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Original Contribution

Arsenic Exposure During Pregnancy and Size at Birth: A Prospective Cohort Study in Bangladesh

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The authors evaluated the association of prenatal arsenic exposure with size at birth (birth weight, birth length, head and chest circumferences). This prospective cohort study, based on 1,578 mother-infant pairs, was conducted in Matlab, Bangladesh, in 2002–2003. Arsenic exposure was assessed by analysis of arsenic in urine collected at around gestational weeks 8 and 30. The association of arsenic exposure with size at birth was assessed by linear regression analyses. In analysis over the full range of exposure (6–978 μg/L), no dose-effect association was found with birth size. However, significant negative dose effects were found with birth weight and head and chest circumferences at a low level of arsenic exposure (<100 μg/L in urine). In this range of exposure, birth weight decreased by 1.68 (standard error (SE), 0.62) g for each 1-μg/L increase of arsenic in urine. For head and chest circumferences, the corresponding reductions were 0.05 (SE, 0.03) mm and 0.14 (SE, 0.03) mm per 1 μg/L, respectively. No further negative effects were shown at higher levels of arsenic exposure. The indicated negative effect on birth size at a low level of arsenic exposure warrants further investigation.

arsenic; Bangladesh; birth weight; cohort studies; maternal exposure; urine

Abbreviations: GW, gestational week; HDSS, health and demographic surveillance system; ICDDR,B, International Centre for Diarrhoeal Disease Research, Bangladesh; MINIMat, Maternal and Infant Nutrition Interventions, Matlab; SD, standard deviation; SE, standard error.

Size at birth is an important determinant of morbidity and mortality in early childhood (1, 2), as well as of chronic diseases in adulthood (3, 4). The intrauterine and early childhood periods are the most biologically sensitive windows for chemicals that may impair growth and organ development. Even the common environmental concentrations of pollutants that would otherwise be harmless might be harmful during early child development (5). Millions of people worldwide, particularly in Bangladesh and West Bengal, India, are using tube-well water with elevated concentrations of arsenic, often due to dissolution of naturally occurring arsenic in the bedrock or by anthropogenic emissions (6–8). Arsenic is a potent and highly reactive toxicant and carcinogen, and there is increasing concern that it may adversely affect intrauterine and child development.

Arsenic easily crosses the placenta in both animals and humans (9, 10), and thus fetuses may be exposed to arsenic. Several studies suggest association between arsenic exposure and adverse pregnancy outcomes, such as spontaneous abortion and stillbirth, and infant death (11–15). A few studies have suggested a negative association between arsenic exposure and birth weight. An overall 29-g reduction of birth weight was observed in an arsenic-exposed area in Taiwan, where the household members used well water with arsenic concentrations varying between undetectable levels and 3,590 μg/L (16). In Chile, a nonsignificant difference of 57 g of birth weight was detected between Antofagasta and Valparaiso, with drinking water arsenic concentrations around 40 μg/L and below 1 μg/L, respectively (17). These studies were ecologic in design, and therefore the differences presented might be biased. They also lack information on other measurements of birth anthropometry. Therefore, the objective of our study was to evaluate the association between individually assessed arsenic exposures in a cohort

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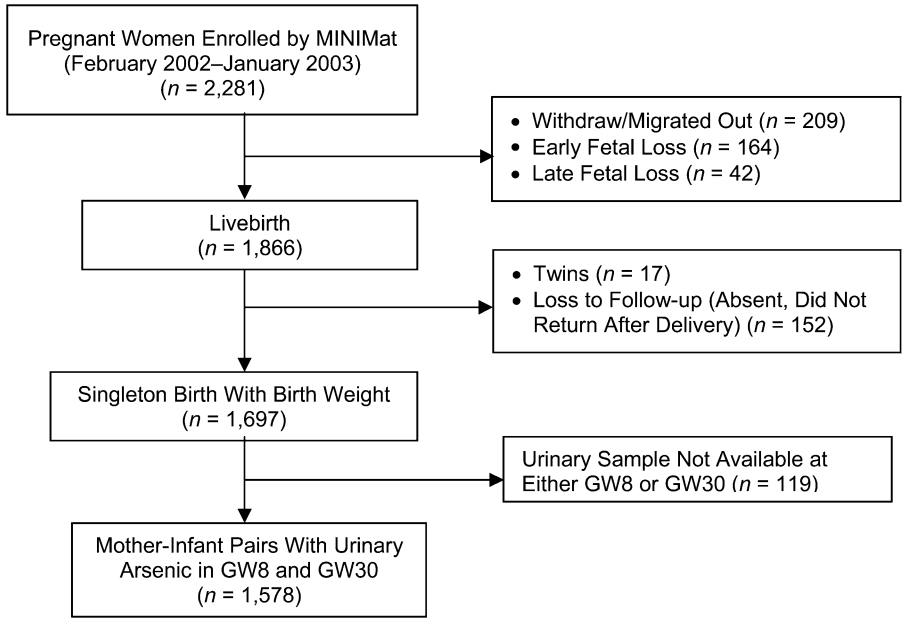

Figure 1. Study participation of the pregnancy cohort based on availability of urine arsenic concentrations at gestational weeks 8 and 30 and measurement of size at birth in Matlab, Bangladesh, 2002–2003. GW, gestational week; MINIMat, Maternal and Infant Nutrition Interventions, Matlab.

of pregnant women in Matlab, Bangladesh, and size at birth (birth weight, birth length, head circumference, and chest circumference).

MATERIALS AND METHODS

Study area

The study was conducted in the Matlab area located 53 km southeast of Dhaka, where the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), has a rural field research station and has been running a health and demographic surveillance system (HDSS) since 1966. Community health research workers visit every household monthly to update vital events in the families. In the area, about 70% of tube wells had an arsenic concentration exceeding the World Health Organization's guideline value of 10 μg/L (18). This study was conducted in the part of the area (about 110,000 inhabitants) where ICDDR,B provides health service to women of reproductive ages and children under 5 years of age.

Study design and subjects

This prospective cohort study was nested into a supplementation trial (Maternal and Infant Nutrition Interventions, Matlab (MINIMat), Study) that enrolled pregnant women from November 2001 to October 2003. Pregnancies were identified at the monthly household visits of community health research workers, who offered a urine pregnancy test to women who had missed a menstrual period. All women with a positive test were invited to visit their health center for further assessment. Women were enrolled in the MINIMat Study if the following eligibility criteria had been met: viable fetus by ultrasound examination, gestational age of less than 13 weeks, women had no severe illness, and women had consented to participation.

Starting in January 2002, women with a pregnancy-positive test were requested to donate a urine sample for arsenic analysis. In addition to this urine sample, commonly collected around gestational week (GW) 8, urine samples were also obtained around GW30 during visits for an antenatal check-up at a health center. To cover a full year of potential variations in arsenic exposure and size at birth, our study included women identified as pregnant from February 1, 2002, to January 31, 2003, and enrolled in the MINIMat Study. Out of 1,697 women with singleton births where sizes at birth were measured, 1,578 had urinary arsenic concentration data at both GW8 and GW30 and, therefore, were included in this analysis (Figure 1).

Ethical consideration

A concurrent study of arsenic and its health consequences in Matlab (known as the AsMat Study) included interviews of all inhabitants in the study area over 4 years of age about their drinking water history and also assessed the arsenic content in the tube-well water in the area by field kits (18). Tube wells with arsenic levels of greater than 50 μg/L were painted red, and those with arsenic levels of 50 μg/L or less were painted green in accordance with the Bangladesh government program. Pregnant women were advised to drink water from the green tube wells. We were not able to inform individual mothers about their level of arsenic exposure

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measured in urine because of delayed analyses of those samples abroad. The study was approved by the Ethical Review Committee of ICDDR,B.

Exposure assessment

Arsenic exposure was assessed by the concentration of inorganic arsenic and methylated metabolites in urine at around week 8 and week 30 in pregnancy. Although the half-time of arsenic in the body is in the order of a few days only, it is likely that women had reached a steady-state level of excretion of arsenic and its metabolites through urine due to continuous exposure via drinking water. In early pregnancy, the urine samples were collected at the woman's home, and later on the samples were collected at the health facility. When collected at home, the samples were chilled with cooling blocks and transported to the Matlab laboratory where they were stored frozen at −70°C. The details of urine sample collection and temperature maintenance during transportation have been described elsewhere (19). The sum of the inorganic arsenic and methylated metabolites in urine was determined by using hydride generation-atomic absorption spectrophotometry in Sweden (19, 20). The detection limit of this spectrophotometric method was 1.3 ± 0.27 μg/L. We also participated in interlaboratory comparisons of arsenic metabolites in urine to verify the analytical accuracy (21). In order to compensate for variation in the dilution of the urine, caused by variation in fluid intake, time of sampling, temperature, and physical activity, we adjusted the obtained concentrations by specific gravity (the average being 1.012 g/mL). The specific gravity adjustment of urine dilution is less influenced by muscle mass and nutritional status than is the more commonly used creatinine adjustment (22–24).

Outcome and covariate

Outcome information was collected prospectively by a team of workers especially recruited and trained with the data tools for the MINIMat Study. About 40% of birth anthropometry was measured in the health facilities, where delivery took place. For women who delivered at home, a birth notification system was established, and birth sizes were measured by paramedics mostly within 24 hours of birth. Anthropometric data were collected following standard procedures (25). Birth weight was taken by electronic scales (SECA, Hamburg, Germany) with a precision of 10 g. Birth length was measured with a locally made wooden scale with a precision of 1 mm. Circumferences (head and chest) were measured by a tape with precision of 1 mm. We included the adjusted birth anthropometry in the analysis for the variation of measurement time after birth as described elsewhere (26).

Covariate information was obtained from 2 databases (i.e., MINIMat Study and HDSS). In the MINIMat Study, information was collected prospectively during household visits of health workers or during routine visits of women at health facilities. Gestational age was calculated by subtracting the last menstrual period date from the date of birth of the infant. The last menstrual period was obtained by interviewing the woman during the process of pregnancy identification. In the analyses, we included the last menstrual period by ultrasound measurement for the women who could not remember their last menstrual period (26 women). Women's height and weight were taken during the first visit to the respective health center (mostly around GW8). Body mass index was calculated as weight (kg)/height $(m)^2$. Educational status was expressed as the number of years of formal schooling completed by the mother. A wealth score, derived largely from household assets, was created by using principal components analysis and categorized into quintiles (27). The history of betel-nut chewing and/or tobacco smoking was obtained. We obtained information on age and parity from the HDSS databases. Season of birth was categorized as premonsoon (January–May), monsoon (June–September), and postmonsoon (October–December).

Statistical analysis

Arsenic exposure was expressed as the average arsenic concentrations in urine (mean concentration of GW8 and GW30) to obtain an exposure measure representing a large part of the pregnancy. The advantage of having arsenic exposure at 2 measurement points was also taken and used to evaluate the outcome by early and late exposures separately.

Associations between covariates and exposure and outcome were evaluated to identify potential confounders. The level of significance was determined by analysis of variance or by Spearman's correlation coefficient as appropriate for the data being analyzed. A covariate was defined as a potential confounder if it was found to be associated with both exposure and outcome at a significance level of $P \leq 0.20$. Any covariate found to change the effect estimate by 5% or more was included in the multivariate model to adjust for potential confounding. Categorical variables were entered in the model by producing dummy variables.

The association between average arsenic exposure and size at birth was assessed with a least-squared linear regression model analysis evaluating any linear association over the full range of exposure. In addition, exposure and outcome data were examined by plotting scattergraphs that included locally weighted regression scatterplot smoothing for a moving fitted-average line (referred to henceforth as the ''loess line''). The loess line indicated a negative dose effect of arsenic exposure on size at birth in the lower range of exposure (<100 μg/L), after which the line leveled out and no further negative dose effect was observed (Figure 2). The suggested pattern of dose effect in the graphs was statistically tested by modeling size at birth as a function of arsenic concentration (continuous variable), level of exposure (categorical variable with exposure of arsenic at <100 μg/L coded = 0 and at ≥100 μg/L coded = 1), and a variable capturing the interaction between these two variables. Coding the variable ''level of exposure'' to 0 provided an estimation of the dose effect of arsenic in the lower range of exposure. We also evaluated the dose effect of arsenic at the higher level of exposure by reversing the codes of the ''level of exposure'' variable and constructing a new interaction variable. The analytical strategy used in this study has been used elsewhere (28, 29).

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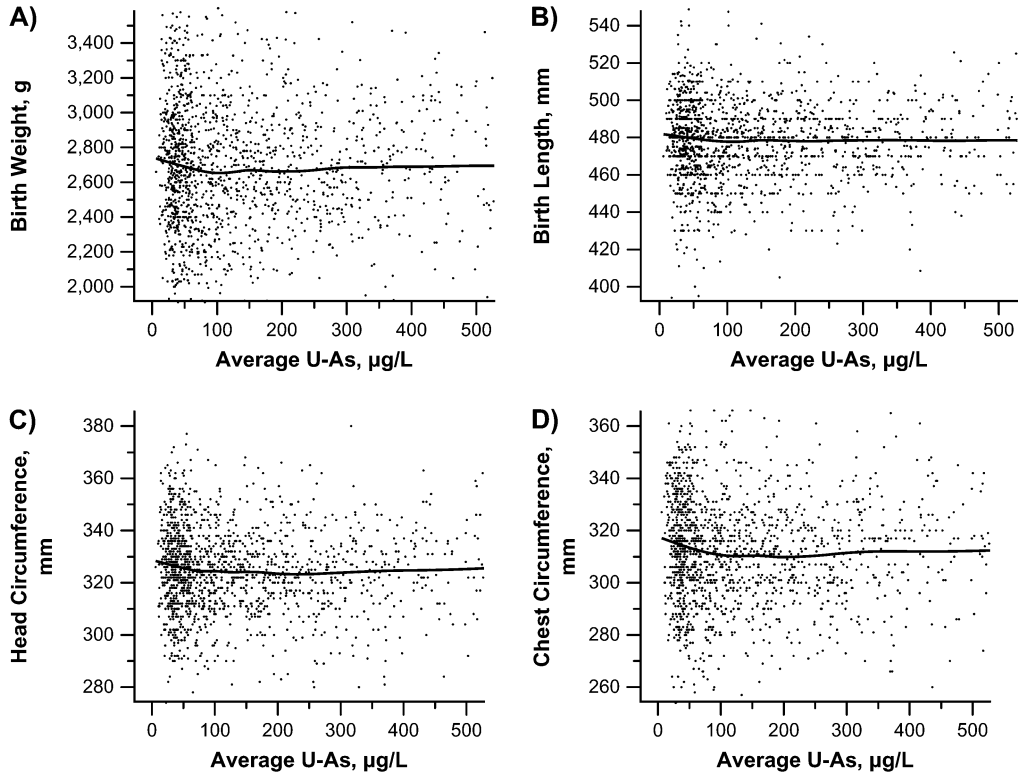

Figure 2. Association between average arsenic exposure and size at birth by locally weighted regression scatterplot smoothing, showing moving average-fitted lines among the pregnant women in Matlab, Bangladesh, 2002–2003. Average U-As, average urinary arsenic concentration of early and late gestational periods. A, birth weight; B, birth length; C, head circumference; D, chest circumference.

To assess the robustness of the dose-effect association between arsenic exposure and size at birth, we also evaluated the multivariate model entering all covariates (asset score, body mass index, height, age, education, season, gestational age at birth, and sex of infant) that were found to be significantly associated with outcome variables in the unadjusted analyses.

The above outlined steps in statistical analyses were also applied when evaluating the effect of low-level arsenic exposure at early (GW8) and late (GW30) gestational periods on size at birth. All the analyses were performed in SPSS, version 14, software (SPSS, Inc., Chicago, Illinois).

RESULTS

In total, 1,578 (93%) mother-infant pairs had data on urinary arsenic concentrations in both early (GW8) and late (GW30) pregnancy. Table 1 presents background characteristics and arsenic concentrations in the urine of study women. Mothers' age ranged from 15 to 44 years with a mean age of 27 years. The mean height and weight of the women at GW8 were 149.6 (standard deviation (SD), 5.2) cm and 45.0 (SD, 6.6) kg, respectively; about one-third of women were malnourished (body mass index < 18.5 kg/m^2). The mean gestational age at birth was 39.3 (SD, 1.7) weeks. Eleven percent of infants were born preterm (<37 weeks). In this cohort, women did not smoke cigarettes; however, about 62% reported betel-nut chewing during pregnancy.

The mean gestational age at the time of urine sample collection in early (GW8) and late (GW30) gestational periods, as determined by last menstrual period, was 8 (SD, 2) weeks and 30 (SD, 6) weeks, respectively. The median arsenic concentration in GW8 was 79 µg/L with a mean of 152 µg/L. In GW30, the median and mean arsenic concentrations were 80 µg/L and 167 µg/L, respectively. Further details about the exposure are published elsewhere (19). Arsenic exposure was not associated with allocation to food and micronutrient randomization groups in the MINIMat Study.

Descriptive data on the outcomes and newborns are given in Table 2. Forty-eight percent of the infants were females. The mean birth weight was 2,681 (SD, 401) g, and 32% had low birth weight (<2,500 g).

The mother's body mass index, education, and asset scores were negatively associated with arsenic exposure and positively associated with size at birth. The mean arsenic concentrations in urine were significantly higher during the postmonsoon period, and size at birth was significantly lower during the same season. Height, age, education, gestational age at birth, and the sex of infants were associated with outcomes but not with exposure. However, betel-nut chewing was associated with arsenic exposure but not with

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Table 1. Characteristics of the Cohort of Pregnant Women in Matlab, Bangladesh, February 2002–January 2003

Variables[a]	No.	%
Age, years		
<25	636	40
25–34	760	48
≥35	182	12
Parity		
0	515	33
1	403	25
2	339	22
≥3	321	20
Body mass index, kg/m^2		
<18.5	474	30
18.5–24	1,026	65
≥25	78	5
Education, total years		
0	549	35
1–5	337	21
>5	692	44
Average urine arsenic concentrations, μg/L[b]		
Mean (SD)	160 (163)	
Median	95	
10th percentile	26	
90th percentile	444	
Lowest	6	
Highest	978	

Abbreviation: SD, standard deviation.
[a] Results are expressed as percentages unless otherwise indicated.
[b] Average arsenic concentrations of early and late gestation.

outcomes (data not shown). Among the potential covariates, body mass index and asset scores were found to change the effect estimate and thus kept in the final multivariate model.

No dose-effect association was observed between arsenic exposure and birth weight when evaluating over the full range of average arsenic exposure (6–978 μg/L) by linear regression analyses (for a 1-μg/L increase of arsenic in urine: β coefficient, −0.01 g; standard error (SE), 0.06). Neither were any of the other anthropometric measurements (length, head circumference, and chest circumference) associated with arsenic exposure (data not shown).

Table 2. Characteristics of Infants of Pregnancy Cohort in Matlab, Bangladesh, 2002–2003

Variables	Female (n = 755), mean (SD)	Male (n = 823), mean (SD)
Birth weight, g	2,633 (378)	2,720 (421)
Birth length, mm	475 (20)	480 (22)
Head circumference, mm	322 (16)	327 (17)
Chest circumference, mm	310 (20)	313 (22)

Abbreviation: SD, standard deviation.

When the loess line indicating negative effects at a low level of average arsenic exposure (51% of women, <100 μg/L) was statistically tested by use of linear regression analysis, a significant dose effect of arsenic exposure on birth weight was confirmed (Table 3). In this range of arsenic exposure, each 1-μg/L increase of arsenic concentration in urine was associated with a 1.68 (SE, 0.62)-g reduction in birth weight consequently, summing up to a 168-g reduction in birth weight when the arsenic exposure exceeded 100 μg/L in urine.

A similar analytical approach was followed in evaluating the effects of arsenic exposure on birth length, chest circumference, and head circumference. In the lower level of arsenic exposure (<100 μg/L), each 1-μg/L increase in average arsenic concentration was associated with a reduction in head circumference of 0.05 (SE, 0.03) mm and in chest circumference of 0.14 (SE, 0.03) mm (Table 3). No association was observed with birth length (Table 3).

In addition to the adjustments for asset scores and body mass index, other covariates (height, age, education, seasonality, gestational age at birth, and sex of infants) were entered into the model. The effect size for birth weight was changed from −1.68 (SE, 0.62) g to −1.48 (SE, 0.56) g for a 1-μg/L increase of arsenic exposure but was still statistically significant as was the interaction term. Introducing these additional covariates did not change the effect estimates for head and chest circumferences.

Evaluation of dose effect in the higher level of exposure by reversing the codes of the categorical variable confirmed that there was no association between arsenic and birth weight at an arsenical exposure level of ≥100 μg/L (for a 1-μg/L increase of arsenic in urine, adjusted for body mass index and asset score: β coefficient, −0.004 g; SE, 0.08) (P = 0.963). Neither did any of the other anthropometric measurements show a dose effect in the higher range of exposure.

When evaluating birth anthropometry by measurement of arsenic at early and late gestational periods, we observed a sharp initial decrease of birth anthropometry with the loess line up to 120 μg/L for GW8 and to 100 μg/L for GW30 (data not shown). Statistical testing of the indicated dose response showed that arsenic exposure in the lower exposure level (<120 μg/L) at GW8 was significantly associated with head and chest circumferences but not with birth weight and birth length. Arsenic exposure in the lower exposure level (<100 μg/L) at week 30 was associated with birth weight and chest circumference but not with head circumference and birth length (Table 4). There was no further reduction of birth anthropometry in the higher exposure level for any of the anthropometric measurements (Table 4).

DISCUSSION

This study evaluated the effect of individually assessed arsenic exposure in pregnant women on size at birth in rural Bangladesh. While there was no dose effect over the full

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Table 3. Linear Regression of Size at Birth in Relation to Average Urine Arsenic Concentrations at Lower and Higher Levels of Arsenic Exposure Among Pregnant Women in Matlab, Bangladesh, 2002–2003

Predicted Variable and Predictor	Unadjusted		Adjusted[a]	
	β Coefficient (SE)	*P* Value	β Coefficient (SE)	*P* Value
Birth weight, g				
U-As concentration[b]	−1.92 (0.64)	0.003	−1.68 (0.62)	0.007
U-As level[c]	−108.59 (44.60)	0.015	−82.42(43.44)	0.058
U-As concentration × U-As level[d]	1.91 (0.65)	0.003	1.68 (0.63)	0.008
Constant	2,782.12 (32.49)	<0.001	2,093.04 (88.15)	<0.001
Birth length, mm				
U-As concentration	−0.07 (0.03)	0.037	−0.06 (0.03)	0.078
U-As level	−2.09 (2.40)	0.384	−0.62 (2.36)	0.792
U-As concentration × U-As level	0.06 (0.03)	0.061	0.05 (0.03)	0.118
Constant	481.55 (2.06)	0.000	459.17 (4.79)	<0.001
Head circumference, mm				
U-As concentration	−0.07 (0.03)	0.017	−0.05 (0.03)	0.041
U-As level	−5.23 (1.91)	0.006	−4.069 (1.88)	0.031
U-As concentration × U-As level	0.07 (0.03)	0.017	0.06 (0.03)	0.040
Constant	328.71 (1.48)	0.000	307.25 (3.81)	<0.001
Chest circumference, mm				
U-As concentration	−0.16 (0.03)	0.000	−0.14 (0.03)	<0.001
U-As level	−9.79 (2.34)	0.000	−8.22 (2.30)	<0.001
U-As concentration × U-As level	0.16 (0.03)	0.000	0.14 (0.03)	<0.001
Constant	321.17 (1.82)	0.000	290.93 (4.66)	<0.001

Abbreviations: SE, standard error; U-As, urinary arsenic.
[a] Adjusted for body mass index and socioeconomic status by asset score.
[b] Average urinary arsenic concentration (μg/L) (mean of gestational weeks 8 and 30).
[c] A categorical variable; lower exposure (<100 μg/L) = 0, higher exposure (≥100 μg/L) = 1.
[d] Interaction term.

range of arsenic exposure, a significant dose effect was found with birth weight in the lower level of exposure. In this range (0–100 μg/L) of exposure, each 1-μg/L increase in urinary arsenic concentration was associated with a 1.68-g reduction in birth weight. The dose effect leveled out, and no additional negative effect was observed when exposure exceeded 100 μg/L. We also observed a 0.05-mm and a 0.14-mm decrease of head and chest circumferences, respectively, for a 1-μg/L increase of arsenic in the exposure range of <100 μg/L concentration in urine.

In this community-based study, exposure and outcome data were prospectively collected, and sample size was reasonably large with wide variation of exposure levels. Details of important covariates that might confound the result were also available for evaluation. Exposure was assessed objectively by measurement of arsenic concentrations in urine. The cohort was recruited over an entire year so that any seasonal variation in exposure and outcome by season would be represented. We have previously demonstrated the advantage of assessing arsenic exposure by measurements of concentrations in urine, compared with water (19), as there is possible additional exposure to arsenic via food. A likely occurrence of using multiple water sources is the fact that many women probably used different water sources after the screening of the wells for arsenic contents (and painting those with high concentrations red); we collected urine samples twice during pregnancy to catch the changes in water sources as far as possible.

The epidemiologic design of the study calls for cautious interpretation of the effect of arsenic at low levels of exposure. The possibility of residual confounding even after adjustment with asset score and body mass index may not be ruled out completely. Even so, further adjustment of biologically important covariates including height, age, education, gestational age, and infant's sex still rendered a significant association with birth size at low exposure levels. We did not measure other concurrent exposure in the study population. The possibility of unmeasured associated exposures at low-dose arsenic levels can not be ruled out. This might particularly be relevant for manganese, which has

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Table 4. Linear Regression of Size at Birth in Relation to Urinary Arsenic Concentrations in Gestational Weeks 8 and 30, at Lower and Higher Levels of Arsenic Exposure Among Pregnant Women in Matlab, Bangladesh, 2002–2003

Predicted Variable and Predictor	Urinary Arsenic in Week 8 (μg/L)		Urinary Arsenic in Week 30 (μg/L)	
	β Coefficient (SE)[a]	*P* Value	β Coefficient (SE)[a]	*P* Value
Birth weight, g				
U-As concentration[b]	−0.59 (0.45)	0.184	−1.71 (0.57)	0.003
U-As level[c]	−61.05 (39.71)	0.124	−38.01 (40.25)	0.345
U-As concentration × U-As level[d]	0.73 (0.45)	0.109	1.58 (80.57)	0.006
Birth length, mm				
U-As concentration	−0.03 (0.02)	0.260	−0.06 (0.03)	0.068
U-As level	−2.34 (2.16)	0.271	2.09 (2.19)	0.339
U-As concentration × U-As level	0.03 (0.02)	0.206	0.04 (0.03)	0.154
Head circumference, mm				
U-As concentration	−0.04 (0.02)	0.027	−0.03 (0.02)	0.250
U-As level	−4.54 (1.72)	0.008	−1.17 (0.74)	0.500
U-As concentration × U-As level	0.05 (0.02)	0.016	0.03 (0.02)	0.299
Chest circumference, mm				
U-As concentration	−0.07 (0.02)	0.004	−0.13 (0.03)	0.000
U-As level	−7.55 (2.10)	0.000	−5.96 (2.13)	0.005
U-As concentration × U-As level	0.08 (0.02)	0.001	0.12 (0.03)	0.000

Abbreviations: SE, standard error; U-As, urinary arsenic.
[a] Adjusted for body mass index and socioeconomic status by asset score.
[b] Urinary arsenic concentration (μg/L) at gestational week 8 or gestational week 30.
[c] Categorical variable; in gestational week 8, lower exposure (<120 μg/L) = 0, higher exposure (≥120 μg/L) = 1; in gestational week 30, lower exposure (<100 μg/L) = 0, higher exposure (≥100 μg/L) = 1.
[d] Interaction term.

been found in high concentrations in tube-well water in Bangladesh (30).

Intrauterine growth depends on multiple factors including maternal nutrition, food, and micronutrient intake during pregnancy; physical activity; and environmental toxic exposures in an interplay with genetic predisposition (31). The mechanisms by which arsenic might affect birth size are not well understood. Arsenic is known to induce oxidative stress by producing free oxygen radicals or perturbation of oxidative defense that may cause placental insufficiency including intrauterine growth retardation (32). Animal studies have documented arsenic as an endocrine disruptor, altering hormone-activated gene transcription mediated by the closely related steroid receptors already at very low doses of exposure (33–35), that may influence the insulin growth factor system, glucose homeostasis, and cellular growth.

Epidemiologic studies of the effect of arsenic on fetal and infant development are scarce, in particular, those addressing effects at low exposure levels. A recent study, based on only 52 pregnant women, reported a significant association between hair arsenic concentrations and birth weight. However, the study population profile was not provided, and it was not clear whether the analyses were adjusted for important covariates such as socioeconomic status and women's anthropometry (36). Further, the hair arsenic concentration may be increased from external use of arsenic-contaminated water. Several studies in Bangladesh have reported increased risk of infant death, blood pressure, and impaired cognitive development at low arsenical exposure levels, supporting our findings of negative effects at low levels of exposure (15, 37, 38). Our report of significantly shorter head circumference may be in line with the reported adverse effect of arsenic exposure on cognitive development in childhood, as found in studies in Bangladesh and elsewhere (38, 39).

As arsenic exposure has been shown to be associated with fetal losses already at low exposure levels (11, 13–15), the effect on birth size found in this study may be underestimated. The negative effect of arsenic on birth weight that we report is on a similar level as what has been reported by cigarette smoking during pregnancy (40). The magnitude of this is, in turn, similar to the maximum of what can be achieved by food supplementation in malnourished women, albeit the latter is an improvement (29) and, therefore, implies being of public health significance. There was no

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further reduction in birth size at a higher level of arsenic exposure. This might be explained partly by the increased proportion of fetal losses at high arsenic exposure. Analysis of the effect of arsenic exposure on fetal losses in this particular cohort is underway.

In conclusion, at a low level of arsenic exposure, we observed a significant negative dose effect of prenatal arsenic exposure on birth weight, head circumference, and chest circumference. The effects on birth size found were robust to adjustment for confounding effect, and the effect estimate observed has public health significance. No additional negative effects were observed as exposure increased further. The indicated negative effect of arsenic already at a low level of exposure warrants further investigations.

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