal or reference BMI 18.50–24.99 $kg \cdot m^{-2}$, low BMI $<$18.50 $kg \cdot m^{-2}$ and high BMI $\geqslant$25 $kg \cdot m^{-2}$). Well water arsenic concentration was coded, with $\geqslant$50 $\mu g \cdot L^{-1}$ as exposed and $<$50 $\mu g \cdot L^{-1}$ as the reference group, in all analyses except for dose–response analyses among the nonsmoker group, in which quintiles of well water arsenic concentration or urinary arsenic excretion were used. Continuous variables included age, educational level and systolic blood pressure. For a sensitivity analysis in nonsmokers, well water arsenic concentrations were also coded as $\geqslant$25, $\geqslant$12.5 and $\geqslant$6.25 $\mu g \cdot L^{-1}$ *versus* other and subsequent adjusted odds ratios for dyspnoea obtained. A p-value $<$0.05 was significant.

Biological interaction was evaluated between arsenic ($\geqslant$50 $\mu g \cdot L^{-1}$ *versus* other) and smoking using prevalence of dyspnoea by joint status of two exposures [13, 14]. Analyses were performed with SPSS 18 (SPSS Inc., Chicago, IL, USA).

RESULTS

Descriptive data, arsenic skin lesion status and arsenic exposure data

The overall mean$\pm$SD (range) population age was 37.1$\pm$10.1 (17–75) yrs. For females and males the ages were 33.6$\pm$8.9 (18–61) yrs and 41.6$\pm$9.9 (20–75) yrs, respectively ($p<0.01$).

Baseline distributions for demographic variables for sex, BMI, smoking status and well arsenic concentration are summarised in table 1. The sex distributions for BMI are significantly different ($p<0.01$), with more females than males in the normal BMI category. The sex distributions for smoking status are also significantly different ($p<0.01$), with 62% of males being smokers compared with 3.7% of females.

Table 2 compares quintiles of well water arsenic exposure *versus* the dichotomous outcome variable, presence or absence of

TABLE 1 Distribution of Health Effects of Arsenic Longitudinal Study (HEALS) participants

	Total	Females	Males
Subjects	11746	6704	5042
BMI $kg \cdot m^{-2}$**			
<18.50	4555 (38.8)	2333 (34.8)	2222 (44.1)
18.50–24.99	6108 (52.0)	3696 (55.1)	2412 (47.8)
>25.00	804 (6.8)	515 (7.7)	289 (5.7)
Missing	279 (2.4)	160 (2.4)	119 (2.4)
Smoking**			
Nonsmoker	7568 (64.4)	6282 (93.7)	1286 (25.5)
Ex-smoker	777 (6.6)	168 (2.5)	609 (12.1)
Smoker	3390 (28.9)	247 (3.7)	3143 (62.3)
Missing	11 (0.1)	7	4
Baseline well arsenic $\mu g \cdot L^{-1}$			
Quintile 1: <7	2325 (19.8)	1318 (19.7)	1007 (20.0)
Quintile 2: 7– <39	2354 (20.0)	1350 (20.1)	1004 (19.9)
Quintile 3: 39– <91	2333 (19.9)	1347 (20.1)	986 (19.6)
Quintile 4: 91– <179	2382 (20.3)	1364 (20.3)	1018 (20.2)
Quintile 5: $\geqslant$179	2352 (20.0)	1325 (19.7)	1027 (20.4)

Data are presented as n or n (%). BMI: body mass index. **: $p<0.01$ by Chi-squared test for the sex distributions of BMI and smoking.

TABLE 2 Logistic regression model in male and female nonsmokers combined, comparing quintiles of well water arsenic concentration with the presence or absence of arsenic skin lesions

Independent variables	Adjusted OR (95% CI)	p-value
Well arsenic quintile#		
1: reference	1.00	
2	1.80 (1.02–3.16)	0.043
3	2.79 (1.62–4.78)	<0.001
4	3.09 (1.82–5.23)	<0.001
5	3.94 (2.36–6.58)	<0.001**
Age	1.05 (1.03–1.06)	<0.001
Education	0.95 (0.92–0.99)	0.007
Sex¶	0.27 (0.20–0.35)	<0.001
Systolic BP	1.01 (0.99–1.01)	0.167
BMI group+		
1	1.41 (1.07–1.87)	0.016
2	0.66 (0.37–1.19)	0.170

BP: blood pressure; BMI: body mass index. #: the reference well water arsenic concentration was <7 μg·L^{-1}, with quintiles as described in table 1; ¶: the reference for sex was male; +: BMI categorised as low (<18.5 kg·m^{-2}; group 1) and high (⩾25 kg·m^{-2}; group 2). **: p<0.01 by Chi-squared test for trend.

arsenic-associated skin lesions. There is a clear dose–response between increasing well water arsenic concentrations and the presence of skin lesions. Using the presence of arsenic skin lesions as the exposure marker of interest revealed a 2.2-fold greater odds of dyspnoea for individuals with arsenic-related skin lesions compared with those without, after adjustment (table 3). This analysis was done in nonsmokers only. Similar results were found when including all subjects, females only and males only (data not shown).

TABLE 3 Logistic regression model in male and female nonsmokers combined, comparing arsenic skin lesions with the primary outcome variable of the presence or absence of dyspnoea

Independent variables	Adjusted OR (95% CI)	p-value
Skin lesions		
No: reference	1.00	
Yes	2.24 (1.52–3.30)	<0.001
Age	1.03 (1.02–1.04)	<0.001
Education	0.96 (0.94–0.99)	0.004
Sex#	1.77 (1.32–2.36)	<0.001
Systolic BP	1.00 (0.99–1.01)	0.385
BMI group¶		
1	1.19 (0.98–1.45)	0.079
2	1.27 (0.92–1.76)	0.148

BP: blood pressure; BMI: body mass index. Similar results were obtained when females and males were analysed separately. #: the reference for sex was male; ¶: BMI categorised as low (<18.5 kg·m^{-2}; group 1) and high (⩾25 kg·m^{-2}; group 2).

The Pearson correlation coefficient between water arsenic concentration and urinary arsenic concentration was 0.556 (p<0.001).

Arsenic as primary exposure variable in the total population

Table 4 is a summary of the adjusted odds ratios for dyspnoea in relation to well water arsenic exposure and smoking status. Both arsenic and smoking, in any of the three smoking categories, were independent and significantly related to dyspnoea. Age and education were directly and inversely associated with increased dyspnoea, respectively.

An analysis eliminating ex-smokers was performed to determine whether there was a dose–response relationship between levels of smoking and dyspnoea (n=10,958). The crude odds ratio for both cigarette groups was significant, with similar odds ratios for females and males combined before adjustment (table 5). No dose response was seen. However, there was a significant adjusted dose response for females and males. Separating groups by sex revealed only 15 females who smoked >10 cigarettes per day; therefore, females could not be analysed by dose response. For males, the crude and adjusted OR Chi-squared test for trend were significant, implying a dose–response relationship between cigarette smoking and dyspnoea.

Biological interaction between arsenic and smoking was not found [13, 14]. In particular, on evaluating all subjects, in the low arsenic nonsmoking group (reference), the prevalence of dyspnoea was 5.4%. The high arsenic (⩾50 μg·L^{-1}) nonsmoking group had a prevalence of dyspnoea of 8.24%. The low arsenic smoking group had a prevalence of dyspnoea of 8.73%. Finally, the high arsenic smoking group had a prevalence of dyspnoea of 8.84%. Biological interaction, or interaction on the additive scale, would only be present if the actual combined prevalence exceeded the theoretical prevalence.

Biological interaction was also evaluated for all males only, all females only, male smokers only (excluding ex-smokers), female smokers only (excluding ex-smokers), male ex-smokers (excluding active smokers) and female ex-smokers (excluding active smokers). No interaction was found.

Arsenic as primary exposure variable, excluding smokers

Table 6 was created by eliminating smokers. The primary exposure variable is elevated well water arsenic concentration (⩾50 μg·L^{-1}) *versus* reference (<50 μg·L^{-1}). Compared with the crude odds ratio, table 6 reveals similar elevated adjusted odd ratios among never-smokers for all subjects, females and males. After exclusion of smokers, the association between arsenic and dyspnoea increased, as seen by increased odds ratio. The odds ratio for dyspnoea was greater for males than females. The sensitivity analysis using well water arsenic cut-off values of ⩾25, ⩾12.5 and ⩾6.25 μg·L^{-1} *versus* other, revealed adjusted odds ratios of 1.62 (95% CI 1.31–2.01), 1.81 (95% CI 1.42–2.31) and 1.80 (95% CI 1.37–2.37), respectively. These results were robust and even higher than the odds ratio of 1.56 (95% CI 1.29–1.88) seen in table 6 using the well water arsenic cut-off of ⩾50 μg·L^{-1}.

Table 7 shows analysis where arsenic categories were divided into quintiles. The reference or lowest quintile was a well water arsenic concentration of <7 μg·L^{-1}. The other quintiles were 7–<39, 39–<91, 91–<179 and 179–864 μg·L^{-1}. A dose response was seen going from quintiles 1 through 4, with odds ratio

TABLE 4 Logistic regression model with the primary exposure variable of well water arsenic exposure, controlling for smoking category, with the outcome variable of interest of the presence or absence of dyspnoea

Independent variables	Smokers plus ex-smokers[#]		Current smokers[¶]		Ex-smokers[+]	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Well arsenic[§]						
Reference	1.00		1.00		1.00	
High	1.32 (1.15–1.52)	<0.001	1.33 (1.14–1.54)	<0.001	1.51 (1.27–1.79)	<0.001
Smoking[f]						
Smoker/ex-smoker	1.44 (1.16–1.78)	0.001				
Current smokers			1.38 (1.09–1.75)	0.008		
Ex-smokers					1.64 (1.22–2.20)	<0.001
Age	1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.04)	<0.001
Education	0.96 (0.92–0.98)	<0.001	0.96 (0.94–0.98)	<0.001	0.96 (0.94–0.99)	0.002
Sex[##]	1.58 (1.28–1.95)	<0.001	1.56 (1.24–1.96)	<0.001	1.60 (1.24–2.05)	<0.001
Systolic BP	1.00 (0.99–1.00)	0.488	1.00 (0.99–1.00)	<0.692	1.00 (0.99–1.01)	0.648
BMI group[¶¶]						
1	1.16 (0.99–1.32)	0.054	1.13 (0.96–1.32)	<0.139	1.24 (1.04–1.49)	0.018
2	1.37 (1.04–1.80)	0.026	1.42 (1.07–1.88)	<0.016	1.24 (0.91–1.70)	0.174

BP: blood pressure; BMI: body mass index. [#]: included the complete dataset, with smokers and ex-smokers combined *versus* nonsmokers; [¶]: included smokers only (ex-smokers were excluded from analysis); [+]: included ex-smokers only (current smokers were excluded from analysis); [§]: the reference well water arsenic concentration was <50 μg·L^{-1}, with high arsenic being ⩾50 μg·L^{-1}; [f]: for all three smoking groups the reference was nonsmokers; [##]: the reference for sex was male; [¶¶]: BMI categorised as low (<18.5 kg·m^{-2}; group 1) and high (⩾25 kg·m^{-2}; group 2).

increasing from 1.00 up to 2.17. The fifth quintile had an odds ratio of 1.84, still significant but smaller than quintiles 3 and 4. The adjusted odds ratios were no different from the crude values (table 7). The Pearson Chi-squared test for well water arsenic concentrations in five groups in relation to the dichotomous outcome variable dyspnoea was significant at p<0.01 (four degrees of freedom, Chi-squared 31.4). The Chi-squared test for trend for increasing odds ratio as well water arsenic concentration increased was significant at p<0.01 (one degree of freedom, Chi-squared 21.4).

TABLE 5 Logistic regression model excluding ex-smokers, comparing smoking dose–response with dyspnoea

Independent variables	Crude OR (95% CI)	p-value	Females and males		Males only[#]	
			Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Females and males						
Nonsmokers	1.00		1.00			
⩽10 cigarettes per day	1.29 (1.08–1.55)	0.005	1.37 (1.07–1.76)	0.013		
>10 cigarettes per day	1.27 (1.03–1.56)	0.026	1.40 (1.04–1.87)	0.027**		
Males only						
Nonsmokers	1.00				1.00	
⩽10 cigarettes per day	1.75 (1.29–2.38)	<0.001			1.46 (1.05–2.03)	0.021
>10 cigarettes per day	1.85 (1.34–2.54)	<0.001**			1.48 (1.06–2.08)	0.022**
Age			1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.04)	<0.001
Education			0.96 (0.94–0.98)	<0.001	0.96 (0.93–0.99)	0.014
Sex			1.56 (1.24–1.97)	<0.001		
High well arsenic[¶]			1.33 (1.14–1.54)	<0.001	1.22 (0.97–1.55)	0.091
Systolic BP			1.00 (0.99–1.00)	0.696	1.00 (0.99–1.00)	0.309
BMI group[+]						
1			1.13 (0.96–1.32)	0.138	1.22 (0.95–1.57)	0.116
2			1.42 (1.07–1.88)	0.016	2.10 (1.30–3.39)	0.002

BP: blood pressure; BMI: body mass index. [#]: females not analysed separately, since there were only 15 females who smoked >10 cigarettes per day; [¶]: high arsenic was ⩾50 μg·L^{-1}; [+]: BMI categorised as low (<18.5 kg·m^{-2}; group 1) and high (⩾25 kg·m^{-2}; group 2). **: p<0.01 by Chi-squared test for trend.

TABLE 6 Logistic regression model in nonsmokers, with the primary exposure variable of well water arsenic and the outcome variable of interest of the presence or absence of dyspnoea

Independent variables	Crude OR (95% CI)	p-value	Females and males		Females only		Males only	
			Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Females and males	1.56 (1.30–1.88)	<0.001						
Females	1.51 (1.24–1.85)	<0.001						
Males	2.01 (1.15–3.52)	0.015						
Well arsenic[#]								
Reference	1.00		1.00		1.00		1.00	
High			1.56 (1.29–1.88)	<0.001	1.51 (1.23–1.84)	<0.001	2.00 (1.14–3.52)	0.016
Age			1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.05)	<0.001	1.03 (1.00–1.05)	0.050
Education			0.96 (0.93–0.99)	0.003	0.96 (0.93–0.99)	0.004	0.98 (0.92–1.04)	0.545
Sex			1.65 (1.24–2.20)	0.001				
Systolic BP			1.00 (0.99–1.01)	0.300	1.00 (0.99–1.01)	0.293	1.00 (0.99–1.02)	0.870
BMI group[¶]								
1			1.20 (0.98–1.46)	0.071	1.15 (0.93–1.42)	0.197	1.67 (0.94–3.00)	0.083
2			1.28 (0.92–1.77)	0.139	1.19 (0.83–1.70)	0.350	1.96 (0.88–4.36)	0.099

BP: blood pressure; BMI: body mass index. [#]: the reference well water arsenic concentration was <50 μg·L^{-1}, with high arsenic being ⩾50 μg·L^{-1}; [¶]: BMI categorised as low (<18.5 kg·m^{-2}; group 1) and high (⩾25 kg·m^{-2}; group 2).

The quintiles of urinary arsenic excretion per gram of creatinine in relation to dyspnoea were also analysed (table 8). Both the crude (not shown) and adjusted values resulted in a significant dose response of increasing urinary arsenic excretion in relation to dyspnoea, as seen with well water arsenic. A similar analysis (data not shown) using urinary excretion of arsenic without adjustment for creatinine also found a significant Chi-squared test for trend dose response ($p<0.01$).

TABLE 7 Logistic regression dose–response model in nonsmokers, with the primary exposure variable of well water arsenic and the outcome variable of interest of the presence or absence of dyspnoea

Independent variables	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Well arsenic quintile[#]				
1: reference	1.00		1.00	
2	1.39 (0.99–1.93)	0.052	1.36 (0.97–1.90)	0.074
3	1.97 (1.44–2.70)	<0.001	1.96 (1.43–2.70)	<0.001
4	2.17 (1.59–2.95)	<0.001	2.14 (1.56–2.92)	<0.001
5	1.84 (1.34–2.53)	<0.001**	1.80 (1.31–2.49)	<0.001**
Age			1.03 (1.02–1.04)	<0.001
Education			0.96 (0.94–0.99)	0.004
Sex			1.65 (1.24–2.19)	0.001
Systolic BP			1.00 (0.99–1.01)	0.323
BMI group[¶]				
1			1.21 (0.99–1.47)	0.064
2			1.29 (0.93–1.79)	0.122

BP: blood pressure; BMI: body mass index. [#]: the reference well water arsenic concentration was <7 μg·L^{-1}, with quintiles as described in table 1; [¶]: BMI categorised as low (<18.5 kg·m^{-2}; group 1) and high (⩾25 kg·m^{-2}; group 2). **: $p<0.01$ by Chi-squared test for trend.

DISCUSSION

High baseline well water arsenic exposure was a significant risk factor for dyspnoea, adjusted for smoking (table 4). This arsenic–dyspnoea association was strong for all three smoking subgroups (table 4). In order to eliminate smoking effects, a separate analysis using only nonsmokers was carried out

TABLE 8 Logistic regression dose–response model in nonsmokers, with the primary exposure variable of urinary arsenic excretion and the outcome variable of interest of the presence or absence of dyspnoea

Independent variables	OR (95% CI)	p-value
Urinary arsenic quintile[#]		
1: reference	1.00	
2	1.37 (0.97–1.92)	0.073
3	1.92 (1.38–2.65)	<0.001
4	1.94 (1.41–2.68)	<0.001
5	1.87 (1.36–2.58)	<0.001**

All data were adjusted for age, education, body mass index, systolic blood pressure and sex. [#]: equal quintiles of urinary arsenic excretion (in μg·L^{-1}) divided by the urinary concentration of creatinine (in g·L^{-1}), resulting in an adjusted concentration of arsenic (in μg·g^{-1} creatinine). **: $p<0.01$ by Chi-squared test for trend.

(tables 6 and 7). An arsenic dose–response curve revealed an increased prevalence of dyspnoea with increasing well water arsenic concentrations using <7 μg·L^{-1} as reference (table 7). The odds ratio for the presence of dyspnoea increased from the reference to the second quintile. This result could argue for reducing the current Bangladesh arsenic water standard to at least the world standard of <10 μg·L^{-1} or lower, *i.e.* to levels <7 μg·L^{-1}.

The positive association between arsenic exposure and respiratory symptoms has been suggested in three cross sectional studies that included only nonsmokers. A small study found a nonsignificant increase in the crude POR with either chronic bronchitis or chronic cough when the reference well water arsenic concentration was <50 μg·L^{-1}. The highest POR was 2.7 (95% CI 0.3–16.9) [15]. A second study compared the age adjusted POR for those exposed to a reference arsenic concentration of <50 μg·L^{-1} *versus* those exposed to levels ≥ 500 μg·L^{-1} [3]. For females, the POR for cough and dyspnoea were 7.8 (95% CI 3.1–19.5) and 23.2 (95% CI 5.8–92.8), respectively. For males, the same POR values were 5.0 (95% CI 2.6–9.9) and 3.7 (95% CI 1.3–10.6), respectively. These high POR were only present in those with skin lesions and were reduced but suggestive in all females and males [3]. A third study, using reference well water arsenic concentrations of <50 μg·L^{-1}, found that 63% of individuals exposed to high well water arsenic concentrations (67–875 μg·L^{-1}) had pulmonary effects including cough, bronchitis and dyspnoea [16]. The comparison had only 7% of these effects [16]. A fourth small study of smokers and nonsmokers with well water arsenic concentrations less than 500 μg·L^{-1} compared subjects with arsenic skin lesions (high exposure) *versus* those without arsenic skin lesions (lower exposure). The nonsmoking group revealed increased POR for dyspnoea, chronic cough and chronic bronchitis in both males and females of values around 2, albeit no statistically significant values were obtained [4].

Lung function testing has been evaluated in subjects with chronic arsenic ingestion in at least three studies [4, 17, 18]. These studies suggest a predominantly obstructive picture secondary to well water arsenic ingestion.

Two studies have looked specifically at whether or not there is an increase in bronchiectasis in subjects exposed to chronically elevated well water arsenic concentrations from 400 to 1,000 μg·L^{-1} [19, 20]. The adjusted odds ratio or standardised rates ranged from 10 to 46 [19, 20]. Both studies suggest that arsenic, which is ingested orally, causes bronchiectasis.

Dyspnoea was used as a proxy for diseases that manifest as shortness of breath, generally cardiac or pulmonary 85% of the time [21, 22]. However, three studies have suggested a reduction in lung function that is obstructive in nature in subjects exposed to elevated water arsenic concentrations [4, 17, 18]. Dyspnoea tends to occur with COPD when the forced expiratory volume in 1 s is reduced to 50% of normal [23]. Therefore, one of the mechanisms of dyspnoea with arsenic exposure might be the development of COPD secondary to arsenic. In addition, lung cancer secondary to arsenic would undoubtedly present with dyspnoea [24–26]. Also, arsenic is associated with bronchiectasis [19, 20], a cause of dyspnoea.

Dyspnoea could also occur in subjects who develop cardiovascular disease secondary to arsenic exposure. Two studies have revealed a dose–response relationship between well water arsenic and heart disease [27, 28]. A third Chilean study found myocardial infarction mortality rate ratios of 1.48 (95% CI 1.37–1.59) and 1.26 (95% CI 1.14–1.40) for males and females, respectively, during a period of excessive arsenic exposure [29]. In Wisconsin, using well water arsenic concentration of <2 *versus* >10 μg·L^{-1}, an increase in heart attacks and coronary bypass surgery were found with odds ratios of 2.08 (95% CI 1.10–4.31) and 2.34 (95% CI 1.12–4.90), respectively [30]. Finally, using a well water arsenic concentration <1 *versus* >10 μg·L^{-1} found mortality rates of 1.10 (95% CI 1.08–1.12) and 1.18 (95% CI 1.15–1.22) for cardiovascular and coronary heart disease, respectively [31]. Therefore, chronic arsenic exposure in drinking water predisposes to heart and lung disease, the two common causes of dyspnoea. Thus, our finding of a dose–response relationship between arsenic exposure and dyspnoea is biologically plausible.

It should be noted that the highest well water concentration of arsenic partially reverses the dose–response trend seen (table 7). The trend still maintained statistical significance probably related to a still very high odds ratio relative and close to the previous odds ratio. This finding could be related to random error, since the case number was limited in the highest level of arsenic exposure. A possible explanation for the finding, if real, is increased mortality at high arsenic exposure levels resulting in a reduced prevalence. Another possibility is a plateau in arsenic toxicity at a certain elevated level, although this would seem to be less likely from a biological point of view, since arsenic is a very toxic metal in humans. A third possibility is that the sickest subjects at baseline (many of whom may have had dyspnoea) with the highest arsenic exposure level may have declined to participate in the study. This selection bias out of the study might have resulted in a slight but spurious reversal of the dose response.

Smoking was also strongly associated with dyspnoea (table 4) with an adjusted dose–response relationship between cigarettes smoked and dyspnoea in males (table 5). Since dyspnoea is associated with an increase in mortality over time [32–36], smoking is clearly a risk factor for mortality in Bangladesh. All things considered, the smoking–dyspnoea relationship found is internally consistent with what is known about smoking and the diseases and deaths it causes [5, 6].

Study strengths include using the baseline arsenic water concentrations of tube wells before they were capped [37] due to high arsenic levels (to protect the residents from arsenic). Another strength was finding a very strong dose–response relationship between well water arsenic concentrations and the presence of arsenic-associated skin lesions (table 2); a finding previously demonstrated with cumulative and time-weighted well water arsenic exposures [38]. Arsenic skin lesions tend to occur 10–23 yrs after chronic arsenic exposure [39]. This finding further validates that well water arsenic exposure as used in this study was a good measure of long-term arsenic exposure in humans. A further strength was finding 2.4-fold (95% CI 1.52–3.30) greater presence of dyspnoea in individuals with arsenic-associated skin lesions relative to those without skin lesions. This is additional evidence that chronic arsenic exposure is a risk factor for developing dyspnoea. Another main strength is that 86% of study participants used one index well exclusively, making well water arsenic concentrations a good index of

exposure [38]. Other study strengths are a very large sample size, data acquisition by trained physician interviewers, individual measurement of exposure, the presence of a significant correlation between well water arsenic concentration and individual urine arsenic concentration (urinary arsenic at baseline was a measure of internal dose of continuing long-term exposure), which validates that the well water arsenic concentrations are the source of exposure, biological plausibility of both arsenic and smoking as aetiological causes of diseases that may result in dyspnoea, and the finding of a dose–response relationship with both well water arsenic concentrations and urinary arsenic excretion and dyspnoea. In addition, the ability to eliminate smoking from arsenic exposure with an increase in the arsenic–dyspnoea association further strengthens the concept that chronic well water arsenic exposure results in dyspnoea. Furthermore, the ability to find an intuitively logical dose–response relationship with smoking and dyspnoea (table 5) serves as an internal standard validating that this arsenic database was collected correctly for other findings. Finally, despite the inability to exactly quantify individual arsenic exposure, a dose response with two different measures of arsenic exposure and dyspnoea was still present.

A study weakness is that dyspnoea signifies disease but explicit diseases were not determined due to the nature of collecting baseline data for cohort studies. Due to the cross-sectional nature, the temporal sequence of the exposure–outcome relationship could not be determined for either exposure, arsenic or smoking. However, since tube wells were placed in the late 1970s and 1980s and this study collected data 20 yrs later, an argument could be made that arsenic exposure preceded dyspnoea [2]. Finally, since the study is not randomised, it is possible that unknown confounders resulted in the findings.

We conclude that both arsenic and smoking have strong and independent associations with the symptom of chronic dyspnoea in Bangladesh. This is the only study to find a dose–response relationship with both exposures and dyspnoea. The arsenic findings are novel. Only one other study has found a significant association between arsenic water exposure and dyspnoea; a tentative dose–response was suggested but limited by small numbers [3]. The current study, due to larger size, is the first to demonstrate a clear dose–response relationship with arsenic water exposure and dyspnoea. In addition, there was a strong association with arsenic skin lesions and dyspnoea and a dose response with arsenic urinary concentrations and dyspnoea, both never before demonstrated with dyspnoea and both associations further validating the water exposure data. The smoking findings, conversely, are not unexpected; albeit never reported before as a dose response with dyspnoea. This suggests, if exposures are causal, that elimination of both would result in a marked reduction in the diseases that generally result in dyspnoea, usually cardiac and lung [21, 22]. This study adds to the list of arsenic-related diseases being detected in Bangladesh and worldwide [5, 6, 19, 20, 24–31, 39, 40].

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STATEMENT OF INTEREST

None declared.

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