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# Arsenic Exposure and Oral Cavity Lesions in Bangladesh

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## Abstract

**Objective—**To evaluate the relationship between arsenic exposure and oral cavity lesions among an arsenic-exposed population in Bangladesh.

**Methods—**We carried out an analysis utilizing the baseline data of the Health Effects of Arsenic Exposure Longitudinal Study (HEALS). HEALS is an ongoing population-based cohort study to investigate health outcomes associated with arsenic exposure via drinking water in Araihazar, Bangladesh. We used multinomial regression models to estimate the risk of oral cavity lesions.

**Results—**Participants with high urinary arsenic levels (286.1–5000.0μg/g) were more likely to develop arsenical lesions of the gums [multinomial odds ratio (M-OR 2.90; 95% CI= 1.11–7.54)], and tongue (M-OR 2.79; 95% CI= 1.51– 5.15), compared with those of urinary arsenic levels of 7.0–134.0μg/g.

**Conclusions—**Higher level of arsenic exposure was positively associated with increased arsenical lesions of the gums and tongue.

Groundwater contamination by arsenic is a major public health concern worldwide. It is affecting 150 million people in more than 70 countries including the USA, Taiwan, Mexico, Mongolia, Argentina, India, Chile, and Bangladesh. [1–4] In half of these affected countries including Bangladesh, arsenic contamination levels are up to 100 times higher than the World Health Organization's (WHO) guideline of 10μg/L. [1, 5] In Bangladesh, about 35–77 million people have been reportedly exposed to arsenic through drinking water. [6, 7] As a result, WHO described the arsenic problem in Bangladesh as "the largest mass poisoning of a population in history". [8] Of note, arsenic exposure has been associated with an increased risk for death in Bangladesh. [9]

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Arsenic is a class 1 human carcinogen and associated with a variety of adverse health outcomes. [10–12] Chronic exposure to arsenic causes various types of skin lesions including raindrop pigmentation, hyper-pigmentation, hyperkeratosis, squamous cell carcinoma, basal cell carcinoma, and Bowen's disease. [10, 13] Such dermal effects are hallmarks of the early stages of arsenic poisoning and are thought to be precursors to the arsenic-induced cancers. [14] Signs and symptoms are also found on other tissues of the body including the tongue, gingival, and buccal mucosa. [15]

Toxic metals have profound effects on oral health. Melanocytes present in the basal cell layer of the oral mucosa are similar to those found in the skin. [16] Oral cancer is the sixth most common cancer worldwide after oral cavity lesions and continues to be a growing health concern. [17] The annual estimated incidence is around 275,000 for oral cancers, two-thirds of which occur in developing countries. [18] In particular, high levels of nickel and chromium were associated with oral cancer within the population in Taiwan. [19]

In addition to these metals, arsenic can also cause similar oral health problems. For example, arsenic is toxic to vital pulp, which can cause severe damage to osteomyelitis of the jaw. [20] In a recent study in Bangladesh, 75.5% of participants showed swelled vallate papillae as an indication of arsenicosis. [21] Exposure to arsenic may also manifest buccal mucus membrane melanosis.[2] However, information on arsenic exposure and oral cavity lesions is very limited. To our knowledge, no study to date has measured the relationship between arsenic exposure and oral cavity arsenical lesions and its associated factors, particularly of the gums, lips, and tongue, in Bangladesh or elsewhere at the population level. In this context, the Health Effects of Arsenic Longitudinal Study (HEALS) data represents a valuable opportunity for investigating the association between arsenic exposure and oral cavity arsenical lesions.

Therefore, in this study, we aimed to explore the relationship between arsenic exposure and oral cavity lesions among arsenic-exposed people in Bangladesh. The information uncovered through this objective might be useful to develop appropriate strategies to support those affected in Bangladesh.

## MATERIALS AND METHODS

### Study area and population

We carried out a cross-sectional analysis utilizing baseline data from the HEALS cohort. Details of the HEALS study procedure have been presented elsewhere. [22, 23] Briefly, HEALS is an ongoing population-based cohort study to investigate both the short-term and long-term health outcomes associated with arsenic exposure through drinking water in Araihazar, Bangladesh. [22] Araihazar is located east of the capital city, Dhaka, with relatively homogeneous socio-cultural characteristics. The total study area is $25km^2$, which was divided into six segments within which six different study teams were primarily assigned to conduct the survey.

Between October 2000 and May 2002, the HEALS team enumerated 65,876 individuals residing in Araihazar, from which they identified a sampling frame of 14,828 eligible residents. Of these 14,828 individuals, 2,778 (19.0%) were not at home during any of the three attempted recruiting visits. Of the remaining 12,050 eligible residents, the team recruited 11,746 married individuals, aged 18–75 years who were residents of the study area for at least 5 years and primarily consumed drinking water from a local tube well, designated as an "index" tube well. Based on the pre-cohort survey list, six trained field staff teams conducted the recruitment and data collection. Each field teams consisted of two interviewers and one field physician.[22] Trained study physicians and research assistants, blinded to the arsenic measurements, conducted in-person interviews and clinical evaluations and collected spot urine and blood samples from the participants in their homes using a structured protocol.

Socio-demographic information was collected including well history, height, weight, and lifestyle characteristics in addition information regarding arsenic exposure related symptoms on gums, lips, and tongue. All information was collected by the trained study physicians and research assistants using a structured questionnaire. The questionnaire was pre-tested and corrected necessarily prior to data collection. Participants were examined by a trained physician for the presence of premalignant lesions in accordance with a structured protocol. The presence, location, and extent of lesion type were duly documented. At the time of recruitment, water sample was collected and arsenic levels tested for 5,966 wells in the study area. A spot urine sample was collected in 50ml acid-washed tubes at baseline 95.6% of the participants. Water and urine samples were kept in portable coolers (carried by the field team) immediately after collection and shipped to the USA within 1–2 months, and were barcoded to minimize sample- handling errors and maintain confidentially.

## Arsenic exposure assessment

At the time of survey, participants identified one or more wells as their primary source of drinking water, on which basis concentration of arsenic exposure was assessed. Levels of arsenic concentration in the water of all wells in the study field were measured using Graphite Furnace Atomic Absorption spectrometry (GFAA), with a detection limit of 5.0μg/L. Samples that fall below the limit of detection were subsequently reanalyzed by use of inductively coupled plasma-mass spectrometry, with a detection limit of 0.1μg/L. The study participants have been subject to a wide range of arsenic exposure at low-to-moderate levels, ranging from 0.1 to 864μg/L, with a mean of 101.6μg/L. [24] About 55.0% (n=6,489) of the participants were exposed to arsenic as per national level of 50μg/L.[22]

All urine samples collected at baseline were analyzed for total arsenic concentration in urine by GFAA, with a detection limit of 2.0μg/L, at a laboratory in USA. The creatinine in urine was measured with a colourimetric diagnostics kit (Sigma, St Louis, MO, USA). The total arsenic in urine was then divided by the concentration of creatinine in the urine to obtain a creatinine-adjusted total arsenic concentration in the urine expressed as μg/g creatinine. Total arsenic in urine range was 7.0–5000.0μg/g creatinine. In this analysis, participants were classified according to the range of arsenic concentration recorded in urine (μg/g). The concentration of total arsenic in urine has often been used as an indicator of recent exposure because urine is the main route of excretion of most arsenic species.[25]

## Outcome assessment

At baseline interview, arsenical lesions of the gums, lips, and tongue were ascertained by trained study physicians. The methods to ascertain arsenicosis have followed the surgical discipline for the quantitative assessment of the extent of body surface involvement in burn patients. [26] In HEALS, melanosis was defined as diffuse or spotted dark-brown or blackish areas on the skin against normal skin complexion. Leucomelanosis consists of hypopigmentation resembling pin heads or rain drops, typically on the body and keratosis consists of nodules or areas of thickening, which may be only palpable or visible on palms and soles. [27] Arsenicosis was diagnosed in the same manner for every segment of the body in the indirect sunlight and started from most unexposed part (ex: abdomen, thigh etc). The body was divided into 11 specific segments. Other pathologies of the oral cavity were defined as any kind of conditions (gum bleeding, discoloration due to betal leaf or smoking, angular stomatitis, blackening of tongue, fungal infection, etc) except arsenicosis symptoms, such as melanosis, leukomelanosis, and keratosis on the gums, lips, and tongue. Normal was defined as free from any symptoms.

Study physicians had sufficient training for the detection and diagnosis of arsenicosis [22] and recorded the presence or absence of arsenicosis of the gums, lips, and tongue. They were trained by external clinicians who are experts on the diagnosis of arsenical lesions in Bangladesh. In these analyses, "suggestive of arsenicosis" was defined as manifestations of any type of arsenicosis symptoms on the gums, lips, and tongue. Participants with arsenical lesions were re-examined by two external experts (a dermatologist from Dhaka Medical College and an occupational physician from the National Institute of Preventive and Social Medicine) to assess the reliability of the original diagnosis. The participants were re-examined at the field clinic in three separate rooms by the three raters (the study physician and two external experts). All raters used the same structured physical examination methods. The experts also checked the miss-classification rate between the lesions due to arsenic exposure and lesions due to others. About 85.0–90.0% of diagnoses were accurate by the study physicians in the field.

### Measurement of lifestyle factors

To evaluate possible factors that might modify associations between arsenic exposure and oral cavity lesions, we collected detailed information on lifestyle factors, including cigarette smoking and betel leaf chewing. For the purpose of analysis, participants were categorized as current smoker or non-smoker and betel leaf chewing or not. Measured socio-demographic factors included sex, age, education, occupation, smoking (yes/no), betel leaf chewing (yes/ no), own cultivation land (yes/no), and TV in home (yes/no). We also collected data on Body Mass Index (BMI) (weight in kg divided by height in $m^2$).

The HEALS protocol was reviewed and approved by the institutional review boards of the University of Chicago, USA; Columbia University, USA; and the Bangladesh Medical Research Council, Bangladesh. Our study protocol was approved by the ethical committee of the Graduate School of Medicine, the University of Tokyo, Japan. Verbal consent was obtained from each eligible respondent who agreed to participate in the HEALS.

### Statistical analysis

Pearson's correlation analysis was performed to describe the correlation between oral cavity arsenical lesions and socio-demographic characteristics, lifestyle characteristics, and urinary arsenic levels. Total arsenic in urine was divided into tertiles, with categories defined as low (7.0–134.0μg/g), medium (134.1–286.0μg/g), and high (286.1–352.0μg/g). Missing values were excluded during the correlations analysis.

Finally, multinomial multivariate regression models were created separately for the gums, lips, and tongue, with adjustment for potential confounders, to determine the factors associated with arsenical lesions. The types of conditions of oral cavity of the gums, lips, and tongue were coded as 1= normal, 2= arsenical lesions, and 3= other pathology. In the present study, 'normal' was used as the reference category. Urinary arsenic concentration levels were used with all other covariates. Differences were considered significant at $P < 0.05$. All analyses were performed using STATA, version 11 (StataCorp LP, College Station, Texas, USA).

## RESULTS

Out of 12,050 eligible participants, 11,746 were included in the HEALS baseline cohort. The response rate was 97.5%. Among 11,746 participants, 42.9% (n=5,042) were male and

57.1% (n=6,704) were female. The mean age of male participants was 41.6 (SD 9.9) years and female was 33.6 (SD 8.8) years. The difference was statistically significant (*P*<0.001). Table 1 shows the distribution of socio-demographic characteristics in relation to oral cavity lesions of the participants. The presence of arsenical lesions of the gums, lips, and tongue increased with age and were more common in male.

Table 2 summarizes the distribution of lifestyle characteristics in relation to oral cavity arsenical lesions. An association between urinary arsenic levels and oral cavity lesions was observed in the tongue (*P*<0.05). We also observed significant differences between cigarette smoking and arsenical lesions of the gums, lips, and tongue.

Table 3 shows the results of multinomial multivariate regression model examining the factors associated with arsenical lesions of the gums. Participants in the highest tertile of urinary arsenic levels (286.1–5000.0μg/g) were more likely to develop arsenical lesions of the gums [multinomial odds ratio (M-OR 2.90; 95% CI= 1.11–7.54)] than those in the lowest tertile (7.0–134.0μg/g). Females were less likely to develop arsenical lesions of the gums (M-OR 0.35; 95% CI= 0.13–0.92) than males. Our results also showed that manual workers were less likely to develop arsenical lesions of the gums (M-OR 0.39; 95% CI= 0.15–0.97), compared with unemployed/homemakers. The other covariates were not associated with arsenical lesions of the gums. With regard to other pathology, age was found to be significantly associated with developing other pathological conditions (blackening or bleeding) of the gums (M-OR 1.05; 95% CI=1.01–1.08). Our results also showed that participants with medium urinary arsenic levels (134.1–286.0μg/g) were more likely to develop other pathology of the gums (M-OR 2.25; 95% CI=1.02–4.97), compared with participants having low urinary arsenic levels of 7.0–134.0μg/g. Participants who smoke cigarettes were more likely to develop other pathologies of the gums (M-OR 3.20; 95% CI=1.39–7.39), compared to those who were not smokers.

Table 4 shows the factors associated with lips' condition. We did not observe any statistically associated factors in developing arsenical lesions in the lips. In the case of other pathology in the lips, age was found to be significantly associated with developing other pathological conditions of the lips (M-OR 1.06; 95% CI=1.01–1.11). Smokers were more likely to develop other pathologies in the lips (M-OR 4.46; 95% CI=1.24–15.98), compared with the non- smokers. Moreover, 21 participants showed discoloration, fungal infections, and white coloration of the lips.

Table 5 shows the association between urinary arsenic levels and arsenical lesions of the tongue. Participants in the highest tertile of urinary arsenic levels were more likely to develop arsenical lesions of the tongue (M-OR 2.79; 95% CI=1.51–5.15), compared with those in the lowest tertile. Our results also showed that participants age was significantly associated with arsenical lesions of the tongue (M-OR 1.03; 95% CI=1.00–1.05). However, other covariates did not show any statistical association with regard to arsenical lesions of the tongue. Regarding other pathology of the tongue, 57 participants exhibited symptoms beyond those suggestive of arsenicosis, including fungal infections, whitish coloration of the whole tongue, and tongue blacking. We also observed smokers were more likely to develop other pathology of the tongue (M-OR 2.49; 95% CI=1.10–5.62), compared with the non-smokers.

## DISCUSSION

Findings from this study suggest that a higher level of urinary arsenic concentration is associated with the higher risk of arsenical lesions of the gums and tongue. To our knowledge, this population-based study is the first study to examine the relationship between levels of urinary arsenic and oral cavity lesions. This result is supported by the prior claims that high levels of toxic-metals (nickel and chromium) have a detrimental impact on oral health. [19] In the present study, we provide further direct evidence that arsenic concentration in urine has a stronger association with arsenicosis symptoms of the gums and tongue. These findings imply that contamination of drinking water with arsenic might also be a risk factor for arsenicosis of the gums and tongue.

A lesion related to arsenic exposure is the early signals of the subsequent development of cancers [28]. Moreover, several studies highlighted that arsenic in drinking water is associated with cancers. [28–32] Exposure to toxic elements was implicated as a factor in the rapidly increasing rates of oral cancer in the population of Taiwan. [33] Thus, ecological studies have illustrated that high levels of nickel and chromium (toxic metals) in the soils are correlated with oral cancer incidence in Taiwan. [34, 35] Thus, arsenic-exposed populations may develop oral cancers of the gums and tongue. Our study suggests that safe drinking water programs might have positive impacts to decrease the rates of arsenical lesions of the gums and tongue.

In this study, females were less likely to develop arsenical lesions of the gums. This might be attributable to the higher arsenic methylation capabilities of females than males, which reduced their risk of developing arsenical lesions of the gums. This result is supported by several studies. [36, 37] In addition, one previous study showed that females of child-bearing age had significantly higher arsenic methylation capacity, compared to males. [38] We also found that manual workers (daily labor, farmer, factory workers, and other paid jobs) had fewer chances to develop arsenical lesions of the gums, compared to unemployed/ homemakers. Most of manual workers were males and about 94.0% (n=6,325) of female participants were homemakers. This result is supported by previous study that showed males had higher prevalent rate of arsenicosis than females. [39] In this study, we observed that males tended to drink less amounts of water (mean 2875ml) than females (mean 3095ml). Since males drank less amount of water, this might be a contributing factor in their lower susceptibility to develop oral cavity lesions of the gums. A recent study reported that lifestyle characteristics of females are most prevalent as they were unknowingly harming their health through increased exposure to arsenic. [40] Therefore, further studies should incorporate health education sessions targeting unemployed/homemakers and covering the health effects of arsenic exposure highlighted in their occupation in affected communities.

Consistent with a previous study [39], our results found that age is associated with developing arsenical lesions of the tongue. It may be because older participants have lived in an arsenic endemic area for a longer period of time. However, health effects caused by arsenic poisoning, younger age people may have a higher tolerant ability for arsenic exposure than older age people. [39] Our study suggests a community-based awareness program for the age-specific arsenic-exposed population in Bangladesh.

In the present study, we observed that smokers have greater chances to develop other pathologies of the gums, lips, and tongue. Smoking is one of the major lifestyle factors influencing human health, and is also associated with poorer arsenic methylation capacity. It is also possible that some chemicals in cigarettes may play a significant role in the future development of oral cancer among arsenic-exposed populations. In a recent hospital-based case-control study and a prospective follow-up study in Taiwan showed that smoking was associated with higher $MMA^{v}$ percentage and lower $DMA^{v}$ percentage in the non-cancerous control participants. [41–42] One previous study also observed that smoking has a large number of chemical carcinogens including arsenic which can result tissue-damaging effects in lips. [43] Since, about one-third (29.0%) of male participants were smokers in this study, community-based health education might be a fruitful approach to the management of common human cancers within arsenic-exposed populations in Bangladesh.

Although a relationship has been studied between quid chewing and increased risk of arsenic-induced skin lesions, [44, 45] our study showed no such association between betel leaf chewing and lesions of the gums, lips, and tongue. Recently, other studies also have found no association between betel leaf chewing and oral or oropharyngeal cancers. [46] This might be attributed to the reduced levels of carcinogenic substances added to certain products by tobacco manufacturing companies.[46] On the other hand, some people might not use lime or *zarda*, which might account for much of the associated risk for development of lesions of the oral cavity.

This study had three limitations. First, this study was limited by its cross-sectional analysis, which means that causality cannot be attributed. Nevertheless, the HEALS is a large-scale, methodologically rigorous epidemiological cohort study in a developing country setting where 60.0% of the participants were exposed to arsenic concentrations of 1–100μg/L. This provides a unique opportunity to assess different ranges of arsenic exposure and the associated health effects. Second, the present study only assessed arsenic concentration levels in the urine and oral cavity lesions of the participants. It is possible that some participants had other environmental exposures, which might affect on the arsenical lesions of oral cavity. A previous study indicated that arsenic and nickel concentrations in farm soils are associated with oral cancer. [34] Third, there might have possible errors during the diagnosis of arsenical lesions of oral cavity between the teams. However, to minimize possible diagnostic errors, participants were diagnosed by trained study physicians for the presence of premalignant lesions following the same protocol.

Despite these limitations, this study had several strengths. First, it used data from a large population-based prospective study. The large sample size enabled adjustment for a large number of potential confounders, and for a fully adjusted multivariate model. Second, although some participants were exposed to high levels of arsenic, most of the participants were exposed relatively low levels of arsenic, making our results generalizable to a wide range of exposures. In addition, the measurement of total arsenic in urine was available on all participants. Therefore, the present study findings will add important information for the protection of arsenic-exposed people in worldwide. Finally, the socio-demographic characteristics of Araihazar are similar to other rural areas of Bangladesh, which implies that inferences from these results may be extended to other regions of Bangladesh, where elevated arsenic concentrations in well water are a common phenomenon.

In conclusion, higher levels of arsenic exposure were positively associated with an increased risk of arsenical lesions of the gums and tongue. It is necessary to introduce suitable mitigation options and provide safe water to avoid such diseases among arsenic-affected people in Bangladesh. The government and related agencies should take effective interventions to minimize arsenic exposure because longer exposure might increase deaths among arsenic-exposed population.

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## References


1. British Geological Survey. Arsenic contamination of groundwater in Bangladesh. Keyworth, UK: British Geological Survey; 2001. Final report, BGS Technical report WC/00/19
2. Rahman MM, Chowdhury UK, Chakraborti D, et al. Chronic arsenic toxicity in Bangladesh and West Bengal, India-a review and commentary. J Toxicol Clin Toxicol. 2001; 39:683–700. [PubMed: 11778666]
3. World Bank. Towards a more effective operational response: arsenic contamination of groundwater in South and East-Asian countries. Vol. 1. Washington, DC: World Bank; 2005. Report no. 31303Available at: http://siteresources.worldbank.org/INTSAREGTOPWATRES/Resources/ArsenicVoll_WholeReport.pdf [Accessed May 2, 2011.]
4. Ravenscroft, P.; Brammer, H.; Richards, KS. Arsenic pollution: a global synthesis. Wilery-Blackwell; UK: 2009.
5. Ahmed MF, Ahuja S, Alauddin M, et al. Ensuring safe drinking water in Bangladesh. Science. 2006; 314:1687–1688. [PubMed: 17170279]
6. Ahsan H, Perrrin M, Graziano J, et al. Associations between drinking and urinary arsenic levels and skin lesions in Bangladesh. J Occup Environ Med. 2000; 42:1195–1201. [PubMed: 11125683]
7. Smith AH, Lingas EO, Rahman M. Contamination of drinking-water by arsenic in Bangladesh: a public health emergency. Bull World Health Organ. 2000; 78:1093–1103. [PubMed: 11019458]
8. World Health Organization. Water, sanitation, and health. Geneva: World Health Organization; 2004.
9. Argos M, Kalra T, Ahsan H, et al. Arsenic exposure from drinking water, all-cause and chronic-disease mortalities in Bangladesh (HEALS): a prospective cohort study. Lancet. 2010; 376:252–258. [PubMed: 20646756]
10. International Agency for Research on Cancer (IARC). *Monographs on the evaluation of carcinogenic risk of chemicals to humans*: some drinking water disinfectants and contaminants, including arsenic. IARC Monorg Eval Carcinog Risks Hum. 2004; 84:1–477.
11. European Chemicals Bureau. European chemical substances information system (ESIS). [Accessed May 24, 2011.] European Chemicals Bureau. 2007. http://ecb.jrc.it/esis
12. Environmental Protection Agency. Integrated Risk Information system (IRIS). [Accessed May 24, 2011.] Environmental Protection Agency. 2007. http:/www.epa.gov./iris
13. Rahman MM, Mandal BK, Saha KC, et al. Arsenic groundwater contamination and sufferings of people in North 24-Pargans, one of the nine arsenic affected districts of West Bengal, India. J Environ Sci Health A Tox Hazard Subst Environ Eng. 2003; 38:25–59. [PubMed: 12635818]
14. National Research Council (NRC). Arsenic in drinking water. Washington, DC: National Academy Press. National Research Council; 1999.
15. Ahmad, SA. Water contamination and health hazard. 1. Udayan Press; Rajshahi: 2000. p. p23
16. Muller S. Melanin-associated pigmented lesions of the oral mucosa: presentation, differential diagnosis, and treatment. Dermatol Ther. 2010; 23:220–29. [PubMed: 20597941]
17. Khlifi R, Hamza-Chaffai A. Head and neck cancer due to heavy metal exposure via tobacco smoking and professional exposure: a review. Toxicol Appl Pharmacol. 2010; 248:71–88. [PubMed: 20708025]
18. Ferlay, J.; Pisani, P.; Parkin, DM. IARC Cancer Base (2002 estimates). IARC press; Lyon: 2004. Cancer incidence, mortality and prevalence worldwide.
19. Yuan TH, Lian IB, Tsai KY, et al. Possible association between nickel and chromium and oral cancer: a case-control study in central Taiwan. Sci Total Environ. 2011; 409:1046–1052. [PubMed: 21195455]
20. Wang X, Zhang J, Liu M, Wei FC. Aseptic necrosis of the maxilla after devitalisation of the teeth with arsenic trioxide. Br J Oral Maxillofac Surg. 2008; 46:79–82.
21. Sarwar AFM, Ahmad SA, Kabir MH, et al. Swelling of vallate papillae of the tongue following arsenic exposure. Bangladesh Med Res Counc Bull. 2010; 36:1–3. [PubMed: 21280550]
22. Ahsan H, Chen Y, Graziano J, et al. Health Effects of Arsenic Longitudinal Study (HEALS): Description of a multidisciplinary epidemiologic investigation. J Expo Sci Environ Epidemiol. 2006; 16:191–205. [PubMed: 16160703]

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23. Parvez F, Chen Y, Ahsan H, et al. Prevalence of arsenic exposure from drinking water and awareness of its health risks in a Bangladeshi population: results from a large population-based study. Environ Health Perspect. 2006; 114:355–359. [PubMed: 16507457]
24. Chen Y, Parvez F, Gamble M, et al. Arsenic exposure at low-to-moderate levels and skin lesions, arsenic metabolism, neurological functions, and biomarkers for respiratory and cardiovascular diseases: Review of recent findings from the Health Effects of Arsenic Longitudinal Study (HEALS) in Bangladesh. Toxicol Appl Pharmacol. 2009; 239:184–192. [PubMed: 19371619]
25. Vahter M. Species differences in the metabolism of arsenic compounds. Appl Organo Chemis. 1994; 8:175–182.
26. Demling, RH.; Way, LW. Current surgical diagnosis and treatment. 10. Appleton and Lange; East Norwalk, CT: 1994. Burn and other thermal injuries.
27. Verret WJ, Chen Y, Ahsan H, et al. A randomized, double-blind placebo-controlled trail evaluating the effects of Vitamin E and Selenium on arsenic-induced skin lesions in Bangladesh. J Occup Environ Med. 2005; 47:1026–1035. [PubMed: 16217243]
28. Yu HS, Liao WT, Chai CY. Arsenic carcinogenesis in the skin. J Biomed Sci. 2006; 13:657–666. [PubMed: 16807664]
29. Celik I, Gallicchio L, Boyd K, et al. Arsenic in drinking water and lung cancer: a systematic review. Environ Res. 2008; 108:48–55. [PubMed: 18511031]
30. Mink PJ, Alexander DD, Barraj LM, et al. Low-level arsenic exposure in drinking water and bladder cancer: a review and meta-analysis. Regul Toxicol Pharmacol. 2008; 52:299–310. [PubMed: 18783726]
31. Liu J, Waalkes MP. Liver is a target of arsenic carcinogenesis. Toxicol Sci. 2008; 105:24–32. [PubMed: 18566022]
32. Yuan Y, Marshall G, Smith AH, et al. Kidney cancer mortality: fifty-year latency patterns related to arsenic exposure. Epidemiology. 2010; 21:103–108. [PubMed: 20010213]
33. Su CC, Tsai KY, Hsu YY, Lin YY, Lian IB. Chronic exposure to heavy metals and incidence of oral cancer in Taiwanese males. Oral Oncol. 2010b; 46:586–590. [PubMed: 20619722]
34. Su CC, Lin YY, Chang TK, et al. Incidence of oral cancer in relation to nickel and arsenic concentrations in farm soils of patients' residential areas in Taiwan. BMC Public Health. 2010a; 10:67.10.1186/1471-2458-10-67 [PubMed: 20152030]
35. Chiang CT, Hwang YH, Yuan TH, et al. Elucidating the underlying causes of oral cancer through spatial clustering in high-risk areas of Taiwan with a distinct gender ratio of incidence. Geospat Health. 2010; 4:230–242. [PubMed: 20503191]
36. Gao J, Yu J, Yang L. Urinary arsenic metabolites of subjects exposed to elevated arsenic present in coal in Shaanxi Province, China. Int J Environ Res Public Health. 2011; 8:1991–2008. [PubMed: 21776214]
37. Lindberg AL, Ekstrom EC, Nermell B, et al. Gender and age differences in the metabolism of inorganic arsenic in a highly exposed population in Bangladesh. Environ Res. 2008; 106:110–120. [PubMed: 17900557]
38. Lindberg AL, Kumar R, Goessler W, et al. Metabolism of low dose inorganic arsenic in a Central European population-influence of gender and genetic polymorphism. Environ Health Perspect. 2007; 115:1081–1086. [PubMed: 17637926]
39. Wang JP, Maddalena R, Zheng B, et al. Arsenicosis status and urinary malondialdehyde (MDA) in people exposed to arsenic contaminated-coal in China. Environ Int. 2009; 35:502–506. [PubMed: 18789824]
40. Al-Rmalli AW, Jenkins RO, Haris PI. Betel quid chewing elevates human exposure to arsenic, cadmium and lead. J Hazard Mater. 2011; 190:69–74. [PubMed: 21440366]
41. Pu YS, Yang SM, Huang YK, et al. Urinary arsenic profile affects the risk of urothelial carcinoma even at low arsenic exposure. Toxicol Appl Pharmacol. 2007; 218:99–106. [PubMed: 17196235]
42. Huang YK, Pu YS, Chung CJ, et al. Plasma folate level, urinary arsenic methylation profiles, and urothelial carcinoma susceptibility. Food Chem Toxicol. 2008; 46:929–38. [PubMed: 18054417]
43. Arain MB, Kazi TG, Baig JA, et al. Respiratory effects in people exposed to arsenic via the drinking water and tobacco smoking in southern part of Pakistan. Sci Total Environ. 2009; 407:5524–30. [PubMed: 19665170]

44. McCarty KM, Houseman EA, Quamruzzaman Q, et al. The impact of diet and betel nut use on skin lesions associated with drinking-water arsenic in Pabna, Bangladesh. Environ Health Perspect. 2006; 114:334–40. [PubMed: 16507454]

45. Pilsner JR, Liu XH, Ahsan H, et al. Folate deficiency, hyperhomocysteinemia, low urinary creatinine, and hypomethylation of leukocyte DNA are risk factors for arsenic-induced skin lesions. Environ Health Perspect. 2009; 117:254–60. [PubMed: 19270796]

46. Critchley JA, Unal B. Health effects associated with smokeless tobacco: a systematic review. Thorax. 2003; 58:435–43. [PubMed: 12728167]

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### Clinical Significance

- Arsenic exposure was significantly associated with arsenical lesions of the gums and tongue among an arsenic-exposed population in Bangladesh.
- Understand the effect of arsenic exposure via drinking water on oral health.

## Table 1

Socio-demographic characteristics of the participants in relation to oral cavity arsenical lesions

| Variables | Normal N (%) | Gums Arsenical lesions N (%) | Other N (%) | p-value | Normal N (%) | Lips Arsenical lesions N (%) | Other N (%) | p-value | Normal N (%) | Tongue Arsenical lesions N (%) | Other N (%) | p- value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age (years) | (N=11,454) | (N=35) | (N=47) | **0.002** | (N=11,497) | (N=17) | (N=21) | **0.008** | (N=11,400) | (N=79) | (N=57) | **<0.001** |
| 17–30 | 3,583(31) | 6(17) | 5(11) | | 3,590(31) | 3(18) | 1(5) | | 3,565(31) | 13(16) | 16(28) | |
| 31–40 | 4,081(36) | 15(43) | 16(34) | | 4,099(36) | 5(29) | 7(33) | | 4,065(36) | 22(28) | 25(44) | |
| 41–75 | 3,790(33) | 14(40) | 26(55) | | 3,808(33) | 9(53) | 13(62) | | 3,770(33) | 44(56) | 16(28) | |
| Sex | (N=11,454) | (N=35) | (N=47) | **0.004** | (N=11,497) | (N=17) | (N=21) | **0.001** | (N=11,400) | (N=79) | (N=57) | **0.004** |
| Male | 4,889(43) | 21(60) | 29(62) | | 4,911(43) | 14(82) | 13(62) | | 4,869(43) | 48(61) | 22(39) | |
| Female | 6,565(57) | 14(40) | 18(38) | | 6,586(57) | 3(18) | 8(38) | | 6,531(57) | 31(39) | 35(61) | |
| Education (years) | (N=11,448) | (N=35) | (N=47) | 0.071 | (N=11,491) | (N=17) | (N=21) | 0.114 | (N=11,394) | (N=79) | (N=57) | 0.316 |
| No education | 5,075(44) | 18(51) | 28(60) | | 5,105(44) | 6(35) | 9(43) | | 5,050(44) | 40(51) | 31(54) | |
| 1–4 years | 1,666(15) | 7(20) | 8(17) | | 1,670(15) | 6(35) | 5(24) | | 1,660(15) | 12(15) | 9(16) | |
| 5–16 years | 4,707(41) | 10(29) | 11(23) | | 4,716(41) | 5(30) | 7(33) | | 4,684(41) | 27(34) | 17(30) | |
| Own cultivation land | (N=11,451) | (N=35) | (N=47) | 0.609 | (N=11,494) | (N=17) | (N=21) | 0.937 | (N=11,397) | (N=79) | (N=57) | 0.510 |
| Yes | 5,698(50) | 17(49) | 20(43) | | 5,714(50) | 9(53) | 11(52) | | 5,674(50) | 36(46) | 25(44) | |
| No | 5,753(50) | 18(51) | 27(57) | | 5,780(50) | 8(47) | 10(48) | | 5,723(50) | 43(54) | 32(56) | |

Two-sided $\chi 2$ test; missing values were excluded from the statistical comparison. Fisher's exact p-values were used where cells less than 5.

Abbreviations: Normal = no symptoms, arsenical lesions = arsenicosis symptoms due to arsenic exposure, other = other pathological conditions except arsenical lesions.

N = number.

**Table 2**

Lifestyle characteristics of the participants in relation to oral cavity arsenical lesions

| Variables | Normal | Gums Arsenical lesions | Other | p-value | Normal | Lips Arsenical lesions | Other | p-value | Normal | Tongue Arsenical lesions | Other | p- value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N (%) | N (%) | N (%) | | N (%) | N (%) | N (%) | | N (%) | N (%) | N (%) | |
| Total arsenic in urine (μg/g) | (N=11,131) | (N=34) | (N=45) | 0.072 | (N=11,171) | (N=17) | (N=21) | 0.238 | (N=11,077) | (N=77) | (N=56) | **0.012** |
| 7.0–134.0 | 3,713(33) | 6(18) | 9(20) | | 3,719(33) | 3(18) | 6(29) | | 3,699(33) | 15(20) | 14(25) | |
| 134.1–286.0 | 3,717(34) | 12(35) | 20(44) | | 3,730(34) | 7(41) | 11(52) | | 3,706(34) | 24(31) | 19(33) | |
| 286.1–5000.0 | 3,701(33) | 16(47) | 16(36) | | 3,722(33) | 7(41) | 4(19) | | 3,672(33) | 38(49) | 23(41) | |
| Mean total arsenic in urine (μg/g) | 282.0 | 515.8 | 324.6 | | 282.8 | 373.4 | 265.6 | | 281.4 | 457.9 | 345.3 | |
| Cigarette smoking | (N=11,452) | (N=35) | (N=47) | **<0.001** | (N=11,495) | (N=17) | (N=21) | **<0.001** | (N=11,398) | (N=79) | (N=57) | **<0.001** |
| Yes | 3,286(29) | 15(43) | 27(57) | | 3,304(29) | 10(59) | 13(62) | | 3,268(29) | 39(49) | 21(37) | |
| No | 8,166(71) | 20(57) | 20(43) | | 8,191(71) | 7(41) | 8(38) | | 8,130(71) | 40(51) | 36(63) | |
| Betel leaf chewing | (N=11,452) | (N=35) | (N=47) | 0.406 | (N=11,495) | (N=17) | (N=21) | 0.857 | (N=11,398) | (N=79) | (N=57) | 0.060 |
| Yes | 4,055(35) | 13(37) | 21(45) | | 4,074(35) | 7(41) | 8(38) | | 4,030(35) | 38(48) | 21(37) | |
| No | 7,397(65) | 22(63) | 26(55) | | 7,421(65) | 10(59) | 13(62) | | 7,368(65) | 41(52) | 36(63) | |

Two-sided $\chi 2$ test; missing values were excluded from the statistical comparison. Fisher's exact p-values were used where cells less than 5.

Abbreviations: Normal = no symptoms, arsenical lesions = arsenicosis symptoms due to arsenic exposure, other = other pathological conditions except arsenical lesions.

N = number.

### Table 3

Adjusted M-OR and 95% CI of the gums by the types of oral cavity arsenical lesions

| Variables | Normal, M-OR (95% CI) | Arsenical lesions, M-OR (95% CI) | Other pathology, M-OR (95% CI) |
|---|---|---|---|
| | 1.00 (Reference) | | |
| Sex (Ref = Male) | | **0.35*(0.13, 0.92)** | 1.09 (0.43, 2.79) |
| Age (years) | | 1.01 (0.98, 1.05) | 1.05** (1.01, 1.08) |
| Education (years) | | | |
| No education (Ref) | | 1.00 | 1.00 |
| 1–4 years | | 1.09 (0.45, 2.65) | 0.94 (0.42, 2.09) |
| 5–16 years | | 0.53 (0.23, 1.23) | 0.50 (0.24, 1.06) |
| BMI (kg/m$^2$) | | 1.00 (0.89, 1.13) | 1.07 (0.97, 1.18) |
| Total arsenic in urine (μg/g) | | | |
| 7.0–134.0 (Ref) | | 1.00 | 1.00 |
| 134.1–286.0 | | 2.01 (0.75, 5.40) | 2.25* (1.02, 4.97) |
| 286.1–5000.0 | | **2.90* (1.11, 7.54)** | 1.95 (0.85, 4.49) |
| Cigarette smoking (yes/no); (Ref, no) | | 1.17 (0.49, 2.83) | 3.20** (1.39, 7.39) |
| Betel leaf chewing (yes/no); (Ref, no) | | 0.86 (0.41, 1.80) | 0.87 (0.47, 1.62) |
| Own cultivation land (yes/no); (Ref, no) | | 1.11 (0.56, 2.21) | 0.83 (0.45, 1.52) |
| TV in home (yes/no); (Ref, no) | | 0.55 (0.24, 1.23) | 0.87 (0.45, 1.66) |
| Occupation | | | |
| Homemaker (Ref) | | 1.00 | 1.00 |
| Non-manual worker | | 0.68 (0.17, 2.70) | 2.11 (0.51, 8.42) |
| Manual worker | | **0.39* (0.15, 0.97)** | 1.85 (0.49, 7.03) |
| N | 11,454 | 35 | 47 |

Abbreviations: CI = confidence interval, M-OR = multinomial odds ratio, N = number, Ref = reference. Normal = no symptoms, arsenical lesions = symptoms due to arsenic exposure, and other pathology = other pathological conditions except arsenical lesions.

* p-value <0.05,

** p-value <0.01.

### Table 4

Adjusted M-OR and 95% CI of the lips by the types of oral cavity arsenical lesions

| Variables | Normal, M-OR (95% CI) | Arsenical lesions, M-OR (95% CI) | Other pathology, M-OR (95% CI) |
|---|---|---|---|
| | 1.00 (Reference) | | |
| Sex (Ref = Male) | | 0.25 (0.50, 1.24) | 1.70 (0.43, 6.69) |
| Age (years) | | 1.03 (0.98, 1.08) | 1.06* (1.01, 1.11) |
| Education (years) | | | |
| No education (Ref) | | 1.00 | 1.00 |
| 1–4 years | | 2.69 (0.86, 8.43) | 1.84 (0.61, 5.58) |
| 5–16 years | | 0.93 (0.27, 3.22) | 1.02 (0.35, 2.93) |
| BMI (kg/m$^2$) | | 1.02 (0.86, 1.21) | 0.99 (0.85, 1.15) |
| Total arsenic in urine (μg/g) | | | |
| 7.0–134.0 (Ref) | | 1.00 | 1.00 |
| 134.1–286.0 | | 2.34 (0.60, 9.14) | 1.82 (0.67, 4.97) |
| 286.1–5000.0 | | 2.68 (0.67, 10.63) | 0.70 (0.19, 2.55) |
| Cigarette smoking (yes/no); (Ref, no) | | 1.35 (0.43, 4.24) | 4.46* (1.24, 15.98) |
| Betel leaf chewing (yes/no); (Ref, no) | | 0.92 (0.33, 2.55) | 0.64 (0.25, 1.60) |
| Own cultivation land (yes/no); (Ref, no) | | 1.22 (0.46, 3.22) | 1.06 (0.44, 2.57) |
| TV in home (yes/no); (Ref, no) | | 0.72 (0.25, 2.08) | 1.13 (0.46, 2.80) |
| Occupation | | | |
| Homemaker (Ref) | | 1.00 | 1.00 |
| Non-manual worker | | 3.20 (0.25, 42.61) | 0.56 (0.09, 3.63) |
| Manual worker | | 1.91 (0.15, 25.06) | 0.43 (0.07, 2.64) |
| N | 11,497 | 17 | 21 |

Abbreviations: CI = confidence interval, M-OR = multinomial odds ratio, N = number, Ref = reference. Normal = no symptoms, arsenical lesions = symptoms due to arsenic exposure, and other pathology = other pathological conditions except arsenical lesions.

* p-value <0.05.

## Table 5

Adjusted M-OR and 95% CI of the tongue by the types of oral cavity arsenical lesions

| Variables | Normal, M-OR (95% CI) | Arsenical lesions, M-OR (95% CI) | Other pathology, M-OR (95% CI) |
|---|---|---|---|
| | 1.00 (Reference) | | |
| Sex (Ref = Male) | | 0.62 (0.31, 1.22) | 1.82 (0.75, 4.46) |
| Age (years) | | **1.03* (1.00, 1.05)** | 0.99 (0.96, 1.02) |
| Education (years) | | | |
| No education (Ref) | | 1.00 | 1.00 |
| 1–4 years | | 0.96 (0.49, 1.84) | 0.81 (0.37, 1.78) |
| 5–16 years | | 0.93 (0.55, 1.57) | 0.63 (0.34, 1.19) |
| BMI (kg/m$^2$) | | 0.98 (0.90, 1.06) | 1.02 (0.93, 1.12) |
| Total arsenic in urine (μg/g) | | | |
| 7.0–134.0 (Ref) | | 1.00 | 1.00 |
| 134.1–286.0 | | 1.61 (0.84, 3.08) | 1.32 (0.66, 2.65) |
| 286.1–5000.0 | | **2.79** (1.51, 5.15)** | 1.56 (0.79, 3.08) |
| Cigarette smoking (yes/no); (Ref, no) | | 1.75 (0.96, 3.19) | 2.49* (1.10, 5.62) |
| Betel leaf chewing (yes/no); (Ref, no) | | 1.26 (0.78, 2.03) | 1.00 (0.56, 1.83) |
| Own cultivation land (yes/no); (Ref, no) | | 0.88 (0.56, 1.39) | 0.73(0.42, 1.26) |
| TV in home (yes/no); (Ref, no) | | 0.80 (0.48, 1.32) | 1.13 (0.64, 1.98) |
| Occupation | | | |
| Homemaker (Ref) | | 1.00 | 1.00 |
| Non-manual worker | | 0.85 (0.31, 2.27) | 1.21 (0.34, 4.33) |
| Manual worker | | 0.56 (0.21, 1.36) | 1.92 (0.66, 5.60) |
| N | 11,400 | 79 | 57 |

Abbreviations: CI = confidence interval, M-OR = multinomial odds ratio, N = number, Ref = reference. Normal = no symptoms, arsenical lesions = symptoms due to arsenic exposure, and other pathology = other pathological conditions except arsenical lesions.

* p-value <0.05,

** p-value <0.01.