ERJ Express. **Published on November 16, 2011 as doi: 10.1183/09031936.00042611**

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

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ABSTRACT: Bangladesh has high well water arsenic exposure. Chronic arsenic ingestion may result in diseases manifest as dyspnea; albeit information is sparse.

Baseline values were obtained from an arsenic study. Trained physicians ascertained data on dyspnea among 11,746 subjects. Data was 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 dyspnea.

The adjusted odds of having dyspnea was 1.32-fold (95% C.I., 1.15-1.52) greater in those exposed to high arsenic well water concentrations (≥ 50 µg/L) as compared to low arsenic exposed nonsmokers ($p < 0.01$). A significant dose-response relationship was found for arsenic (as-well-as smoking) in relation to dyspnea**.** In nonsmokers, the adjusted odds of having dyspnea 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 ug/L, respectively, compared to the referent arsenic concentration of less than 7 ug/L ($p < 0.01$, Chi square test for trend).

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

KEY WORDS: Arsenicosis, Dyspnea Dose-Response, Environmental Dyspnea

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 U.S. standards for acceptable arsenic content of drinking water is less than 10 µg/L [2]. The Bangladesh standard is less than 50 µg/L and it has been estimated that about 1/100 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 dyspnea has been suggested in cross sectional studies [3,4]. One large study compared arsenic well water at $\geq$ 500 µg/L to those with < 50 µg/L and found an age-adjusted prevalence odds ratios (POR) of 23.2 (95% C.I., 5.8 – 92.8) and 3.7 (1.3 – 10.6) for nonsmoking women and men for presence of dyspnea, respectively [3]. These high POR occurred only in those with arsenic skin lesions [3]. A second study found nonsignificant POR 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 in nonsmoking subgroups, respectively [4]. The arsenic well water concentrations were described as 100 µg/L or more in 90% or more of those with skin lesions [4].

Bangladesh is 8th in the world in total 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, diarrheal disease, TB, and cancers of the trachea, bronchus, and lung), smoking is a risk factor for all but HIV/AIDS and diarrheal diseases [5,6]. Most of these smoking related diseases can also present with dyspnea.

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

completely eliminate arsenic from well water and reduce the Bangladesh arsenic water standard to that of the WHO.

MATERIALS AND METHODS

Data source and approvals

Study subject baseline data was 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 and Institutional Review Boards of Columbia University and University of Chicago.

Subjects and demographics

Baseline data was collected as detailed [7]. In brief, eligibility for HEALS included: being aged 18 years or more, being married (stability of residence), and having resided in Araihazar for 5 years or more.

After obtaining consent, a 45 minute interview collected demographics including age, gender, BMI, educational attainment (0 – 16 years), occupational history, and smoking (past, present, 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 exam included an assessment of arsenic related skin lesions [7].

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

Laboratory analysis

Arsenic well water concentrations were analyzed at the Geochemistry Research Laboratory of Columbia University [9] by graphite furnace atomic absorption (GFAA). The detection limit for GFAA was 5 μg/L. Water samples with concentrations at the detection limit were reanalyzed by inductively coupled plasma-mass spectrometry with a detection limit of 0.1 μg/L [10].

Urinary arsenic concentration (UAs) was measured by GFAA spectrometry [11]. Urinary creatinine was measured by a colourimetric diagnostics kit (Sigma, St. Louis, MO) and the total arsenic in urine in μg/L was divided by the concentration of creatinine in gm/L to obtain an arsenic adjusted concentration in μg/gm creatinine [12].

Statistical Analysis

Pearson Chi-Square test was used to compare categorical data between genders for BMI, smoking, and arsenic concentrations, and for calculating arsenic well water concentrations by 5 groups from high to low with dyspnea as the outcome. Chi-Square test for trend (linear-by-linear association) was used to determine if increasing cigarette consumption or increasing well water or urinary arsenic concentrations result in a significant increase in prevalence of dyspnea. 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 OR for dyspnea. BMI was categorized in three groups (normal or referent BMI, 18.50 – 24.99, low BMI < 18.50, high BMI ≥ 25). Well water arsenic concentration was coded as ≥ 50 µg/L as exposed and < 50 µg/L as referent group in all analysis except for dose-response analyses among the nonsmoker group, in which quintiles of arsenic well water concentration or urinary arsenic excretion were used. Continuous variables included age, educational level, and systolic BP**.** For a sensitivity analysis in nonsmokers, well water arsenic concentrations were also coded as ≥ 25, ≥ 12.5, and ≥ 6.25 ug/L versus other and subsequent adjusted OR for dyspnea obtained. A p value < 0.05 was significant. Biological interaction was evaluated between arsenic (≥ 50 µg/L versus other) and smoking using prevalence of dyspnea by joint status of two exposures [13,14]. Analyses were done with SPSS 18 (SPSS Inc., Chicago, Ill).

RESULTS

Descriptive data, Arsenic skin lesion status and arsenic exposure data.

The overall average population age was 37.1 ± 10.1 years (range: 17-75). For women and men the average ages were 33.6 ± 8.9 (range:18-61) and 41.6 ± 9.9 (range:20-75), respectively ($p < 0.01$).

Baseline distributions for demographic variables for gender, BMI, smoking status and well arsenic (AS) concentration are summarized in table 1. The gender distributions for BMI are significantly different ($p < 0.01$) with more women than men in the normal BMI

category. The gender distributions for smoking status are significantly different ($p < 0.01$) with 62% of men being smoker relative to 3.7% for women.

Table 2A compares quintiles of arsenic well water exposure versus the dichotomous outcome variable, presence or absence of arsenic associated skin lesions. There is a clear dose-response with increasing arsenic well water concentrations and the presence of skin lesions. Table 2B using the presence of arsenic skin lesions as the exposure marker of interest revealed a 2.2-fold greater odds of dyspnea compared to individuals without arsenic related skin lesions after adjustment. This analysis was done in nonsmokers only. Similar results were present when including all subjects, women only, and men only (data not shown).

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

TABLE 1. Distribution of HEALS participants by gender, BMI, smoking status, and baseline well water arsenic concentration in quintiles.

	Total (n = 11,746)	Female (n = 6704)	Male (n = 5042)
BMI*			
< 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
Well As Conc. (ug/L)			
< 7 µg/L	2325 (19.8%)	1318 (19.7%)	1007 (20.0%)
7 to < 39 µg/L	2354 (20.0%)	1350 (20.1%)	1004 (19.9%)
39 to < 91 µg/L	2333 (19.9%)	1347 (20.1%)	986 (19.6%)

91 to < 179 µg/L	2382 (20.3%)	1364 (20.3%)	1018 (20.2%)
≥ 179 µg/L	2352 (20.0%)	1325 (19.7%)	1027 (20.4%)

* the gender distribution of BMI and smoking are significantly different, $p < 0.01$, chi-square

BMI = body mass index, As = arsenic, Conc. = concentration

TABLE 2. Logistic regression model in combined male and female nonsmokers. Table 2A compares quintiles of arsenic well water concentration versus the presence or absence of arsenic skin lesions. Table 2B compares arsenic skin lesions with the primary outcome variable the presence/absence of dyspnea.

Table 2A. Adjusted OR for Skin Lesions in Relation to Well Water Arsenic Exposure

Independent variables	OR	95% C.I. for OR	Significance
Referent (1)	1.00		
As Well Water (2)	1.80	1.02 - 3.16	0.043
As We;; Water (3)	2.79	1.62 – 4.78	< 0.001
As Well Water (4)	3.09	1.82 – 5.23	< 0.001
As Well Water (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
Gender	0.27	0.20 – 0.35	< 0.001
Systolic BP	1.01	0.99 – 1.01	0.167
BMI (1)	1.41	1.07 – 1.87	0.016
BMI (2)	0.66	0.37 – 1.19	0.170

Referent As Well Water concentration was < 7 ug/L with quintiles as noted in table 1.
# $p < 0.01$, chi-square test for trend. The referent for gender was male.

Table 2B. Adjusted OR for Dyspnea in Relation to Arsenical Skin Lesion Presence

Independent variables	OR	95% C.I. for OR	Significance
Referent, no As Skin Lesions	1.00		
As Skin Lesions	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
Gender	1.77	1.32 – 2.36	< 0.001
Systolic BP	1.00	0.99 – 1.01	0.385
BMI (1)	1.19	0.98 – 1.45	0.079
BMI (2)	1.27	0.92 – 1.76	0.148

As = arsenic, BMI = body mass index
Similar results were obtained when women and men were analyzed separately.
The referent for gender was male.

Arsenic as primary exposure variable in the total population

Table 3 is a summary of the adjusted OR for dyspnea 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 dyspnea. Age and education were directly and inversely associated with increased dyspnea, respectively.

An analysis was done eliminating ex-smokers to determine if there was a dose-response relationship between levels of smoking and dyspnea (n = 10,958). The crude OR for both cigarette groups was significant with similar OR for women and men combined before adjustment (Table 4A). No dose-response was seen. However, there was a significant adjusted dose-response for women and men (Table 4B). Separating groups by gender revealed only 15 women who smoked more than 10 cigarettes/day and therefore women could not be analyzed by dose-response. For men, the crude and adjusted OR chi-square test for trend were significant implying a dose-response relationship between cigarette smoking and dyspnea (tables 4A and 4C).

Biologic interaction between arsenic and smoking was not found [13,14]. In particular, on evaluating all subjects, in the low arsenic nonsmoking group (referent) the prevalence of dyspnea was 5.4%. The high arsenic (> 50 µg/L), nonsmoking group had a prevalence of dyspnea of 8.24%. The smoking low arsenic group had a prevalence of dyspnea of 8.73%. Finally the smoking and high arsenic group had a prevalence of dyspnea 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 men only, all women only, men smokers only (excluding ex-smokers), women smokers only (excluding ex-smokers), men ex-smokers (excluding active smokers) and women ex-smokers (excluding active smokers). No interaction was found.

TABLE 3. Logistic regression model with the primary exposure variable arsenic well water exposure; controlling for smokers plus ex-smokers (3A), current smokers (3B), or ex-smokers (3C) with dyspnea presence/absence as the outcome variable of interest.

Table 3A

Independent variables	OR	95% C.I. for OR	Significance
Referent As < 50 µg/L		1.00	
As Well Water	1.32	1.15 – 1.52	< 0.001
Smoker/Ex-smoker	1.44	1.16 – 1.78	0.001
Age	1.03	1.02 – 1.04	< 0.001
Education	0.96	0.92 – 0.98	< 0.001
Gender	1.58	1.28 – 1.95	< 0.001
Systolic BP	1.00	0.99 – 1.00	0.488
BMI (1)		1.16	0.99 – 1.32	0.054
BMI (2)		1.37	1.04 – 1.80	0.026

Table 3B

Independent variables	OR	95% C.I. for OR	Significance
Referent As < 50 µg/L		1.00	
As Well Water	1.33	1.14 – 1.54	< 0.001

Current smokers	1.38	1.09 – 1.75	0.008
Age	1.03	1.02 – 1.04	< 0.001
Education	0.96	0.94 – 0.98	< 0.001
Gender	1.56	1.24 – 1.96	< 0.001
Systolic BP	1.00	0.99 – 1.00	< 0.692
BMI (1)	1.13	0.96 – 1.32	< 0.139
BMI (2)	1.42	1.07 – 1.88	< 0.016

Table 3C

Independent variables	OR	95% C.I. for OR	Significance
Referent As < 50 µg/L	1.00		
As Well Water	1.51	1.27 – 1.79	< 0.001
Ex-smokers	1.64	1.22 – 2.20	< 0.001
Age	1.03	1.02 – 1.04	< 0.001
Education	0.96	0.94 – 0.99	0.002
Gender	1.60	1.24 – 2.05	< 0.001
Systolic BP	1.00	0.99 – 1.01	0.648
BMI (1)	1.24	1.04 – 1.49	0.018
BMI (2)	1.24	0.91 – 1.70	0.174

Table 3A includes the complete data set with smokers and ex-smokers combined versus nonsmokers. Table 3B includes smokers only (ex-smokers were excluded from analysis). Table 3C includes Ex-smokers only (current smokers were excluded from analysis). For all three smoking groups the referent was nonsmokers. Gender referent was male.

TABLE 4. Logistic regression model excluding ex-smokers. Includes all subjects or men only as specified. Evaluation of smoking dose-response versus dyspnea, crude and adjusted OR.

Table 4A - Crude OR for Dyspnea in Relation to Smoking Dose-Response

Independent variables	OR	95% C.I. for OR	Significance
Women and Men			
Nonsmokers	1.00		
≤ 10 cig/day	1.29	1.08 – 1.55	0.005
> 10 cig/day	1.27	1.03 – 1.56	0.026
Men only			
Nonsmokers	1.00		
≤ 10 cig/day	1.75	1.29 – 2.38	< 0.001
> 10 cig/day*	1.85	1.34 – 2.54	< 0.001

Table 4B - Adjusted OR for Women and Men

Independent variables	OR	95% C.I. for OR	Significance
Women and Men			
Nonsmokers	1.00		
≤ 10 cig/day	1.37	1.07 – 1.76	0.013
> 10 cig/day*	1.40	1.04 – 1.87	0.027
Age	1.03	1.02 – 1.04	< 0.001
Education	0.96	0.94 – 0.98	< 0.001
Gender	1.56	1.24 – 1.97	< 0.001

As Well Water	1.33	1.14 – 1.54	< 0.001
Systolic BP	1.00	0.99 – 1.00	0.696
BMI (1)		1.13	0.96 – 1.32	0.138
BMI (2)		1.42	1.07 – 1.88	0.016

Table 4C - Adjusted OR for Men

Independent variables	OR	95% C.I. for OR	Significance
Men only			
Nonsmokers	1.00		
≤ 10 cig/day	1.46	1.05 – 2.03	0.021
> 10 cig/day*	1.48	1.06 – 2.08	0.022
Age	1.03	1.02 – 1.04	< 0.001
Education	0.96	0.93 – 0.99	0.014
As Well Water	1.22	0.97 – 1.55	0.091
Systolic BP	1.00	0.99 – 1.00	0.309
BMI (1)		1.22	0.95 – 1.57	0.116
BMI (2)		2.10	1.30 – 3.39	0.002

* $p < 0.01$ chi-square test for trend. Women not analyzed separately since there were only 15 women who smoked more than 10 cigarettes/day.

Arsenic as primary exposure variable, excluding smokers

Table 5 was created eliminating smokers. The primary exposure variable is elevated arsenic well water concentration (≥ 50 µg/L) versus referent (< 50 µg/L). Compared to the crude OR, Tables 5A, 5B, and 5C reveal similar elevated adjusted OR for all subjects, women, and men among never smokers, respectively. After exclusion of smokers the association between arsenic and dyspnea increased as seen by increased OR. The OR for dyspnea was greater for men than women. The sensitivity analysis using arsenic well water cut-off values of ≥ 25, ≥ 12.5, and ≥ 6.25 ug/L versus other revealed adjusted ORs of 1.62 (1.31-2.01), 1.81 (1.42-2.31), and 1.80 (1.37-2.37), respectively. These results were robust and even higher than the reported OR of 1.56 (1.29-1.88) seen in table 5 using the arsenic well water cut-off of ≥ 50 ug/L.

Table 6A divided arsenic categories into quintiles. The referent or lowest quintile was an arsenic well water concentration less than 7 µg/L. The other quintiles were 7 to < 39

μg/L, ≥ 39 to < 91 μg/L, 91 to < 179 μg/L, and 179 to 864 μg/L . A dose-response was seen going from quintiles 1 through 4 with OR increasing from 1.00 up to 2.17. The fifth quintile had an OR of 1.84, still significant but smaller than quintiles 3 and 4. The adjusted ORs were no different than the crude values as can be seen from Table 6. Pearson Chi-Square test for arsenic well water concentrations in five groups in relation to the dichotomous outcome variable dyspnea was significant at $p < 0.01$ ($df = 4$, $\chi^2 = 31.4$). Chi-square test for trend for increasing OR as arsenic well water concentration increased was significant at $p < 0.01$ ($df = 1$. $\chi^2 = 21.4$).

Table 6B looked at quintiles of urinary arsenic excretion per gm of creatinine in relation to dyspnea. Both the crude (not shown) and adjusted values resulted in a significant dose-response of increasing urinary arsenic excretion in relation to dyspnea 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-square test for trend dose-response ($p < 0.01$).

Table 5. Logistic regression model in nonsmokers with the primary exposure arsenic and dyspnea as the outcome of interest. First section is crude OR in all subjects combined, women only, and men only. Sections 5A, 5B, and 5C are adjusted OR for all subjects, females only and males, respectively.

Crude OR for Dyspnea in Relation to Well Water Arsenic Concentration

Independent variables	OR	95% C.I. for OR	Significance
Referent As < 50 µg/L		1.00	
Women and Men	1.56	1.30 – 1.88	< 0.001
Women	1.51	1.24 – 1.85	< 0.001
Men	2.01	1.15 – 3.52	0.015

Table 5A - Adjusted OR-Women & Men

Independent variables	OR	95% C.I. for OR	Significance
Referent As < 50 µg/L		1.00	
As Well Water	1.56	1.29 – 1.88	< 0.001
Age	1.03	1.02 – 1.04	< 0.001
Education	0.96	0.93 – 0.99	0.003
Gender	1.65	1.24 – 2.20	0.001
Systolic BP	1.00	0.99 – 1.01	0.300
BMI (1)	1.20	0.98 – 1.46	0.071

BMI (2)	1.28	0.92 – 1.77	0.139

Table 5B - Adjusted OR-Women Only

Independent variables	OR	95% C.I. for OR	Significance
Referent As < 50 µg/L	1.00		
As Well Water	1.51	1.23 – 1.84	< 0.001
Age	1.03	1.02 – 1.05	< 0.001
Education	0.96	0.93 – 0.99	0.004
Systolic BP	1.00	0.99 – 1.01	0.293
BMI (1)	1.15	0.93 – 1.42	0.197
BMI (2)	1.19	0.83 – 1.70	0.350

Table 5C - Adjusted OR-Men Only

Independent variables	OR	95% C.I. for OR	Significance
Referent As < 50 µg/L	1.00		
As Well Water	2.00	1.14 – 3.52	0.016
Age	1.03	1.00 – 1.05	0.050
Education	0.98	0.92 – 1.04	0.545
Systolic BP	1.00	0.99 – 1.02	0.870
BMI (1)	1.67	0.94 – 3.00	0.083
BMI (2)	1.96	0.88 – 4.36	0.099

TABLE 6. Logistic regression dose response model in nonsmokers with the primary exposure variable well water arsenic in Table 6A and urinary arsenic excretion in Table 6B. Dyspnea is the outcome of interest. All subjects subdivided into equal quintiles above referent.

Table 6A. Crude OR for Dyspnea in Relation to Well Water Arsenic Concentration

Independent variables	OR	95% C.I. for OR	Significance
Referent (1)	1.00		
As Well Water (2)	1.39	0.99 – 1.93	0.052
As Well Water (3)	1.97	1.44 – 2.70	< 0.001
As Well Water (4)	2.17	1.59 – 2.95	< 0.001
As Well Water (5)#	1.84	1.34 – 2.53	< 0.001

Table 6A. Adjusted OR for Dyspnea in Relation to Well Water Arsenic Concentration

Independent variables	OR	95% C.I. for OR	Significance
Referent (1)	1.00		
As Well Water (2)	1.36	0.97 – 1.90	0.074
As Well Water (3)	1.96	1.43 – 2.70	< 0.001
As Well Water (4)	2.14	1.56 – 2.92	< 0.001
As Well Water (5)#	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
BMI (1)	1.21	0.99 – 1.47	0.064
BMI (2)	1.29	0.93 – 1.79	0.122
Systolic BP	1.00	0.99 – 1.01	0.323
Gender	1.65	1.24 – 2.19	0.001

Referent As Well Water concentration was < 7 µg/L. As Well Water (2), (3), (4), and (5) were equal quintiles above referent as delimited in results. Individual quintile concentrations for arsenic can be obtained from table 1. As = arsenic. # p < 0.01, chi-square test for trend

Table 6B. Adjusted OR for Dyspnea in Relation to Urinary Arsenic Concentration

Independent variables	OR	95% C.I. for OR		Significance
Referent (1)	1.00			
Urin As (µg/gm Cr) (2)		1.37	0.97 – 1.92	0.073
Urin As (µg/gm Cr) (3)		1.92	1.38 – 2.65	< 0.001
Urin As (µg/gm Cr) (4)		1.94	1.41 – 2.68	< 0.001
Urin As (µg/gm Cr) (5)#		1.87	1.36 – 2.58	< 0.001

All adjusted for age, education, BMI, systolic BP, and gender. These were equal quintiles of urinary arsenic excretion in µg/L divided by urinary creatinine in gm/liter resulting in µg urinary As/gm creatinine. Urin = urinary. As = arsenic. # p < 0.01, chi-square test for trend

DISCUSSION

High baseline arsenic well water exposure was a significant risk factor for dyspnea, adjusted for smoking (table 3). This arsenic-dyspnea association was strong for all three smoking subgroups (Table 3). In order to eliminate smoking effects, a separate analysis using only nonsmokers was done (tables 5 and 6). An arsenic dose-response curve revealed an increased prevalence of dyspnea with increasing arsenic well water concentrations using less than 7 µg/L as referent (table 6). The OR for the presence of dyspnea increased from the referent to the second quintile. This result could argue for reducing the current Bangladesh arsenic water standard to at least the world standard of less than 10 µg/L or lower ie to levels less than 7 µg/L.

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 referent well water arsenic concentration was < 50 µg/L. The highest POR was 2.7 (0.3 – 16.9) [15]. A second study compared the age adjusted POR for those exposed to a referent arsenic concentration of < 50 µg/L versus those exposed to levels ≥ 500 µg/L [3]. For women, the POR for cough and dyspnea were 7.8 (3.1 – 19.5) and 23.2 (5.8 – 92.8), respectively. For men, the same POR values were 5.0 (2.6 – 9.9) and 3.7 (1.3 – 10.6), respectively. These high POR were only present in those with skin lesions and were reduced but suggestive in all women and men [3]. A third study, using referent arsenic well water concentrations of < 50 µg/L, found that 63% of individuals exposed to high arsenic well water concentrations (67 – 875 µg/L) had pulmonary effects including cough, bronchitis, and dyspnea [16]. The comparison had only 7% of these effects [16]. A fourth small study of smokers and nonsmokers with arsenic well water concentrations less than 500 µg/L compared subjects with arsenic skin lesions (high exposure) versus those without arsenic skin lesions (lower exposure). The nonsmoking group revealed increased POR for dyspnea, 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 ug/L [19,20]. The adjusted OR or standardized rates ranged from 10 to 46 [19,20]. Both studies suggest that arsenic, which is ingested orally, causes bronchiectasis.

Dyspnea 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]. Dyspnea tends to occur with COPD when the FEV_1 is reduced to 50% of normal [23]. Therefore, one of the mechanisms of dyspnea with arsenic exposure might be the development of COPD secondary to arsenic. In addition, lung cancer secondary to arsenic would undoubtedly present with dyspnea [24,25,26]. Also, arsenic is associated with bronchiectasis [19,20], a cause of dyspnea.

Dyspnea 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 (1.37-1.59) and 1.26 (1.14-1.40) for men and women, respectively, during a period of excessive arsenic exposure [29]. In Wisconsin, using arsenic well water concentration of < 2 versus > 10 μg/L, an increase in heart attacks and coronary bypass surgery were found with OR of 2.08 (1.10-4.31) and 2.34 (1.12-4.90), respectively [30]. Finally, using an arsenic well water concentration less than 1 versus > 10 μg/L found mortality rates of 1.10 (1.08-1.12) and 1.18 (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 dyspnea. Thus, our finding of a dose-response relationship between arsenic exposure and dyspnea is biologically plausible.

It should be noted that the highest well water concentration of arsenic partially reverses the dose-response trend seen (Table 6A). The trend still maintained statistical significant probably related to a still very high OR relative and close to the previous OR. 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 biologic point of view since arsenic is a very toxic metal in humans. A third possibility is the sickest subjects at baseline (many of whom may have had dyspnea) 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 dyspnea (table 3) with an adjusted dose-response relationship between cigarettes smoked and dyspnea in men (table 4C). Since dyspnea 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-dyspnea

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 arsenic well water concentrations and the presence of arsenic associated skin lesions (Table 2A); a finding previously demonstrated with cumulative and time-weighted arsenic well water exposures [38]. Arsenic skin lesions tend to occur 10 to 23 years after chronic arsenic exposure [39]. This finding further validates that arsenic well water 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% C.I., 1.52 – 3.30) greater presence of dyspnea 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 dyspnea. Another main strength is that 86% of study participants used one index well exclusively, making arsenic well water 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 arsenic well water 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 arsenic well water concentrations are the source of exposure, biological plausibility of both arsenic and smoking as etiologic causes of diseases that may result in dyspnea, and the finding

of a dose-response relationship with both arsenic well water concentrations and urinary arsenic excretion and dyspnea. In addition, the ability to eliminate smoking from arsenic exposure with an increase in the arsenic-dyspnea association further strengthens the concept that chronic arsenic well water exposure results in dyspnea. Furthermore, the ability to find an intuitively logical dose-response relationship with smoking and dyspnea (table 4) serves as an internal standard validating that this arsenic data base 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 dyspnea was still present.

A study weakness is that dyspnea 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 years later, an argument could be made that arsenic exposure preceded dyspnea [2]. Finally, since the study is not randomized, 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 dyspnea in Bangladesh. This is the only study to find a dose-response relationship with both exposures and dyspnea. The arsenic findings are novel. Only one other study has found a significant association between arsenic water

exposure and dyspnea with a tentative dose-response 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 dyspnea. In addition, there was a strong association with arsenic skin lesions and dyspnea and a dose-response with arsenic urinary concentrations and dyspnea, both never before demonstrated with dyspnea and both associations further validating the water exposure data. The smoking findings, on the other hand, are not unexpected; albeit never reported before as a dose-response with dyspnea. This suggests, if exposures are causal, that elimination of both would result in a marked reduction in the diseases that generally result in dyspnea, usually cardiac and lung [21, 22]. This study adds to the list of arsenic related diseases being detected in Bangladesh and world-wide [5,6,19,20,24-31,39,40].

SUPPORT STATEMENT
This work was supported by NIH grants P42ES10349, R01CA107431, and R01CA102484.

ACKNOWLEDGEMENTS
Presented in part in abstract form at the 2011 American Thoracic Society meeting. (Denver, CO, USA). We dedicate this manuscript to the memory of Alvin S. Teirstein, M.D., previous section chief of Pulmonary Disease, Mt. Sinai Hospital, New York.

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