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Arsenic exposure alters lung function and airway inflammation in children: A cohort study in rural Bangladesh

Sultan Ahmed [a], Evana Akhtar [a], Adity Roy [a], Ondine S. von Ehrenstein [b], Marie Vahter [c], Yukiko Wagatsuma [d], Rubhana Raqib [a,*]

[a] Infectious Diseases Division, icddr,b, Dhaka 1212, Bangladesh
[b] Departments of Community Health Sciences and Epidemiology, Fielding School of Public Health, University of California Los Angeles, CA 90095, USA
[c] Institute of Environmental Medicine, Karolinska Institutet, SE-171 77 Stockholm, Sweden
[d] Department of Clinical Trial and Clinical Epidemiology, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki 305-8575, Japan

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ABSTRACT

Exposure to arsenic has been associated with increased risk of reduced lung function in adults, but the adverse impacts in early life are unclear. We aim to examine whether prenatal and childhood arsenic exposure is associated with reduced lung function and increased airway inflammation in school-aged children. Children born in the MINIMat cohort in rural Bangladesh were evaluated at 9 years of age ($n = 540$). Arsenic exposure was assessed in urine (U-As) that was collected from mothers during early pregnancy and their children aged 4.5 and 9 years. In the 9-year-old children, lung function was assessed using spirometry and airway inflammation was assessed by the NIOX MINO system. C-reactive protein (CRP) and Clara cell secretory protein (CC16) concentrations were measured in plasma by immunoassays. The U-As concentrations in 9-year-old children were lower (median 53 μg/l) compared to their mothers (median 76 μg/l). Maternal U-As ($\log_2$ transformed) was inversely associated with forced vital capacity (FVC) and forced expiratory volume at 1 s (FEV1) ($\beta = -12$; 95% CI: −22, −1.5; $p = 0.031$ and $\beta = -12$; 95% CI: −22, −1.9; $p = 0.023$, respectively) in all children, and the associations were stronger in boys and among children with adequate height and weight, as well as among those whose mothers had higher percentages of methylarsonic acid (MMA) and lower percentages of dimethylarsinic acid (DMA). U-As ($\log_2$ transformed) at 4.5 and 9 years was positively associated with fractional exhaled nitric oxide (FE_{NO}) concentrations in boys ($\beta = 0.89$; 95% CI: 0.13, 1.66; $p = 0.022$ and $\beta = 0.88$; 95% CI: 0.16, 1.61; $p = 0.017$, respectively) but not in girls. Increased CC16 concentrations were associated with higher lung function indices. In conclusion, our findings suggest that prenatal arsenic exposure is related to impaired lung function, while childhood exposure may increase airway inflammation, particularly in boys.

1. Introduction

Exposure to inorganic arsenic, a well-documented carcinogen (IARC, 2012), is a global public health concern. The main exposure route is through drinking water but also through consumption of certain foods, such as rice. In addition to being a well-established cause of lung, skin, and bladder cancers, arsenic has also been associated with numerous noncancer health effects, including respiratory diseases (Arain et al., 2009; Dangleben et al., 2013; Ferrario et al., 2016; IARC, 2012; Sanchez et al., 2016). Indeed, an increased risk of bronchiectasis was observed in adults with arsenic induced skin lesions in West Bengal, India (Mazumder et al., 2005). Furthermore, in an arsenic affected area of Chile, *in utero* and early childhood arsenic exposure has been associated with increased mortality from lung cancer, bronchiectasis, and tuberculosis in adulthood (Smith et al., 2006; Smith et al., 2011).

Early life arsenic exposure has also been associated with increased risk of lower respiratory tract infection and diarrhea in young children (Rahman et al., 2011; Raqib et al., 2009). In New Hampshire, maternal urinary arsenic concentration was related to increased risk of respiratory infections in infants (Farzan et al., 2016). In Bangladesh, *in utero* and early childhood arsenic exposure through drinking water has been associated with increased prevalence of respiratory symptoms like shortness of breath, chronic cough, and wheezing in children (Smith et al., 2013). The risk of pneumonia has been shown to grow with increasing arsenic exposure in children under 5 years of age (George et al., 2015). These effects may be related to arsenic-mediated reduced lung function (Sanchez et al., 2016). In fact, a study in West Bengal reported that high levels of arsenic in drinking water was associated with lower FVC and FEV1 in men with skin lesions (von Ehrenstein et al., 2005). Similar

* Corresponding author at: Immunobiology, Nutrition and Toxicology Laboratory, Infectious Diseases Division, icddr,b, 68 Shaheed Tajuddin Ahmed Sarani, Mohakhali, Dhaka 1212, Bangladesh.
E-mail address: rubhana@icddrb.org (R. Raqib).

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observations were noted in relation to low-to-moderate concentrations of arsenic in drinking water by Bangladeshi adults (Parvez et al., 2013).

A pilot study using a convenience sample and retrospective exposure assessment in northern Chile suggested that prenatal or early childhood arsenic exposure may be related to reduced FVC and FEV1 in adults (Dauphine et al., 2011). Overall, there are few studies suggesting adverse effects of arsenic exposure on lung function in adults, with little or no information available in children. In particular, prospectively collected data on arsenic exposure in early pregnancy, and aspects such as demography, morbidity, and other pregnancy-related factors, are lacking. Therefore, children born in our prospective mother-child cohort (the MINIMat cohort) in rural Bangladesh were followed-up (Ahmed et al., 2014; Gardner et al., 2011) at 9 years of age with the aim of examining potential impacts of prenatal and childhood arsenic exposure on lung function and airway inflammation.

2. Materials and methods

2.1. Study area

The study was conducted in the Matlab subdistrict, a rural area of Bangladesh, 53 km southeast of Dhaka, where icddr,b (an international health research institute based in Dhaka, Bangladesh) maintains a health research and training center with a hospital and four subcenters. Here, the icddr,b has been operating a health and demographic surveillance system (HDSS) covering about 220,000 inhabitants in >140 villages since mid-1966. Demographic and selected health data are updated by community health research workers every 2 months. In the study area, elevated arsenic concentrations in groundwater are common (Rahman et al., 2006). >95% of the population uses groundwater as their main drinking water, retrieved from hand-pumped tube wells (Icddr, 2006). Earlier screening of water arsenic in all the functioning tube wells showed a wide range of arsenic concentrations, with 70% of the wells containing above 10 μg/l (WHO guideline value), 50% above the Bangladesh national standard of 50 μg/l, and 30% above 200 μg/l (Rahman et al., 2006; Vahter et al., 2006). More recently (2013 2014), another survey showed 43% of tube wells containing arsenic above the WHO guideline value, and 34% of tube wells containing more arsenic than the Bangladesh national standard (Nahian, 2016). Thus, over time average arsenic exposure has decreased to some extent due to mitigation activities (switching to deeper tube wells) but still remains elevated (Kippler et al., 2016b).

2.2. Study design and participants

The current study is a part of our ongoing research in Matlab concerning the effects of arsenic and other contaminants in drinking water and food on pregnancy outcomes, as well as child health and development (Ahmed et al., 2014; Gardner et al., 2013; Kippler et al., 2012; Raqib et al., 2009; Vahter et al., 2006). It was nested into a large, randomized, population-based food and micronutrient supplementation trial among pregnant women– the Maternal and Infant Nutrition Interventions, Matlab (MINIMat trial, ISRCTN16581394)-that was conducted between November 2001 and October 2003 and described in detail elsewhere (Persson et al., 2012). The enrolled women ($n = 4436$) were randomly assigned a daily dose of one of three micronutrient supplementations: (i) 30 mg iron and 400 μg folic acid (30Fe400F), (ii) 60 mg iron and 400 μg folic acid (60Fe400F), and (iii) the UNICEF preparation of multiple micronutrients including 30 mg iron and 400 μg folic acid (MM).

We aimed to reassess 640 children at 9 years of age from the MINIMat cohort born between June 2003 and June 2004. The selection criteria of these children were described in detail during the follow-up at 4.5 years of age (Ahmed et al., 2014; Ahmed et al., 2013). Since then, 42 children had migrated from the study area and 47 children were either absent ($n = 8$) or their parents did not give consent to participate ($n = 39$). Finally, 551 children participated in the follow-up study at 9 years of age; of these children, six refused or were unwilling and five were not able to perform the spirometry test. Upon enrollment, children were examined by general physician and were found to be healthy, without any history of immune-related diseases. The distribution of these children among the three arms of the supplementation was 187:186:167 (30Fe400F, 60Fe400F, and MM groups, respectively).

The study was approved by the Research Review and the Ethical Review Committees at icbbr,b, Bangladesh, and the Regional Ethical Committee at Karolinska Institutet, Sweden. Written informed consent was obtained from the legal guardian of each child prior to participation, and the child was free to refrain from any part of the study.

2.3. Assessment of arsenic exposure

Arsenic exposure was assessed based on the concentration of the sum of inorganic arsenic [arsenite (As III), and arsenate (As V)] and its methylated metabolites [methylarsonic acid (MMA) and dimethylarsinic acid (DMA)] in urine, hereinafter referred to as urinary arsenic (U-As). Although the half-life of inorganic arsenic (iAs) in the body is relatively short, the continued daily exposure through water and food results in fairly stable steady-state concentrations in urine in this highly exposed population (Kippler et al., 2016a). Maternal urine in early pregnancy (gestational week 8 [GW8]) and child urine at 4.5 years of age were collected as described previously (Ahmed et al., 2014; Vahter et al., 2006). In the 9-year old children, spot urine samples were collected at the health clinics and were stored at −70 °C.

The arsenic metabolite concentrations in maternal and child urine were measured at the Karolinska Institutet, Sweden, using high-performance liquid chromatography online with hydride generation and inductively coupled plasma mass spectrometry (HPLC-HG-ICPMS). In all maternal and child urine samples, iAs and its methylated metabolite concentrations were above the lower limit of detection, which was 0.2 μg/l for inorganic As (III), MMA, and DMA, and 0.5 μg/l for inorganic As (V). The intra- and inter-assay coefficients of variation were similar, approximately 4% based on a reference urine sample (CRM No.18, National Institute for Environmental Studies, Tsukuba City, Japan). The certified reference value of DMA was 36 ± 9 μg/l (mean ± SD); using the reference material the DMA concentration was 43 ± 1.4 μg/l ($n = 96$), which was similar to that obtained previously (Ahmed et al., 2014; Gardner et al., 2011). In the current study, an additional urine sample was obtained from about 10% of 9-year-old children, 21 days after the first urine collection. We found a good agreement between the two arsenic measures in the urine ($r_s = 0.86$, $p < 0.001$), indicating a steady-state level of excretion in the urine over time due to continuous exposure.

U-As concentration was adjusted to the average specific gravity (1.012 at all time points), measured by a digital refractometer (RD712 Clinical Refractometer; EUROMEX, Arnhem, the Netherlands) to compensate for variation in dilution (Nermell et al., 2008).

2.4. Lung function measurement

Children's lung function was assessed using an electronic spirometer (Chestgraph HI-101, CHEST Ltd., Tokyo, Japan) in accordance with the American Thoracic Society (ATS) recommendation (American ThoracicSociety, 1995). To minimize diurnal variation, lung function was measured in the morning between 7 a.m. and 9 a.m. A trained technician, who was unaware of the children's arsenic exposure, explained the procedure in detail to the participants and let them practice until they felt comfortable. Children rested for at least 10 min after arrival to the sub-centers. Lung function was measured in standing position, using a nose clip and a disposable mouthpiece. Following the demonstration and practice, children were requested to breathe-in as deeply as possible and then blow as hard and long as possible into the spirometer. Children were requested to perform repeated forced vital capacity