Pre- and postnatal arsenic exposure and child development at 18 months of age: a cohort study in rural Bangladesh

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Background Exposure to arsenic through drinking water has been associated with impaired cognitive function in school-aged children in cross-sectional studies; however, there are few longitudinal studies and little information on effects of exposure in early life when the brain is generally most vulnerable.

Methods A longitudinal cohort study beginning in early pregnancy was conducted in rural Bangladesh, where arsenic concentrations in well water vary considerably. We assessed the effects of pre- and postnatal arsenic exposure on development of 2112 children at 18 months of age with Bayley Scales of Infant Development-II (mental and psychomotor development indices), Wolke’s Behavior Rating Scale and maternal report of language. We related the measures of child development to arsenic concentrations in maternal urine in gestational weeks 9 and 30 and child’s urinary arsenic at 18 months of age. Details of socio-economic background, home stimulation and anthropometric measurements of mothers and children were also available.

Results Median maternal urinary arsenic concentration averaged over early and late gestation was 96 μg/l, whereas children’s urine contained 35 μg/l of arsenic. There was no significant effect of any of the arsenic exposure measures on any of the child development measures after controlling for social and economic confounders, child’s age and sex.

Conclusion Contrary to expectations, we found no indications of adverse effects of pre- or postnatal arsenic exposure on child development at 18 months. It remains possible that duration of exposure is critical and that effects will become apparent later in childhood.

Keywords Pregnancy, maternal urine, child urine, mental and psychomotor development, arsenic exposure, drinking water
Introduction

Arsenic is a well-documented toxicant and carcinogen, which often occurs at elevated concentrations in drinking water. Experimental animal studies have shown arsenic’s neurotoxicity, but human data are scarce. A 50-year follow-up of over 600 infants, who survived poisoning by arsenic-contaminated milk, showed effects like mental retardation and neurological diseases. More importantly, recent epidemiological studies in school-aged children reported associations between cognitive or neurobehavioural function and arsenic exposure through drinking water or industrial pollution. However, these studies were all cross-sectional, it is unknown when these associations developed.

The brain is particularly vulnerable to toxic insult during early development and arsenic easily crosses the placenta and may affect fetal neurodevelopment. We therefore studied the longitudinal effects of arsenic exposure in pregnancy on child development at 7 months of age in rural Bangladesh. Although there was significant association between maternal arsenic exposure and reduced birth weight, we found no significant association between maternal urinary arsenic (U-As) in pregnancy and infant problem-solving or motor development. However, we only measured infants’ problem solving and motor development and it is possible that other cognitive functions were affected or with increasing maturity, children would develop new functions that may be affected. Furthermore, undernutrition is highly prevalent in Bangladeshi children in their second year and it might increase children’s vulnerability to arsenic due to low intake of antioxidants and nutrients essential for arsenic metabolism. Arsenic is methylated via one-carbon metabolism to methylvanularic acid (MMA) and dimethylarsinic acid (DMA). High fraction of MMA in urine is an established risk factor for adverse effects in adults. However, little is known about potential effects in early life. The aim of this study is to assess cognitive, motor and language development at 18 months of age, when tests are more predictive of later function than at 7 months of age. We assessed concurrent urinary concentrations of arsenic metabolites as markers of exposure and metabolism.

Methods

Study area and population

The study was located in Matlab, 53 km southeast of Dhaka, Bangladesh. International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B) Health and Demographic Surveillance System (HDSS) routinely collects vital information in the area. Approximately 70% of the 13,286 wells in the area, used by >95% of the population, contained arsenic concentrations >10 μg/l. The water used by the present cohort of pregnant women had a median of 66 μg arsenic/l (10th, 90th percentiles: 1, 410 μg/l).

This study was nested into a large community-based randomized trial (MINIMat) of the effects of food and micronutrient supplementation on pregnancy outcomes and child development. A sub-sample (n = 2853) of the MINIMat cohort, comprising all singleton infants born between May 2002 and December 2003, was selected for developmental assessments at 7 and 18 months of age. Supplements had small benefits on development of infants of mothers with low body mass index (BMI) only, but showed no effect at 18 months of age (Hamadani, personal communication).

Measurements

Exposure assessment

Although water arsenic measures were available, we based exposure assessment on U-As, because tube wells with >50 μg/l arsenic were painted red and families were encouraged to use other wells. Moreover, primipara women in Bangladesh often move to their parent’s house in late pregnancy using other water sources. Furthermore, U-As reflects exposure to arsenic from all sources, including food. We collected urine in early pregnancy, usually in gestational week (GW) 8 (10th, 90th percentiles: 7, 12 weeks), and 30 (29, 33). U-As concentrations in early and late pregnancy were moderately correlated (r = 0.62, n = 1702) and the mean of the two measures was used. To assess postnatal exposure, we measured children’s U-As at 18 months of age.

Spot urine samples were collected from mothers in plastic cups and from children in plastic bags placed in potties. The samples were transferred to polyethylene containers and stored at −70°C until analysis at Karolinska Institute. Maternal urine was analysed for the sum concentration of metabolites of inorganic arsenic, using hydride generation atomic absorption spectroscopy, whereas children’s urine were analysed for concentrations of the different arsenic metabolites (MMA, DMA and remaining unmethylated inorganic arsenic), using high pressure liquid chromatography on line with hydride generation and inductively coupled mass spectrometry (HPLC-ICPMS). We applied adequate quality control, showing excellent agreement between the two methods (r = 0.98; n = 319) as well as with reference materials. U-As concentrations were adjusted for variation in urine dilution by specific gravity (average 1.012 g/ml for mothers’ urine and 1.009 g/ml for the children’s urine), which was less dependent on age, nutritional status and arsenic exposure than was creatinine adjustment.

Socio-economic status and anthropometry

Socio-economic status (SES) information including parental characteristics, family structure, number of...
family possessions, occasional or constant imbalance between income and expenditure in the previous month, and housing quality was collected through home interviews as previously reported. Maternal weight and height were measured at recruitment (about GW 9) and mothers’ BMI—weight (Kg)/height (m)$^2$—was calculated. Birth weight was measured using electronic beam scales, precise to 10 g, and length with an infantometer and head circumference with a non-stretchable tape to the nearest 1 mm. At 18 months of age the child’s weight, height and head circumference were measured by research assistants, according to standard procedures. Children’s heights and weights were converted to standard scores using the WHO growth standards.

### Mental and psychomotor function

Children’s mental and psychomotor development indices (MDI and PDI, respectively) were measured using the revised version of Bayley Scales of Infant Development (BSID-II) by one of the five psychologists at the sub-centre close to their residence at 18 months of age. Psychologists were trained and before the study began the inter-observer reliabilities of each of the five testers with the trainer in 10 children ranged from $r = 0.88$ to $0.99$—intraclass correlations (ICCs)—for both MDI and PDI. The Bayley test is not standardized in Bangladesh, but has been used in recent studies when scores of urban and rural children were in the normal range and good short-term test–retest reliabilities were achieved.

### Language development and home environment

The children were visited at their homes by four interviewers, who assessed their language comprehension and expression based on mothers’ report, using an inventory (Grantam-McGregor and Hamadani, personal communication) based on the MacArthur’s Communicative Development Inventory. At the same visit the interviewers assessed the quality of the home environment, using the Home Observation for Measurement of Environment (HOME). The instrument was previously modified for Bangladesh. For example, to get some variation in this population the cut-off level was reduced to score a positive response in several items; for example, one child’s book was accepted as positive rather than positive response in several items; for example, one child’s book was accepted as positive rather than positive response in several items; for example, one child’s book was accepted as positive rather than positive response, because the child at the time of testing was correlated to MDI ($r = -0.20, P < 0.001$), PDI ($r = -0.15, P < 0.001$) and comprehension ($r = -0.08, P < 0.001$) scores whereas both age ($r = 0.12, P < 0.001$) and sex ($r = 0.11, P < 0.001$) were related to language expression scores.

We therefore controlled for age (and sex for expression) in any analyses relating to those developmental measures. We first categorized mothers’ children’s U-As concentrations into quartiles and conducted one-way analysis of variance (ANOVA) to examine the difference in developmental scores. We then conducted partial correlations between the developmental and socio-demographic variables controlling for age (and sex), and bivariate correlations between U-As concentration and socio-demographic variables to explore possible confounders. Variables that were correlated with any of the developmental scores as well as mothers’ or children’s U-As concentrations were considered to be possible confounders in further analyses. Mothers’ and fathers’ education were highly correlated ($r = 0.63, P < 0.001$) so only mothers’ education was used in the regressions.

To examine the effect of prenatal and early childhood arsenic exposure on child development adjusting for age and any potential confounder, we conducted multiple linear regression analysis of each developmental outcome.

We entered age (and sex) and the child’s U-As in the first step, HOME in the second step, and remaining potential confounders—assets, housing, mother’s education, mother’s BMI (except for expression), gestational age, number of children in the household (except for PDI), birth length and head circumference, 18-month weight-for-height z score (WHZ) and dummy variables representing testers—in the analyses of MDI and PDI and interviewers in the analyses of language comprehension and expression. We entered HOME separately because of its strong association with some of the developmental outcomes. In a similar set of regressions, we entered mean maternal U-As instead of the child’s U-As. Effect sizes were calculated by dividing the regression coefficient by the standard deviation of the sample. We examined interactions between arsenic and SES variables, as well as arsenic and weight-for-height. We also assessed whether the original nutritional supplementation groups modified the arsenic effects.

We examined the possible effect of arsenic metabolism in children by entering the percentage DMA in the regression models after entering child U-As. Finally, we stratified the sample by percentage MMA dichotomizing them at the median and repeating the same regression models to determine if the effect of arsenic in children with high-percentage MMA varied.

We finally examined the combined effect of arsenic exposure during pregnancy and childhood by...
comparing children exposed to the highest quartile of arsenic in both periods with those exposed to the lowest quartile at the same times. We entered dummy variables for high and low exposure instead of the arsenic concentration variables in the multiple regressions.

**Ethics**

Informed written consent was obtained from mothers at enrollment and again for the tests on the children at age 18 months. The project was approved by ICDDR,B’s research and ethical review committees and the Ethical Committee at the Karolinska Institute.

The parallel arsenic screening project painted the tube wells red if they contained arsenic levels >50 μg/l and green if it was below that and the residents were encouraged to take water from green-painted wells whenever possible. Pregnant women were given priority for mitigation options.44

**Results**

Of the total 2853 children, 2112 (72%) had their development assessed at 18 months of age. Main reasons for loss to follow-up were being away from home on visits (n = 351, 47% of all 741 lost to follow-up), refusal (n = 185, 25%), death (n = 89, 12%), moving out of area (n = 52, 7%), disability (n = 5, 1%) and illness at the time of testing (n = 59, 8%). The non-tested children had slightly lower birth weights [mean ± standard deviation (SD): 2644 ± 452 vs 2698 ± 393; 95% confidence interval (CI) of mean difference 18.6, 89.2; P = 0.003] and smaller head circumference (32.3 ± 2.0 vs 32.5 ± 1.7; 95% CI 0.02, 0.3; P = 0.03) than those tested.

Of the 2112 children tested at 18 months of age, 2009 had data on U-As. One child with extremely high U-As (1800 μg/l; meeting criteria for outlier) was excluded and analyses were then based on 2008 children, 1702 had information on their mothers’ U-As for 2008 children, 1702 had information on their mothers’ U-As for 364 (32.3, 18.1–69.9; Mann–Whitney U-test P = 0.199, 2.7; PDI: −0.09, −3.0, 2.8; comprehension: 0.81, −0.91, 2.5; expression: −0.005, −0.06, 0.06). In case arsenic affected pre- or postnatal child growth or gestational age, all the regressions were repeated without birth size, gestational age and current nutritional status, but the relation with arsenic remained non-significant. Moreover, no effect of arsenic metabolism or nutritional supplementation in pregnancy was found.

Finally, in order to assess the robustness of our findings considering the loss to follow-up, we repeated the multiple regressions using inverse probability weighting.45 We estimated the probability of being tested using a logistic regression and used the inverse of the predicted probability as weights in the multiple linear regressions and the results did not change.
Discussion
This is the first longitudinal study relating early-life arsenic exposure to child development. In bivariate analyses, prenatal arsenic exposure was related to MDI and language development at 18 months of age, whereas exposure in early childhood was related to all four developmental outcomes (MDI, PDI, language comprehension and expression). However, after controlling for social background none of associations remained significant and the effect sizes were minimal. Furthermore, nutritional status or socio-economic background did not modify the effect of arsenic exposure on child development.

Although there was considerable loss to follow-up, little difference between lost and tested children was found. The lost to follow-up children had slightly lower birth-weights and head circumferences, but neither had an independent effect on child development outcomes and they did not modify the effect of arsenic. Furthermore, adjusting for the characteristics of the lost to follow-up children through inverse probability weighting did not change the results. It is, therefore, unlikely that these small differences biased the findings.

There are no Bangladeshi standardized tests for this age group, but BSID-II has been used in previous studies here and appears to be valid in this population. In the present study the scores correlated with SES and nutritional status in theoretically expected ways. The language test was developed for Bangladeshi children based on the mothers’ report, which is recognized as a valid method and has been used in several studies in developing countries.

### Table 1 Characteristics of the study cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole sample Mean ± SD or % (n)</th>
<th>Sample analysed for child arsenic Mean ± SD or % (n = 1745)</th>
<th>Sample analysed for mother’s arsenic Mean ± SD or % (n = 1555)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor housing</td>
<td>21 (2005)</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Income–expenditure deficit</td>
<td>18 (2004)</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Assetsa</td>
<td>0.31 (−0.07, 1.9) (2005)</td>
<td>0.23 (−1.9, 1.8)</td>
<td>0.21 (−1.9, 1.9)</td>
</tr>
<tr>
<td>Fathers’ education (&lt;5th grade)</td>
<td>43 (2009)</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Mothers’ education (&lt;5th grade)</td>
<td>44 (2009)</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Mothers’ BMI (Kg/m²)</td>
<td>20.1 ± 2.6 (2002)</td>
<td>20.1 ± 2.6</td>
<td>20.1 ± 2.6</td>
</tr>
<tr>
<td>Arsenic in mothers’ urine; mean of GW 8 and 30 (µg/l)a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>96.3 (46, 219) (1703)</td>
<td>96.3 (46.6, 218.9)</td>
<td>94.4 (45, 216)</td>
</tr>
<tr>
<td><strong>Children’s characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>53 (2009)</td>
<td>53</td>
<td>51</td>
</tr>
<tr>
<td><strong>Birth measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (g)</td>
<td>2699.2 ± 390.1 (1910)</td>
<td>2700.0 ± 395.2</td>
<td>2702.0 ± 395.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>47.8 ± 2.1 (1908)</td>
<td>47.8 ± 2.1</td>
<td>47.8 ± 2.1</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>32.5 ± 1.7 (1909)</td>
<td>32.5 ± 1.7</td>
<td>32.5 ± 1.7</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.1 ± 1.6 (2008)</td>
<td>39.2 ± 1.6</td>
<td>39.2 ± 1.6</td>
</tr>
<tr>
<td><strong>18-month measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (months)</td>
<td>18.6 ± 1.2 (2009)</td>
<td>18.5 ± 1.1</td>
<td>18.5 ± 1.1</td>
</tr>
<tr>
<td>HAZ</td>
<td>−2.0 ± 1.05 (1873)</td>
<td>−2.0 ± 1.05</td>
<td>−2.0 ± 1.06</td>
</tr>
<tr>
<td>WAZ</td>
<td>−1.6 ± 1.0 (1874)</td>
<td>−1.6 ± 1.0</td>
<td>−1.6 ± 1.0</td>
</tr>
<tr>
<td>WHZ</td>
<td>−0.9 ± 1.0 (1875)</td>
<td>−0.9 ± 1.0</td>
<td>−0.9 ± 1.0</td>
</tr>
<tr>
<td>MDI</td>
<td>78.9 ± 12.3 (2009)</td>
<td>78.9 ± 12.3</td>
<td>78.7 ± 12.9</td>
</tr>
<tr>
<td>PDI</td>
<td>93.8 ± 13.4 (2009)</td>
<td>93.7 ± 13.5</td>
<td>93.6 ± 13.7</td>
</tr>
<tr>
<td>Comprehension</td>
<td>38.3 ± 7.7 (1965)</td>
<td>38.1 ± 7.6</td>
<td>38.0 ± 7.6</td>
</tr>
<tr>
<td>Expressiona</td>
<td>11.0 (7, 15) (1964)</td>
<td>10.0 (7, 15)</td>
<td>10.0 (7, 15)</td>
</tr>
<tr>
<td>Total HOME</td>
<td>83.6 ± 7.0 (1959)</td>
<td>83.5 ± 7.0</td>
<td>83.5 ± 7.1</td>
</tr>
<tr>
<td>Arsenic in child’s urine (µg/l)a</td>
<td>34.6 (18, 80.2) (2008)</td>
<td>35.0 (18.2, 80.8)</td>
<td>34.4 (18.2, 78.9)</td>
</tr>
</tbody>
</table>

aMedian, interquartile range.
BMI, body mass index; MDI, mental development index, PDI, psychomotor development index; HAZ, height for age z score; WAZ, weight for age z score; WHZ, weight for height z score; HOME, home observation for measurement of environment.
Table 3  Bivariate associations of maternal and child characteristics with mean maternal and child arsenic exposure and developmental outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mother's Mean U-As (log)</th>
<th>Child's measures</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>U-As (log) 18 months</td>
<td>MDI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s BMI</td>
<td>0.07**</td>
<td>-0.03</td>
<td>0.08**</td>
<td>0.09**</td>
<td>0.07**</td>
</tr>
<tr>
<td>Mother’s education</td>
<td>-0.10**</td>
<td>-0.07**</td>
<td>0.23**</td>
<td>0.14**</td>
<td>0.29**</td>
</tr>
<tr>
<td>Father’s education</td>
<td>-0.10**</td>
<td>-0.06**</td>
<td>0.21**</td>
<td>0.15**</td>
<td>0.30**</td>
</tr>
<tr>
<td>Income/expenditure deficit</td>
<td>-0.008</td>
<td>0.03</td>
<td>0.09**</td>
<td>0.08**</td>
<td>0.22**</td>
</tr>
<tr>
<td>Assets</td>
<td>-0.11**</td>
<td>-0.07**</td>
<td>0.25**</td>
<td>0.17**</td>
<td>0.33**</td>
</tr>
<tr>
<td>Housing</td>
<td>-0.19**</td>
<td>-0.10**</td>
<td>0.15**</td>
<td>0.08**</td>
<td>0.17**</td>
</tr>
<tr>
<td>Gestational age</td>
<td>-0.04</td>
<td>-0.06**</td>
<td>0.10**</td>
<td>0.15**</td>
<td>0.09**</td>
</tr>
<tr>
<td>Birth weight (gm)</td>
<td>-0.04</td>
<td>-0.03</td>
<td>0.13**</td>
<td>0.12**</td>
<td>0.09**</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>-0.04</td>
<td>-0.06**</td>
<td>0.10**</td>
<td>0.12**</td>
<td>0.10**</td>
</tr>
<tr>
<td>Birth head circumference</td>
<td>-0.06**</td>
<td>-0.08**</td>
<td>0.10**</td>
<td>0.11**</td>
<td>0.13**</td>
</tr>
<tr>
<td>HAZ at 18 months</td>
<td>-0.01</td>
<td>0.002</td>
<td>0.23**</td>
<td>0.28**</td>
<td>0.22**</td>
</tr>
<tr>
<td>WAZ at 18 months</td>
<td>-0.05</td>
<td>-0.04</td>
<td>0.23**</td>
<td>0.25**</td>
<td>0.22**</td>
</tr>
<tr>
<td>WHZ at 18 months</td>
<td>-0.05**</td>
<td>-0.06**</td>
<td>0.15**</td>
<td>0.15**</td>
<td>0.15**</td>
</tr>
<tr>
<td>HOME</td>
<td>-0.17**</td>
<td>-0.17**</td>
<td>0.27**</td>
<td>0.19**</td>
<td>0.60**</td>
</tr>
<tr>
<td>No. of children &lt;6 yrs</td>
<td>0.13**</td>
<td>0.13**</td>
<td>-0.05**</td>
<td>-0.04</td>
<td>-0.06**</td>
</tr>
</tbody>
</table>

*Pearsons correlations.
**Partial correlations controlling for age.
***Partial correlations controlling for age and sex.

*BMI, body mass index; MDI, mental development index; PDI, psychomotor development index; HAZ, height for age z score; WAZ, weight for age z score; WHZ, weight for height z score; HOME, home observation for measurement of environment; U-As, urinary arsenic.
### Table 4 Regression coefficients and 95% CI for the effect of child urinary arsenic (logged μg/l) on the developmental outcomes, adjusting for age (and sex for expression), HOME and other potential confounders

<table>
<thead>
<tr>
<th>Covariates used</th>
<th>MDI $n = 1745$</th>
<th>P-value</th>
<th>PDI $n = 1745$</th>
<th>P-value</th>
<th>Language comprehension, $n = 1142$</th>
<th>P-value</th>
<th>Language expression, $n = 1142$</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Arsenic effect adjusting for age (and sex for expression)</td>
<td>$-1.0 (-2.3, 0.3)$</td>
<td>0.123</td>
<td>$-1.2 (-2.6, 0.3)$</td>
<td>0.110</td>
<td>$-2.6 (-3.7, 1.6)$</td>
<td>$&lt;0.001$</td>
<td>$-0.06 (-0.09, 0.03)$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>2. Arsenic effect adjusting for step 1 and HOME</td>
<td>$0.18 (-1.1, 1.4)$</td>
<td>0.782</td>
<td>$-0.2 (-1.6, 1.2)$</td>
<td>0.756</td>
<td>$-0.8 (-1.6, 0.07)$</td>
<td>0.073</td>
<td>$-0.02 (-0.05, 0.006)$</td>
<td>$0.122$</td>
</tr>
<tr>
<td>3. Arsenic effect adjusting for step 1 and 2 and all other potential confounders</td>
<td>$0.3 (-0.9, 1.5)$</td>
<td>0.640</td>
<td>$-0.07 (-1.5, 1.3)$</td>
<td>0.916</td>
<td>$0.25 (-0.6, 1.0)$</td>
<td>0.542</td>
<td>$-0.001 (-0.03, 0.03)$</td>
<td>$0.929$</td>
</tr>
</tbody>
</table>

$R^2$ | 0.16 | 0.10 | 0.50 | 0.31

Other significant covariates | Age, gestational age, HOME, WHZ, mother’s education, assets and Bayley testers | Age, gestational age, HOME, WHZ, assets and Bayley testers | HOME and interviewers | Age, sex, HOME, assets and interviewers

Step 1: age (and sex for language expression) and child urinary arsenic entered.
Step 2: HOME entered.
Step 3: All other potential confounders (assets, housing, mother’s education, mother’s BMI (except for expression), gestational age, number of children in the household (except for PDI), birth length and head circumference, 18-month WHZ, and dummy variables for testers or interviewers) entered.

MDI, mental development index; PDI, psychomotor development index; WHZ, weight for height z score; HOME, home observation for measurement of environment.

### Table 5 Regression coefficients and 95% CI for the effect of mother’s U-As (logged μg/l) on the developmental outcomes adjusting for age (and sex for expression), HOME and other potential confounders

<table>
<thead>
<tr>
<th>Covariates used</th>
<th>MDI $n = 1555$</th>
<th>P-value</th>
<th>PDI $n = 1555$</th>
<th>P-value</th>
<th>Language comprehension, $n = 991$</th>
<th>P-value</th>
<th>Language expression, $n = 992$</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Arsenic effect adjusting for age (and sex for expression)</td>
<td>$-1.3 (-2.7, 0.1)$</td>
<td>0.075</td>
<td>$-1.1 (-2.7, 0.5)$</td>
<td>0.191</td>
<td>$-3.6 (-4.8, -2.4)$</td>
<td>$&lt;0.001$</td>
<td>$-0.08 (-0.1, -0.04)$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>2. Arsenic effect adjusting for step 1 and HOME</td>
<td>$0.18 (-1.2, 1.6)$</td>
<td>0.801</td>
<td>$0.2 (-1.4, 1.8)$</td>
<td>0.817</td>
<td>$-1.2 (-2.2, -0.25)$</td>
<td>0.014</td>
<td>$-0.02 (-0.05, 0.007)$</td>
<td>$0.136$</td>
</tr>
<tr>
<td>3. Arsenic effect adjusting for step 1 and 2 and all other potential confounders</td>
<td>$0.5 (-0.9, 1.8)$</td>
<td>0.526</td>
<td>$0.3 (-1.3, 1.9)$</td>
<td>0.729</td>
<td>$-0.3 (-1.3, 0.6)$</td>
<td>0.506</td>
<td>$-0.009 (-0.04, 0.02)$</td>
<td>$0.582$</td>
</tr>
</tbody>
</table>

$R^2$ | 0.16 | 0.10 | 0.49 | 0.30

Other significant covariates | Age, gestational age, HOME, WHZ, assets and Bayley testers | Age, gestational age, HOME, WHZ, assets and Bayley testers | Age, HOME and interviewers | Age, sex, gestational age, HOME, WHZ, assets and interviewers

Step 1: age (and sex for language expression) and mother’s urinary arsenic entered.
Step 2: HOME entered.
Step 3: All other potential confounders (assets, housing, mother’s education, mother’s BMI (except for expression), gestational age, number of children in the household (except for PDI), birth length and head circumference, 18-month WHZ, and dummy variables for Bayley testers or language interviewers) entered.

MDI, mental development index; PDI, psychomotor development index; WHZ, weight for height z score; HOME, home observation for measurement of environment.
to assess motor and language development. The language inventory used in this study had good test–retest reliability and concurrent validity (Grantham-McGregor and Hamadani, personal communication). Although there were five psychologists they were rotated around the study area throughout the study and we controlled for tester in the analyses. Hence they are unlikely to affect the results.

We based the exposure assessment on the U-As concentration because it captures the actual exposure from both water and food and thus provides a more reliable exposure measure than water arsenic concentrations, which are used in most epidemiological studies on arsenic-related health effects. To compensate for more long-term variability we included measurements of maternal urine in both early and late gestation. We considered using arsenic in toenail samples, which represent exposure over a few months, but most women used light sandals or no shoes, and the contamination risk from soil and water would be difficult to overcome.

This was a large, population-based study, including children with individual measures of pre- and postnatal arsenic exposure. We were able to show significant effects of several covariates including age, gestational age, HOME, WHZ, mother’s education and assets. The developmental tests were reliable and sensitive; the effect sizes and estimates of their standard errors were very small and ruled out effects as small as 0.037 \( z \)-scores, therefore the absence of an effect of arsenic exposure appears to be valid and it is highly unlikely that our conclusions were due to lack of power.

The lack of effect of prenatal arsenic exposure on child development at 18 months of age concurs with our findings of no effect on problem-solving ability and motor development at 7 months of age in the same children. Similarly, in India, life-time exposure to arsenic-contaminated water, including that used by pregnant mothers, was not related to cognition in 5–10-year-old children. However, children’s U-As concentration was associated with small decrements in their intellectual function. Other cross-sectional studies involving school-aged children reported associations between cognition and concurrent arsenic exposure via drinking water.

Duration of exposure may be a critical factor in causing cognitive deficits. The finding that arsenic exposure had smaller effects on cognition at 6 years than at 10 years of age supports this hypothesis. It is also possible that only higher cognitive functions that develop with increasing age are affected. Absence of any prenatal arsenic neurotoxicity is in contrast to many neurotoxic chemicals, for example lead and methylmercury, which largely exert their effects before birth when most of the basic brain structures are laid down, and in the early postnatal period when neuron proliferation and migration take place.

However, endocrine disrupting and epigenetic substances like arsenic may especially be hazardous during development of synaptic connections, receptors and transmitter systems, which continue for years after birth and for the epigenetic imprinting, causing long-term consequences.

Breast feeding decreases the risk of early-life arsenic exposure, as breast milk contains very little arsenic and also seems to promote efficient arsenic methylation. In this study, 92% of the children were partly breastfed at 12 months, and this probably explains lower U-As in children than their mothers.

Although folic acid facilitates the methylation of arsenic, found only marginal effect of folate status on arsenic methylation in the studied pregnant women. Still, it remains possible that the folic acid supplementation, used by all studied women in pregnancy, protected the fetus from arsenic toxicity. The children, however, were not supplemented and generally had poor nutritional status, and showed an age-related decrease in arsenic methylation efficiency.

Manganese is another prevalent neurotoxic metal in the drinking water in Bangladesh, and one study has reported its association with low IQ in older children. In a parallel study we found that water concentrations of manganese and arsenic were inversely related. It is therefore possible that manganese could have reduced any association between arsenic and child development.

Poorer families generally had higher arsenic exposure and the effect of poverty on child development is well documented. Psychosocial stimulation at home was particularly important for the child’s development and similar findings have been reported in many countries. When we adjusted for socioeconomic conditions all associations between arsenic exposure and test scores disappeared, showing that measured associations between arsenic and child development may be due to numerous confounding factors. Therefore, further research is warranted to clarify the effect of arsenic, alone or in combination with other toxic substances, at a later age.

Conclusion

Contrary to our hypothesis we did not detect effects of pre- or postnatal arsenic exposure on children’s development at 18 months of age. We intend to continue following these children to determine whether effects become apparent in later childhood.

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Conflict of interest: None declared.

KEY MESSAGES

- This is the first longitudinal study relating pre- and postnatal arsenic exposure to early child development.
- Children in Matlab, Bangladesh, are exposed to high levels of arsenic.
- Poorer families generally had a higher arsenic exposure.
- No association was observed between pre- or postnatal arsenic exposure and child development at 18 months of age, after adjusting for socio-economic background.

References


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