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ORIGINAL PAPER

Lung function decrement with arsenic exposure to drinking groundwater along River Indus: a comparative cross-sectional study

Asaad Ahmed Nafees · Ambreen Kazi · Zafar Fatmi · Muhammad Irfan · Arif Ali · Fujio Kayama

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Abstract This study was designed to determine the association between chronic arsenic exposure through drinking groundwater and decrement in lung function, particularly among individuals who do not have signs of arsenic lesions, among an adult population. This was a comparative cross-sectional study conducted during the months of January to March 2009. One hundred participants ≥15 years of age in each group, i.e. exposed (≥100 μg/l) and unexposed (≤10 μg/l) to arsenic, determined by testing drinking water samples (using portable kits), were compared for effects on lung function using spirometry. A structured and validated questionnaire was administered. Examination for arsenic skin lesions was also done. There was a decline in the mean adjusted FEV1 of 154.3 ml (95% CI: −324.7, 16.0; $p = 0.076$), in mean adjusted FVC of 221.9 ml (95% CI: −419.5, −24.3; $p = 0.028$), and in FEV1/FVC ratio of 2.0 (95% CI: 25.3, 29.4; $p = 0.884$) among participants who were exposed to arsenic compared to those unexposed. A separate model comprising a total of 160 participants, 60 exposed to arsenic concentrations ≥250 μg/l and 100 unexposed at arsenic concentrations of ≤10 μg/l, showed a decrement in mean adjusted FEV1 of 226.4 ml (95% CI: −430.4, −22.4; $p = 0.030$), in mean adjusted FVC of 354.8 ml (95% CI: −583.6, −126.0; $p = 0.003$), and in FEV1/FVC ratio of 9.9 (95% CI: −21.8, 41.6; $p = 0.539$) among participants who were exposed to arsenic in drinking groundwater. This study demonstrated that decrement in lung function is associated with chronic exposure to arsenic in drinking groundwater, occurring independently, and even before any manifestation, of arsenic skin lesions or respiratory symptoms. The study also demonstrated a dose-response effect of arsenic exposure and lung function decrement.

Keywords Arsenic · Groundwater · Lung function decrement · Respiratory symptoms · Pakistan

A. A. Nafees · A. Kazi · Z. Fatmi (✉) · A. Ali
Division of Environmental Health Sciences, Department of Community Health Sciences, Aga Khan University, Stadium Road, P. O. Box-3500, Karachi 74800, Pakistan
e-mail: zafar.fatmi@aku.edu

A. A. Nafees
e-mail: asaad.nafees@aku.edu

A. Kazi
e-mail: ambreen.kazi@aku.edu

M. Irfan
Section of Pulmonology, Department of Medicine, Aga Khan University, Karachi, Pakistan

F. Kayama
Division of Environmental Medicine, Center for Community Medicine, Jichi Medical School, Shimotsuke-shi, Tochigi-ken, Japan

Introduction

Arsenic contamination in groundwater is a worldwide phenomenon, occurring particularly along the delta and banks of large rivers including the Ganges in India and Bangladesh, the Mekong in Vietnam and Cambodia and the Indus in Pakistan (Chakraborti et al. 2003; Fatmi et al. 2009; Buschmann et al. 2008). Globally, the countries with documented evidence of adverse health effects include Bangladesh, China, India (West Bengal), Chile, the United States of America and Pakistan (Fatmi et al. 2009; World Health Organization 2009; Marshall et al. 2007).

The region of South Asia bears the major brunt of health effects of arsenic exposure through groundwater (Fewtrell et al. 2005). In West Bengal, India, seven of the 16 districts have been reported to have mean arsenic concentrations of groundwater above 50 μg/l (World Health Organization 2001). In Bangladesh alone, 35–57 million people are estimated to be exposed to arsenic through drinking water (Kinniburgh and Smedley 2001). An estimated 13 million of the population of the United States, mostly in the western states, were exposed to arsenic in drinking water at or above 10 μg/l (World Health Organization 2001). Population in the cities of the region II, northern Chile have been exposed to high levels of arsenic, near 1,000 μg/l for over a decade, resulting in large increase in total population cancer mortality rates and other health effects (Marshall et al. 2007; Liaw et al. 2008). In China, eight provinces and 37 counties have been identified as epidemic areas of arsenicosis where more than three million people are estimated to be exposed to high levels of arsenic (Sun 2004).

Recent evidence suggests that arsenic affects almost every organ system of the body (World Health Organization 2001). The evidence for burden of disease of arsenic due to drinking groundwater is still very sparse and accumulating (Rahman et al. 2009). Arsenic leads to non-cancerous (non-malignant) and cancerous (malignant) health effects including cardiovascular disease (National Research Council 2001; Lee et al. 2005; Chen et al. 2009; Rahman et al. 2009), peripheral neuropathy (Mukherjee et al. 2003), decreased intellectual function (von Ehrenstein et al. 2007), skin lesions (Haque et al. 2003; McDonald et al. 2007; Kadono et al. 2002), skin cancers (Karagas et al. 2001; Chen and Ahsan 2004), bladder cancer (Bates et al. 2004) and lung cancer (Ferreccio et al. 1998). Non-cancerous health effects of arsenic are commoner than cancerous health effects and lead to high burden of disease (Rahman et al. 2009). It is estimated that arsenic skin lesions result in 143 disability adjusted life years (DALYs) per 1,000 population in Bangladesh (Fewtrell et al. 2005).

Non-malignant respiratory effects have been shown to be one of the important manifestations of prolonged exposure to arsenic in drinking groundwater (Mazumder et al. 2000; Parvez et al. 2008). Previous studies which reported respiratory effects due to arsenic exposure through groundwater were mostly conducted on individuals with arsenic skin lesions (Mazumder et al. 2000; Milton and Rahman 2002; Mazumder et al. 2005; Milton et al. 2003; von Ehrenstein et al. 2005). Therefore, respiratory effects due to arsenic exposure in individuals who do not have any manifestation of arsenic skin lesions have not been previously explored (Parvez et al. 2008). Furthermore, most of these studies were questionnaire based and relied on symptoms as reported by study participants thus prone to reporting bias (Mazumder et al. 2000, 2005; Milton and Rahman 2002; Milton et al. 2003). Although few studies have attempted to objectively assess the effect of chronic arsenic exposure on lung function using spirometry. They are limited in scope either because they lack a comparison group (von Ehrenstein et al. 2005) or they are not population based (De et al. 2004). Therefore there is a scarcity of well-conducted population-based epidemiological studies with predefined comparison groups to determine the affects of arsenic in drinking water on lung function.

Approximately 55% of the population in Pakistan use groundwater for drinking purposes, and this proportion is even higher in rural areas, i.e. 67% (Federal Bureau of Statistics, Statistics Division, Government of Pakistan 2007). A national survey of arsenic affected drinking groundwater sources was carried out in 35 out of 104 districts in Pakistan (Ahmad et al. 2004). Out of 8,712 samples, 9% had arsenic concentrations above 10 μg/l, the guideline value set by the World Health Organization (World Health Organization 2008) and 0.70% were above 50 μg/l, which is the national recommended value for Pakistan (Government of Pakistan, Pakistan Environmental Protection Agency, Ministry of

Environment 2008). Most of the affected drinking water sources were along the banks of the rivers in the thickly populated provinces of Punjab and Sindh (Ahmad et al. 2004). In Sindh province the districts of Dadu and Khairpur, due to proximity to the River Indus, were heavily affected with arsenic where 18 and 21% of the drinking water sources, respectively, were above 10 μg/l (Ahmad et al. 2004). The only study conducted on health effects of arsenic in Pakistan in the district Khairpur determined that the prevalence of definitive cases of arsenicosis, i.e. characteristic skin lesions of arsenic, were 3.4 per 1,000, and suspected cases, i.e. any sign of arsenic skin lesions, were 13.0 per 1,000 among people ≥15 years of age. The study also reported that the proportion of affected wells and concentration of arsenic is lower in Pakistan compared to China, Bangladesh and West Bengal, India (Fatmi et al. 2009).

Our study was designed to determine the association between chronic arsenic exposure through drinking groundwater and decrement in lung function, particularly among individuals who do not have signs of arsenic lesions, among an adult population.

Materials and methods

Study design and population

This is a comparative cross-sectional study conducted during the months of January to March 2009. Populations exposed and unexposed to arsenic, determined by testing drinking water samples, were compared for affects on lung function using spirometry.

The study was conducted in two villages: Mehtani and Mian Jan Muhammad Abbassi of Union Council Agra, of *taluka* (sub-district) Gambat, district Khairpur, Sindh province in Pakistan. These villages were selected due to their proximity to the banks of the River Indus and had high proportion of drinking water sources contaminated with arsenic (Fatmi et al. 2009). According to the last census the population of Union Council Agra was 21,749 (Government of Sindh 2000). Most rely on agriculture and speak the Sindhi language.

Selection of study participants

The exposed group were participants ≥15 years of age whose primary drinking water source had an arsenic concentration ≥100 μg/l, and the unexposed (control) group were those whose primary drinking water source had an arsenic concentration ≤10 μg/l. Both groups were using the same source of drinking water for at least 1 year and gave consent to voluntarily participate in the survey. Once the water source had been tested and the households could be selected as either the exposed or unexposed group, all adult members present at that time was invited to participate. Sampling continued from house to house till we achieved our target of 100 participants in each group (total sample size of 200). Two trained data collectors conducted the interviews and examined the patients in supervision of a physician.

Interviews

A modified version of the validated (Brodkin et al. 1993) American Thoracic Society Division of Lung Disease questionnaire (ATS-DLD-78A; Ferris 1978) was used. The questionnaire was translated into Sindhi and back translated into English; it was then pretested in another Sindhi speaking community before use in this study. It includes questions regarding cough, phlegm, wheezing, shortness of breath, other chest and past illnesses and family history. Questions pertaining to economic status (monthly household income), education, occupation, type of house (thatched/mud, concrete/brick or a mix of the two, as proxy for socio economic status), duration of living in the house and land ownership. In addition, active and passive smoking of cigarettes and *beerie* (small locally made cigarette without filter commonly smoked in South Asia) or *huqqa* (local name for water-pipe), indoor air pollution (using biomass for cooking), use of traditional medicine (assumed to contain arsenic) and number of years of current water source usage were added to the questionnaire as confounders.

Lung function measurements

Lung function measurements were performed with a portable spirometer (Vitalograph New Alpha 6000;

Vitalograph Ltd., Buckingham, England) according to the American Thoracic Society guidelines (Standardization of Spirometry 1995). The absolute values of forced vital capacity (FVC), forced expiratory volume in the first second (FEV1) and their ratio (FEV1/FVC) were recorded in milliliters (ml). Participants were asked to refrain from smoking for at least 1 h before the test. All tests were done in the standing position without the nose clips. The procedure was explained to the participants and they were asked to practice until they felt comfortable. Results of three acceptable readings were recorded and the best of the three readings was used for further analysis. The tests were conducted by a trained technician who was well versed with the local language.

Anthropometric measurements

Standing height (in cm) was measured for all participants along the wall using a measuring tape without shoes, and weight (in kg) was measured using a bathroom scale in light clothing and without shoes.

Physical examination of skin

Physical examination of skin was conducted on all subjects. Any arsenic skin manifestation, i.e. hypo and/ or hyperpigmentation of skin unexposed to sunlight, or symmetrical bilateral hyperkeratosis of palms and/or soles was defined as a suspected case. Hyperkeratosis on both palms and soles with or without hypo and/or hyperpigmentation on skin unexposed to sunlight was defined as a definitive case.

Arsenic exposure assessment

Water samples were tested at the field site using portable kits (Arsenic Quick Kit, Industrial Test Systems, Inc., Rock Hill, USA). In cases where more than one water source was used for drinking purposes, the source which was most frequently being used for drinking water was then tested for arsenic contamination and analysis. On the basis of arsenic concentration, participants were categorized either as exposed or unexposed.

Ethical approval

The study was approved by Ethics Review Committee of Aga Khan University. Written informed consent was taken from all participants.

Statistical methods

The data was entered on EpiData 3.1, while analysis was done using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Frequency distributions were calculated for age, sex, socio-economic, life style and anthropometric factors among arsenic exposed and unexposed groups. Separate analyses were done to determine association between the three lung function indices, i.e. FVC, FEV1 and FEV1/FVC ratio, and the exposure status including confounding variables through univariate linear regression analysis. Two populations were used for analysis based on exposure levels of arsenic in drinking water, populations with exposure i.e. $\geq$100 and $\geq$250 μg/l, and exposure of $\leq$10 μg/l, were considered as control group.

Linearity of all continuous variables was assessed by doing quartile analysis. Multi-colinearity was assessed between all independent variables. Biologically plausible interactions were checked and, where significant, interaction terms were included in the final model. Variables which were significant at $p \leq 0.25$ or which had a biologically plausible association with the outcome (such as active or passive smoking and indoor air pollution) were assessed further in the multivariate linear regression analysis.

Multivariate logistic regression analysis was also done to determine association between exposure (at two levels $\geq$100 and $\geq$250 μg/l) to arsenic in groundwater and respiratory symptoms (cough, phlegm, wheezing and breathlessness) after controlling for confounders.

Results

Frequency distributions for age, sex, socio-economic, life style and anthropometric factors according to the exposure status are presented in Table 1. Overall, 200 participants were enrolled in the study, 100 each in the exposed and the unexposed groups. Distribution

Table 1 Frequency distribution of age, sex, socio-economic, life style and anthropometric factors of adults, ≥15 years of age exposed (≥100 μg/l) and unexposed (≤10 μg/l) to arsenic through underground drinking water, Taluka Gambat, District Khairpur, Sindh, Pakistan, 2009

Variable	Unexposed ($N = 100$)	Exposed ($N = 100$)	p-value
Age (years)			
15–24	18 (18.0)	26 (26.0)	0.335
25–34	38 (38.0)	25 (25.0)	
35–44	21 (21.0)	25 (25.0)	
45–54	17 (17.0)	17(17.0)	
≥55	6 (6.0)	7 (7.0)	
Sex			
Male	47 (47.0)	44 (44.0)	0.670
Female	53 (53.0)	56 (56.0)	
Education[a]			
No formal education	63 (63.6)	56 (56.0)	0.473
Primary	21 (21.2)	23 (23.0)	
Secondary and above	15 (15.2)	21 (21.0)	
Occupation[a]			
Unemployed	5 (5.0)	8 (8.1)	0.006
Housewife	53 (53.0)	55 (55.6)	
Farmer	34 (34.0)	16 (16.2)	
Service (private & government)	8 (8.0)	20 (20.2)	
Type of house[b]			
Pucca	22 (22.0)	24 (24.0)	0.945
Kutcha-pucca	43 (43.0)	42 (42.0)	
Kutcha	35 (35.0)	34 (34.0)	
Economic status[c]			
High	27 (27.8)	40 (43.0)	0.006
Middle	56 (57.7)	32 (34.4)	
Low	14 (14.4)	21 (22.6)	
Land ownership[d]			
None	29 (29.0)	46 (46.0)	0.002
1–9	47 (47.0)	23 (23.0)	
≥10	24 (24.0)	31 (31.0)	
Smoking status[e]			
Ever smoker	22 (22.0)	21 (21.0)	0.863
Never smoker	78 (78.0)	79 (79.0)	
Exposure to passive smoking[f]			
Exposed	68 (68.0)	59 (59.0)	0.186
Not exposed	32 (32.0)	41 (41.0)	
Exposure to indoor air pollution using biomass for cooking[g]			
Does not cook meals	46 (46.9)	45 (46.4)	0.939
Cooks meals	52 (53.1)	52 (53.6)	
Duration of living in house (years)			
1–29	45 (45.0)	54 (54.0)	0.203
≥30	55 (55.0)	46 (46.0)	
Height (cm), mean (SE)	161.2 (0.89)	159.8 (0.84)	0.243
Weight (kg), mean (SE)	58.4 (1.24)	60.2 (1.34)	0.332
Current water source usage (years), mean (SE)	18.85 (1.23)	12.25 (0.58)	<0.001

Values presented as n (%) unless otherwise noted

[a] Decrease in frequency is due to missing information

[b] Kutcha stands for thatched/mud dwelling, pucca for concrete/brick dwelling, kutcha-pucca implies a mix of the two (proxy for socio-economic status)

[c] Based on tertiles of the monthly household income of participants (high = Rs 10,000–50,000; middle = Rs 5,000–9,999; low = Rs 1,000–4,999)

[d] Unit of land is *Jaraib*, where 1 acre = 2 *jaraib*

[e] Smoking status defined as ever or never smoker

[f] Question asked: does anyone smoke anywhere inside this house?

[g] Question asked: how many meals do you usually cook per day?

of most of the characteristics including age, sex, type of house, smoking status, exposure to passive smoking and exposure to indoor air pollution was similar among participants exposed and unexposed to arsenic. However, few parameters had some differences in two groups, such as the educational status, where participants who were unexposed to arsenic were more likely to be uneducated (63.6%) as compared to participants who were exposed (56.0%). Unexposed were more likely to work as farmers (34.0%) as compared to exposed (16.2%). According to economic status based on monthly income most of the unexposed were distributed in the middle class (57.7%) whereas fewer were distributed in this class among the exposed (34.4%). A greater proportion of the exposed participants (46.0%) did not own any land as compared to the unexposed (29.0%). Majority of the participants in the unexposed group had been living in the same house for 30 years or more (55.0%), which was less in the exposed group (46.0%). Mean height among the unexposed was 161.2 cm; it was 159.8 cm among the exposed ($p = 0.243$). Mean weight was 58.4 kg among the

unexposed while it was 60.2 kg among the exposed ($p = 0.332$). Mean duration of current water source usage among the unexposed was 18.9 years; it was 12.3 years among the exposed ($p < 0.001$). Among the exposed group two suspected and one confirmed case of arsenicosis were identified.

On univariate analysis age, sex, primary and no formal education, occupation, type of house, low economic status, land ownership, smoking status, exposure to indoor air pollution through cooking, duration of living in the house, height and weight were found to be significantly associated with decrements in any one or all of the lung function indices, i.e. FEV1, FVC and FEV1/FVC ratio (Table 2).

Multivariate linear regression analysis adjusted for age, sex, height and smoking status shows that there was a decline in mean FEV1 of 154.3 ml (95% CI: −324.7, 16.0; $p = 0.076$), in mean FVC of 221.9 ml (95% CI: −419.5, −24.3; $p = 0.028$), and in FEV1/FVC ratio of 2.0 ml (95% CI: −25.3, 29.4; $p = 0.884$), among participants who were exposed to arsenic (≥100 μg/l) compared to those unexposed (≤10 μg/l; Table 3). A separate analysis was done to investigate the effects on lung function at higher concentrations of arsenic in groundwater. This model consists of a total of 160 participants, 60 exposed at arsenic concentrations ≥250 μg/l and 100 unexposed at arsenic concentrations of ≤10 μg/l. The adjusted lung function indices showed a declining trend with increasing dose of arsenic with decrement in mean FEV1 of 226.4 ml (95% CI: −430.4, −22.4; $p = 0.030$), in mean FVC of 354.8 ml (95% CI: −583.6, −126.0; $p = 0.003$), and in FEV1/FVC ratio of 9.9 ml (95% CI: −21.8, 41.6; $p = 0.539$), among participants who were exposed to arsenic in drinking groundwater (Table 4).

No significant association was found between exposure to arsenic in groundwater and respiratory symptoms (cough, phlegm, wheezing and breathlessness) assessed through multivariate logistic regression.

Discussion

Results of this study showed that there was a significant reduction in lung function indices—FEV1 and FVC—of participants who were chronically exposed to arsenic of ≥250 μg/l through underground drinking water. There was a decline of 226 ml in the mean adjusted FEV1 and 354 ml in the mean adjusted FVC in participants exposed to arsenic as compared to those who were not exposed. This association was not significant with FEV1/FVC ratio. The findings were less pronounced at lower levels of arsenic exposure, i.e. ≥100 μg/l, where a significant decline (∼221 ml) was found only in FVC while no significant reduction was found in FEV1 or FEV1/FVC ratio. This study demonstrated a dose–response relationship of increasing arsenic exposure and decrement in lung function. There are no universally-defined normal cut-off values for the lung function indices as they vary according to multiple biological parameters—(height, weight, age, sex and ethnicity) and other socioeconomic, environmental and chrono-biological factors (Crapo 2004). However, declining lung function over a period of time is associated with a wide range of respiratory symptoms and illnesses (Sears 2007; Chien et al. 2007; Donaldson et al. 2002). Studies have shown that lung function changes may be present well before the occurrence of well defined signs and symptoms of respiratory diseases (Ichinose et al. 1993). Therefore, spirometry has been suggested to be used as a predictor for disease occurrence in future (Albers et al. 2008; Dezateux et al. 2001; Tager et al. 1993; Taussig et al. 2003; Turner et al. 2004). The development of frank signs and symptoms of respiratory diseases due to continued exposure of arsenic is inevitable and is a predictor of future burden of respiratory diseases among the population.

The relationship between arsenic exposure and respiratory symptoms has already been determined in a previous study (Milton and Rahman 2002). However, in the current study exposure status was not based on the presence or absence of arsenic skin lesions as was done in previous studies; therefore, results from this study provide additional information that effects of chronic arsenic exposure on lung function appear well before the development of any signs of skin lesion. In addition, the finding of no significant difference in standard respiratory symptoms among the exposed and unexposed groups further strengthens the hypothesis that arsenic affects the lung function well in advance of any symptomatic disease appearance. These findings are corroborated by a recent study on arsenic exposed population in Bangladesh which found no association of respiratory symptoms with arsenic skin lesions after controlling for confounders (Parvez et al. 2010). Therefore, it is

Table 2 Univariate linear regression analysis of lung function in ml and exposure status, age, sex, socio-economic, life style and anthropometric factors, Taluka Gambat, District Khairpur, Sindh, Pakistan, 2009

Variable	FEV1					FVC					FEV1/FVC				
	Value (ml)	SE	95% CI		*p*-value	Value (ml)	SE	95% CI		*p*-value	Ratio	SE	95% CI		*p*-value
Exposure status[a]	−164.5	117.1	−395.5	66.5	0.162	−255.9	141.3	−534.7	22.8	0.072	6.9	15.5	−23.6	37.5	0.655
Age (years)	−25.7	4.7	−34.9	−16.4	<0.001	−19.8	5.9	−31.5	−8.1	0.001	−3.9	0.6	−5.1	−2.8	<0.001
Sex[b]	−798.3	102.6	−1,000.7	−595.9	<0.001	−1,120.1	117.1	−1,351.1	−889.0	<0.001	8.3	15.5	−22.3	38.9	0.592
Education															
Secondary and above	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Primary	−340.4	166.5	−668.9	−11.9	0.042	−308.8	203.4	−710.1	92.4	0.131	−30.6	23.9	−77.6	16.5	0.202
No formal education	−835.2	140.8	−1,112.9	−557.5	<0.001	−940.5	171.9	−1,279.7	−601.3	<0.001	−44.6	20.2	−84.3	−4.8	0.28
Occupation															
Unemployed	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
House wife	−215.7	202.9	−616.0	184.6	0.289	−473.8	232.5	−932.5	−15.2	0.043	52.5	30.6	−7.9	112.9	0.088
Farmer	637.4	215.8	211.7	1,063.1	0.004	810.7	247.2	322.9	1,298.5	0.001	29.8	32.6	−34.5	94.1	
Service (private & government)	723.0	232.5	264.4	1,181.7	0.002	599.3	266.3	73.9	1,124.7	0.026	94.1	35.1	24.9	163.4	0.008
Type of house[c]															
Pucca	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Kutcha-pucca	−571.9	143.9	−855.8	−288.0	<0.001	−809.6	171.7	−1,148.5	−470.8	<0.001	15.9	19.9	−23.3	55.1	0.423
Kutcha	−600.1	149.1	−894.2	−305.9	<0.001	−785.1	177.9	−1,136.1	−434.1	<0.001	−0.2	20.6	−40.8	40.4	0.993
Economic status[d]															
High	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Middle	−123.7	131.5	−383.3	135.9	0.348	−262.8	157.0	−572.6	47.1	0.096	12.9	18.2	−22.9	48.9	0.476
Low	−505.9	168.9	−839.3	−172.4	0.003	−798.5	201.7	−1,196.5	−400.4	<0.001	21.8	23.4	−24.3	67.9	0.352
Land ownership[e]															
≥10	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
1–9	−192.2	150.9	−490.0	105.6	0.204	−364.7	180.7	−721.2	−8.3	0.045	16.5	19.9	−22.8	55.9	0.408
None	−251.2	147.3	−541.8	39.4	0.090	−469.8	176.3	−817.7	−121.9	0.008	23.0	19.5	−15.4	61.4	0.238
Smoking status[f]	−129.6	146.2	−418.1	158.8	0.376	157.3	177.1	−192.0	506.6	0.376	−85.5	18.2	−121.4	−49.5	<0.001
Exposure to passive smoking[g]	−16.6	121.7	−256.7	223.5	0.892	−98.2	147.2	−388.6	192.3	0.506	8.1	16.0	−23.5	39.7	0.613

Table 2 continued

Variable	FEV1					FVC					FEV1/FVC				
	Value (ml)	SE	95% CI		*p*-value	Value (ml)	SE	95% CI		*p*-value	Ratio	SE	95% CI		*p*-value
Exposure to indoor air pollution using biomass for cooking[h]	−729.6	105.2	−938.4	−520.8	<0.001	−1,028.7	123.9	−1,273.1	−784.3	<0.001	6.4	15.4	−24.0	36.9	0.677
Duration of living in the house[i]	−21.6	3.9	−29.4	−13.8	<0.001	−19.4	4.9	−29.2	−9.7	<0.001	−2.7	0.5	−3.7	−1.7	<0.001
Height (cm)	52.3	5.6	41.2	63.4	<0.001	74.6	6.1	62.5	86.8	<0.001	−0.7	0.9	−2.5	1.1	0.437
Weight (kg)	17.1	4.4	8.5	25.8	<0.001	26.9	5.2	16.7	37.1	<0.001	−0.6	0.6	−1.7	0.6	0.352
Current water source usage (years)	−9.4	6.1	−21.4	2.6	0.124	−14.6	7.4	−29.0	−0.6	0.049	0.8	0.8	−0.8	2.4	0.329

FEV1 forced expiratory volume in the first second, *FVC* forced vital capacity, *SE* standard error, *CI* confidence interval

Sample size was 200 (100 exposed, 100 unexposed)

[a] Exposure status: Exposed at ≥100 μg/l or unexposed at ≤10 μg/l of arsenic in groundwater

[b] Male gender taken as reference

[c] Kutcha stands for thatched/mud dwelling, pucca for concrete/brick dwelling, kutcha-pucca for a mix of the two (proxy for socio-economic status)

[d] Based on tertiles of the monthly household income of participants (high = Rs 10,000–50,000; middle = Rs 5,000–9,999; low = Rs 1,000–4,999)

[e] Unit of land is *Jaraib*, where 1 acre = 2 *jaraib*

[f] Smoking status defined as ever or never smoker

[g] Question asked: does anyone smoke anywhere inside this house?

[h] Question asked: how many meals do you usually cook per day?

[i] Duration of living in house: 1–29 years (reference) or ≥30 years

Table 3 Multivariate linear regression analysis of lung function in ml and arsenic exposure at ≥100 μg/l, adjusted for age, sex, height and smoking status, Taluka Gambat, District Khairpur, Sindh, Pakistan, 2009

Variable	FEV1 (ml)					FVC (ml)					FEV1/FVC				
	Value (ml)	SE	95% CI		*p*-value	Value (ml)	SE	95% CI		*p*-value	Ratio	SE	95% CI		*p*-value
Arsenic exposure	−154.3	86.3	−324.7	16.0	0.076	−221.9	100.2	−419.5	−24.3	0.028	2.0	13.8	−25.3	29.4	0.884
Age (years)	−22.9	4.0	−30.8	−15.0	<0.001	−18.5	4.6	−27.7	−9.4	<0.001	−3.3	0.6	−4.6	−2.1	<0.001
Sex[a]	−266.9	129.8	−523.14	−10.7	0.041	−340.9	150.6	−638.2	−43.7	0.025	−0.6	20.8	−41.7	40.5	0.976
Height (cm)	42.1	7.3	27.6	56.6	<0.001	59.8	8.5	42.9	76.6	<0.001	−0.2	1.2	−2.6	2.1	0.837
Smoking status[b]	−179.9	119.7	−416.1	56.3	0.135	−45.2	138.9	−319.2	228.8	0.745	−50.5	19.2	−88.4	−12.6	0.009

FEV1 forced expiratory volume in the first second, *FVC* forced vital capacity, *SE* standard error, *CI* confidence interval

R-square values: FEV1 = 47.8%, FVC = 52.1%, ratio = 22.4%

Sample size was 200 (100 exposed, 100 unexposed)

[a] Male gender taken as reference

[b] Smoking status defined as ever or never smoker

Table 4 Multivariate linear regression analysis of lung function in ml and arsenic exposure at ≥250 μg/l, adjusted for age, sex, height and smoking status, Taluka Gambat, District Khairpur, Sindh, Pakistan, 2009

Variable	FEV1 (ml)					FVC (ml)					FEV1/FVC				
	Value (ml)	SE	95% CI		*p*-value	Value (ml)	SE	95% CI		*p*-value	Ratio	SE	95% CI		*p*-value
Arsenic exposure	−226.4	103.2	−430.4	−22.4	0.030	−354.8	115.7	−583.6	−126.0	0.003	9.9	16.0	−21.8	41.6	0.539
Age (years)	−25.9	4.4	−34.6	−17.3	<0.001	−22.3	4.9	−32.0	−12.6	<0.001	−3.4	0.6	−4.7	−2.1	<0.001
Sex[a]	−295.1	145.5	−582.8	−7.5	0.044	−425.1	163.2	−747.8	−102.6	0.010	8.6	22.6	−36.1	53.3	0.703
Height (cm)	36.3	8.4	19.6	53.0	<0.001	51.6	9.4	32.9	70.4	<0.001	−0.3	1.3	−2.9	2.3	0.828
Smoking status[b]	−86.7	135.0	−353.5	180.1	0.522	99.3	151.4	−199.9	398.5	0.513	−52.7	20.9	−94.1	−11.2	0.013

FEV1 forced expiratory volume in the first second, *FVC* forced vital capacity, *SE* standard error, *CI* confidence interval

R-square values: FEV1 = 47.2%, FVC = 54.3%, ratio = 25.7%

Sample size = 160 (exposed = 60, unexposed = 100)

[a] Male gender taken as reference

[b] Smoking status defined as ever or never smoker

wise to presume that there is a greater burden of respiratory diseases than suggested by previous studies (Mazumder et al. 2000; Milton and Rahman 2002). The study participants at this point only had respiratory effects on lung function, which could be measured objectively, and it would take more time for them to develop signs and symptoms of the disease, which could be detected at a later stage in the disease process.

Evidence is available regarding the malignant respiratory effects of chronic arsenic exposure through groundwater (Chen et al. 1992; Tsuda et al. 1995; Ferreccio et al. 2000; Ferreccio et al. 1998). There are only a few studies available regarding the non-malignant respiratory effects, especially in terms of decrements in lung function. Two studies were identified which also reported decrements in lung function in participants chronically exposed to arsenic through groundwater. In a study by De et al., the analysis was done on percent of the predicted values (De et al. 2004) whereas in another study by Von Ehrenstein et al., as well as in our study, the analysis was done on the absolute values of lung function indices (von Ehrenstein et al. 2005). The predicted percentages are derived through reference values based on age, gender, height and ethnicity and are used to compare results with those of the healthy population in order to classify the lung function as normal or abnormal (American Thoracic Society, medical section of the American Lung Association 1991; Sood et al. 2007). Moreover, since in this study the absolute lung function indices were compared for differences between the two groups there was no need to classify participants as normal or abnormal; therefore, no need to use the percent predicted values. Furthermore, age, gender and height variables were adjusted in our final multivariate model and the source population belonged to the same ethnic background.

In this study the reduction was found in FEV1 and FVC but not in FEV1/FVC ratio. This finding is similar to the study by von Ehrenstein et al., which showed a statistically significant decline in FEV1 and FVC among men with arsenic skin lesions but not in FEV1/FVC ratio. However, the study by De et al. showed a significant decline in all the three indices. The decrease in FEV1 and FVC is suggestive of a restrictive lung disease (von Ehrenstein et al. 2005). Other studies show that the abnormalities are varied and include obstructive, restrictive and combined obstructive and restrictive lung disease (Guha Mazumder 2007).

The finding of worsening affect on lung function indices with increasing arsenic exposure (dose–response effect) in our study was consistent with other studies (De et al. 2004; von Ehrenstein et al. 2005). The lung function decline was more pronounced at arsenic exposure $\geq$250 μg/l compared to $\geq$150 μg/l.

The exposure measurement in this study was done by determining arsenic concentration in groundwater used for drinking purposes through spot testing using arsenic kits. Results from arsenic testing kits have been shown to be consistent with those from Mercury/Hydride System Atomic Absorption Spectrophotometer (HG-AAS; Fatmi et al. 2009). Other studies have also determined exposure by taking biological samples such as spot or 24 h urine sample, skin, hair and nail samples (Fatmi et al. 2009; Hall et al. 2006; Kazi et al. 2009). Testing of such biological samples is technically difficult and time consuming and logistically less feasible in rural areas. Errors in arsenic level measurement may be increased by HG-AAS in rural studies from logistic reasons due to change in arsenic forms during transport. Also, sample tagging is much more reliable if done in the field. Furthermore, concentration of arsenic in drinking water has been shown to have a good correlation with concentration in biological samples such as urine, blood, hair and nails (Hall et al. 2006; Kazi et al. 2009; Pandey et al. 2007). However, cumulative exposure dose could not be calculated as has been done by some other studies.

Although groundwater mostly contains the more toxic, i.e. inorganic form of arsenic, oral arsenic exposure can also occur through food items such as fish, fruits and vegetables which contain the less toxic, i.e. organic, forms of arsenic (Mandal and Suzuki 2002). A study conducted in the southeast part of Sindh showed that leafy vegetables (spinach, coriander and peppermint) contain higher arsenic levels (0.90–1.20 mg/kg) as compared to ground vegetables and grain crops. The estimated daily intake of total arsenic in the diet was 9.7–12.2 μg/kg body weight/day. This study also found the concentration of arsenic in foodstuff as well as the daily dietary intake of arsenic from foodstuff in this part of Sindh to be higher as compared to other countries

(Arain et al. 2009). Therefore the overall arsenic exposure would be higher, contributed by other sources, than estimated in our study.

The patho-physiologic mechanism by which ingested arsenic leads to impairments of lung function is not very clear. Evidence suggests that arsenic alters the inflammatory response in lungs as opposed to direct toxicity (De et al. 2004). Laboratory studies in mice have indicated that environmentally relevant levels of arsenic in drinking water can induce alterations in lung gene and protein expression (Andrew et al. 2007; Lantz et al. 2007). A recent study on animal lungs revealed significant alterations in the expression of many genes with functions in cell adhesion and migration, receptors, differentiation and proliferation, and aspects of the innate immune response (Kozul et al. 2009). In this study confirmation of mRNA and protein expression changes in key genes of this response revealed that genes for interleukin 1β, interleukin 1 receptor, a number of toll-like receptors, and several cytokines and cytokine receptors were significantly altered in the lungs of arsenic exposed mice. Further human-based investigations are needed to understand the pathology and patho-physiology of arsenic-induced decline of lung function in humans and particularly in the absence of respiratory symptoms, as reported by this study. In-utero and postnatal exposure to arsenic may affect the normal lung growth and development which may lead to higher morbidity due to lung disease in early childhood and later on in the adult life (Mazumder 2007; Lantz et al. 2009; Soto-Martinez and Sly 2009).

To exclude any effect of confounding, potential confounders including age, sex, height, weight, economic status, education, occupation, type of house, duration living in the house, land ownership, active and passive smoking, indoor air pollution (using biomass for cooking), use of traditional medicine and number of years of current water source usage were assessed in the multivariate model. However, only age, sex, height and smoking status were retained in the final model since they were found to confound the association between lung function indices and arsenic exposure.

Limitations of the study include a small sample size of 200 individuals, 100 each in the exposed and the non-exposed groups. However, as a preliminary investigation we believe that our study adds significantly to the scarcely available epidemiologic evidence regarding the effects of arsenic exposure through groundwater on the lung function and is therefore worth reporting. Another limitation is the way exposure was measured in our study through spot testing of samples from the drinking water source, where exposure through food items was not taken into account and no biological indices of arsenic exposure such as urine, blood or hair arsenic concentrations were used. Lastly, although our study took into account the length of exposure through the same water source, we do not have information regarding the change of exposure over time for individuals. However, we assume that the exposure status has not changed for this population over time. The rural populations are generally very stable and very little, if any, in-migration occurs in this population. A possibility of out-migration exists, but would not have any effect on exposure in this study as those individuals could not be included in the study. Detrimental effects of arsenic exposure on development of lung function in utero and early childhood periods would have occurred; however, they could not be ascertained.

Conclusion

Characteristic arsenic skin lesions, hyperkeratosis of palms and soles and pigmentation, are considered to be the first manifestation of arsenic exposure. This study demonstrated that decrement in lung function is associated with chronic exposure to arsenic in drinking groundwater. Decrement in lung function due to arsenic exposure in drinking groundwater may be considered to occur independently, and even before any manifestation of arsenic skin lesions or respiratory symptoms. Therefore, mitigation measures to decrease the burden of arsenic exposure should be considered a priority and included in water policies. Millions of people living along the banks of the River Indus, particularly in the Punjab and Sindh provinces, in Pakistan are exposed to similar levels of arsenic and should be targeted for mitigation and focused intervention for provision of improved water supply.

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