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Investigating causal relation between prenatal arsenic exposure and birthweight: Are smaller infants more susceptible?

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Abstract

Background—Shortening of gestation and intrauterine growth restriction (IUGR) are the two main determinants of birthweight. Low birthweight has been linked with prenatal arsenic exposure, but the causal relation between arsenic and birthweight is not well understood..

Objectives—We applied a quantile causal mediation analysis approach to determine the association between prenatal arsenic exposure and birthweight in relation to shortening of gestation and IUGR, and whether the susceptibility of arsenic exposure varies by infant birth sizes.

Methods—In a longitudinal birth cohort in Bangladesh, we measured arsenic in drinking water (n=1,182) collected at enrollment and maternal toenails (n=1,104) collected ≤1-month postpartum using inductively coupled plasma mass spectrometry. Gestational age was determined using

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ultrasound at ≤16 weeks' gestation. Demographic information was collected using a structured questionnaire.

Results—Of 1,184 singleton livebirths, 16.4% (n=194) were low birthweight (<2500 g), 21.9% (n=259) preterm (<37 weeks' gestation), and 9.2% (n=109) both low birthweight and preterm. The median concentrations of arsenic in drinking water and maternal toenails were 2.2 μg/L (range: bellow the level of detection [LOD]–1400) and 1.2 μg/g (range: <LOD–46.6), respectively. Prenatal arsenic exposure was negatively associated with birthweight, where the magnitude of the association varied across birthweight percentiles. The effect of arsenic on birthweight mediated via shortening of gestation affected all infants irrespective of birth sizes (β range: 10th percentile= −19.7g [95% CI: −26.7, −103.3] to 90th percentile= −10.9g [95% CI: −18.5, −5.9] per natural log water arsenic increase), whereas the effect via pathways independent of gestational age affected only the smaller infants (β range: 10th percentile= −28.0g [95% CI: −43.8, −9.9] to 20th percentile= −14.9g [95% CI: −30.3, −1.7] per natural log water arsenic increase). Similar pattern was observed for maternal toenail arsenic.

Conclusions—The susceptibility of prenatal arsenic exposure varied by infant birth sizes, placing smaller infants at greater risk of lower birthweight by shortening of gestation and possibly growth restriction. It is important to mitigate prenatal arsenic exposure to improve perinatal outcomes in Bangladesh.

1. BACKGROUND

Low birthweight (<2500 g at birth) is an important population indicator for neonatal mortality and a determinant of infant and childhood morbidity (1). Each year, an estimated 21 million infants are born with low birthweight worldwide, more than half of them are in South Asia (2). In Bangladesh, the incidence of low birthweight is estimated to be 22%, which is among the highest in the world (3), and in rural areas the estimates are as high as 31–47% (4). Low birthweight has two main causal components: preterm birth (<37 weeks of gestation) and intrauterine growth restriction (IUGR), which is commonly assessed as small for gestational age (<10th percentile of the birthweight-for-gestational age sex-specific reference population) (3). These components of low birthweight generally differ in their etiologies and risks of mortality, morbidity and impaired growth (5, 6); therefore, it is important to distinguish between them in order to identify true causal determinants of low birthweight and develop effective public health interventions (6).

An environmental factor potentially implicated in low birthweight is prenatal exposure to inorganic arsenic. Over a hundred million people worldwide are believed to be exposed to inorganic arsenic in drinking water sourced from groundwater at levels higher than the World Health Organization (WHO) recommended level of 10 μg/L.(7) But, the arsenic problem in Bangladesh is perhaps most devastating, as 40 million people, or a quarter of the country's population, are still exposed to higher concentrations of arsenic through drinking water (8). In rural areas, where 70% of the total population live (10), the problem is much more highly prevalent, as 97% of them relies on groundwater for drinking purposes (9).

Arsenic can cross the placenta readily,(11) and prenatal arsenic exposure has been associated with spontaneous abortion,(12–14), preterm birth,(15–17) and intrauterine growth restriction

(18–21). However, the epidemiological evidence for an association between prenatal arsenic exposure and birthweight is less consistent. While ten studies (22–30) reported a null or positive associations between arsenic exposure and birthweight, 14 other studies (16, 17, 20, 21, 31–41), including 6 large prospective cohort studies, reported negative associations. The negative associations reported in those studies were consistent despite the use of different exposure measures in drinking water (17, 33, 35), maternal urine (36, 38, 39, 41), toenail (35), hair (34), whole blood (21, 32, 37), soil around the residence (40), and placental tissue (20). Further, while these studies were largely conducted among populations with frequent exposure to higher levels (>10 μg/L) of arsenic through drinking water in Bangladesh (34–36), India (16), Chile (33), and Taiwan (17), several recent studies in the United States (21, 38, 39) and China (32, 37) have corroborated the negative association among populations exposed to relatively lower levels of exposure.

Most studies have also focused on birthweight as a single entity and have not used a causal framework that includes both shortening of gestation and IUGR for analysis. Mediation analysis can help identify the association between arsenic exposure and birthweight in relation to shortening of gestation and IUGR by decomposing the total effect of arsenic exposure on birthweight into indirect effect via pathways mediated through gestational age and direct effect via pathways independent of gestational age, respectively (42). Therefore, the indirect effect will estimate how much of the effect of arsenic exposure on birthweight will be via changing gestational age, whereas the direct effect will estimate how much of the effect of arsenic exposure on birthweight will be independent of gestational age. In other words, the direct effect will estimate the effect of arsenic exposure on birthweight via pathways other than changing gestational age, which will essentially include any change in birthweight that is also via intrauterine growth restriction. The total effect, estimated as the sum of the direct and indirect effect, will represent the overall effect of arsenic on birthweight. Recently, using structural equation modeling technique, our group identified that prenatal arsenic exposure was negatively associated with birthweight, which primarily mediated via shortening of gestational age. In contrast, the effect of arsenic exposure independent of gestational age was in the positive direction, and not statistically significant (35), highlighting the importance of estimating pathway-specific effects to capture the underlying heterogeneity of this complex exposure-outcome relation.

Previous studies also did not examine whether the susceptibility of arsenic exposure vary by infant birth sizes. A recent study in Mexico identified that prenatal lead exposure lowers birthweight-for-gestational age z-score, and that the magnitude of the association was larger for smaller infants (43). Both arsenic and lead has been implicated in hypoxia (44, 45) and generating oxidative stress (44, 46), which have been linked with the disruption of normal placentation, leading to adverse fetal growth outcomes (47, 48). Built upon these research, we investigated whether prenatal arsenic exposure disproportionately effect infants at the extremes of birthweight distribution. Traditional regression modeling approaches, also known as ordinal least square (OLS) regression, which have been consistently used in previous studies cannot answer this question, as OLS based regression implicitly assumes that the association between arsenic and birthweight is homogenous across birthweight percentiles. In other words, OLS based regression methods estimate the change in mean outcome variable (e.g. birthweight) in relation to the exposure of interest (e.g. arsenic

exposure) and thus, summarizes the effect estimates that might have differed across the range of outcome distribution (e.g. birthweight percentiles), including those with opposing signs (49). This could potentially limit our chance to identify sensitive sub-population, who might be disproportionately affected by the exposure. For example, if arsenic exposure disproportionately affects infants at the tails of birthweight distribution, who are often at a greater risk of perinatal mortality and morbidity (50), that evidence essentially could empower public health interventions.

Quantile regression, on the other hand, allows for the effect of the exposure (e.g. arsenic) to vary across all quantiles of a response variable (e.g. birthweight) distribution and provide a more complete view of possible causal relationships between the exposure and outcome variables (49). Causal mediation modeling techniques can be combined with quantile regression to identify the causal association between prenatal arsenic exposure and birthweight in relation to gestational age across birthweight percentiles (also called quantile causal mediation analysis) (51). This method has been demonstrated previously in social science research (52). Using this modeling approach, we will be able to determine whether prenatal arsenic exposure effects birthweight via shortening gestation as well as intrauterine growth restriction and that whether infants at the tails of birthweight distribution are more susceptible to arsenic exposure. We hypothesized that arsenic exposure will be associated with lower birthweight via shortening gestational age as well as intrauterine growth restriction and that the magnitude of the association will vary by infant birth sizes.

2. METHODS

2.1 Study population

A longitudinal birth cohort was established in Bangladesh between 2008–2011. Community health care workers in the recruitment areas verbally advertised the study in the villages. Pregnant women interested in participating in the study were referred to the clinic, where their eligibility was confirmed. The details of this study, including recruitment and enrollment process were previously described (53). Briefly, women were eligible to participate if they were 18 years or older with an ultrasound confirmed singleton pregnancy of ≤16 weeks' gestation, used a tube well as their primary source of drinking water and had been using the same drinking water source for more than six months, and intended to live in her current residence throughout her pregnancy. Of 1,613 pregnant women innitially recruited, 99 dropped out (n=99), 121 withdrawn from the study, 132 reported miscarriage, 72 reported stillbirth, and 5 reported multiple pregnancies. Complete covariate data were available for 1,180 participants in case of drinking water arsenic exposure and 1,093 participants in case of maternal toenail arsenic exposure. All subjects provided written informed consent before participation. Participants were informed and counseled on safe drinking water options if their water samples contained arsenic above Bangladeshi standard (i.e. <50μg/L). Prenatal care and multivitamins were provided to all participants. All protocols were reviewed and approved by the Human Research Committees at Harvard T.H. Chan School of Public Health and Dhaka Community Hospital Trust.

2.2 Exposure Assessment

Arsenic was measured in drinking water (n=1,182) from tubewells that women identified as their principal water source at the time of enrollment. Details of sample collection and measurement procedures have been previously described.(35) Briefly, water samples were collected in 50-ml polypropylene tubes (BD Falcon, BD Bioscience, Bedford, MA) and preserved with Reagent Grade nitric acid (Merck, Germany) to a pH<2. Field blanks were collected and analyzed for arsenic to evaluate exogenous contaminants. Samples were kept at room temperature until analysis by inductively coupled plasma mass spectrometry (ICP-MS) following US EPA method 200.8 (Environmental Laboratory Services, North Syracuse, New York). The average percent recovery of arsenic was 101% (range: 92%–110%). Samples with arsenic concentrations below the limit of detection (LOD) (n=242) ranging from 0.5–1.0 μg/L were reassigned half the value of the LOD for statistical analysis.

Arsenic was also measured in maternal toenails collected ≤1-month post-partum. We collected toenail material from all 10 toes and pooled them for analysis. Pooled toenail samples were sonicated in 1% Triton X-100 solution (Sigma-Aldrich, Inc., St. Louis, MO) and rinsed repeatedly with Milli-Q water (Millipore Corporation, Billerica, MA) to remove external contamination before microwave acid digestion using Trace Select Ultra Pure nitric acid (Fischer Scientific, Pittsburgh, PA). Digested samples were diluted with Milli-Q water before analyzing for total arsenic using ICP-MS. The reported arsenic concentrations were blank-corrected and normalized using arsenic concentration of certified human hair reference material (CRM Hair; Shanghi Institute of Nuclear Research, China). The average percent recovery and relative standard deviation of CRM hair for arsenic was 94.1% and 5.2% respectively. Toenail clippings were collected from 1,118 mothers at <1-month post-partum with a history of singleton livebirth, 1,093 of them were used in the analysis after excluding samples with toe mass ≤5mg (n=16) and/or relative standard deviation ≥25% (n=9). One samples with arsenic concentrations below the LOD ranging from 0.09–0.7 ng/L were reassigned half the value of LOD for statistical analysis.

2.3 Outcome and covariates

The study involved four scheduled visits occurring at the time of enrollment, around 28th weeks' gestation, at the time of delivery, and ≤1 month post-partum. During those visits trained interviewers used structured questionnaires to collect demographic, medical, and environmental information. All pregnancies were dated either by crown-rump length (CRL) at 7–16 weeks or mean sac diameter (MSD) at 4–6 weeks. Fetal CRL and MSD were measured by a trained family physician by ultrasound using the formulae proposed by Robinson and Hellman, respectively (54, 55). Maternal blood samples were collected at the time of enrollment to measure hemoglobin levels. Maternal height and weight were recorded at first clinic visit and at monthly house visits following enrollment, when they also received prenatal vitamins. To ensure collection of high quality birth measurements, healthcare workers were trained following a standard protocol. All births were attended by trained healthcare workers. Birthweight was measured within 120 minutes after delivery on a pediatric scale calibrated and rounded to the nearest 10 grams before each measurement.

2.4 Statistical Analysis

Arsenic concentrations in drinking water, and maternal toenail were right skewed and subsequently transformed to their natural log. Mean birthweight across categories of all covariates were analyzed using T-test or analysis variance (ANOVA) in bivariate models. The distribution of birthweight was checked and a histogram indicated no gross violation for normality assumption.

Mediation analysis for the association between prenatal arsenic exposure and birthweight was implemented considering gestational age as a mediator for 10th to 90th percentiles of birthweight following the method described by Imai et al, (51). The directed acyclic graph (DAG) in Figure 1 explains the conceptual model for causal mediation analysis (56). We hypothesized that gestational age will lie within the causal pathway between prenatal arsenic exposure and birthweight. We used quantile regressions to model percentiles of birthweight (outcome models) and linear regression to model for gestational age (mediator model). In the schema bellow, equation 1 and equation 2 represents the outcome and mediator model, respectively, where Y represents the outcome, birthweight; M denotes the mediator, gestational age; A denotes exposure, prenatal arsenic exposure; and C denotes the covariates. Following this notation, ($a - a^*$) indicates 1 unit change in exposure from $a^*=0$ to a level $a=1$.

$$Q_Y(\tau|A,M,C)=\theta_0+\theta_1(\tau)A+\theta_2(\tau)M+\theta_2'C \quad (1$$

$$\mathrm{E(M|A,C)}=\beta_0+\beta_1(\mathrm{A})+\beta_2'\mathbf{C} \quad (2)$$

The outcome and mediator models were combined to estimate the direct, indirect and total effects of arsenic exposure on birthweight at 5th to 95th percentiles of birthweight distribution. Analyses were repeated for drinking water arsenic and maternal toenail arsenic. The natural direct effect (NDE) is given by: $\theta_1(\tau)\ (a-a^*)$, which expresses how much the birthweight would change if natural log arsenic exposure were set at level $a=1$ versus level $a^*=0$, but for each individual gestational age were kept at the level it would have taken in the absence of arsenic exposure. The natural indirect effect is given by: $\theta_2(\tau) * \beta_1\ (a-a^*)$, which expresses how much the birth weight would change on average if natural log arsenic exposure were controlled at $a=1$, but gestational age were changed from the level it would take if $a^* = 0$ to the level it would take if $a = 1$. The total effect (TE) is given by: NDE + NIE, which expresses how much the birth weight would change overall for a change in natural log arsenic exposure from level $a^* = 0$ to level $a = 1$. Proportion mediated (PM%) was estimated using the formula, PM%=NIE/TE*100, which expresses how much of the overall effect of arsenic on birthweight is mediated via changing gestational age.

We selected a set of a priori covariates to adjust for the mediator and outcomes models that were previously found to be associated with gestational age and birthweight. Models for gestational age were adjusted for natural log transformed arsenic exposure (continuous), maternal age (continuous), education (no formal education, primary, secondary or higher),

number of past pregnancies (0, 1, ≥2), enrollment BMI (<18.5, 18.5–24.9, >24.9), secondhand smoke (yes, no), and infant sex (male, female), and maternal blood hemoglobin level at enrollment (continuous). The models of birthweight were additionally adjusted for gestational age and included an interaction term between natural log arsenic exposure and blood hemoglobin level. Direct and indirect effects were averaged across all individuals. Bias corrected confidence intervals were estimated from 1000 Monte Carlo draws for nonparametric bootstrap. Analyses assume that conditional on the covariates, there is no confounding of 1) the exposure-outcome relation, 2) exposure-mediator relation, (3) mediator-outcome relation and that (4) there is no effect of the exposure that itself confounds the mediator-outcome relation (42). Analyses were implemented with R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) using the R-package “mediation” (57).

3. RESULTS

Table 1 summarizes demographic characteristics of the study population and their bivariate associations with birthweight. Average birthweight was 2837g (standard deviation: 408g; range: 800–4,800g). Nearly 22% (n=259) of the infants were born preterm (<37 weeks of gestation), 19% (n=223) small-for-gestational age,(58) 16.4% (n=194) low birthweight and 9.2% (n=109) both preterm and low birthweight. Arsenic exposures were relatively modest but spanned a wide range. The median concentrations of arsenic exposure were 2.2μg/L (range: <LOD–1400μg/L) for drinking water arsenic, and 1.2μg/g (range: <LOD–46.6μg/g) for maternal toenail arsenic. Drinking water arsenic concentration showed a modest correlation with maternal toenail arsenic ($\sigma_{spearman}$=0.48; 95% CI: 0.44–0.53).

The adjusted indirect, direct, and total effects of drinking water arsenic exposure on birthweight across birthweight percentiles were presented in Figure 2 (A1–A3) and Supplemental Table 1, whereas the adjusted indirect, direct, and total effects of toenail arsenic on birthweight across birthweight percentiles were presented in Figure 2 (B1–B3) and Supplemental Table 2.. Our results suggested a heterogeneous relation between arsenic and birthweight across birthweight percentiles, which involved pathways mediated through gestational age as well as pathways independent of gestational age. The magnitude of our observed causal relations was consistent regardless of whether arsenic was measured in drinking water or maternal toenails. The indirect effects mediated through gestational age were negative and statistically significant for all infants irrespective of birth sizes, although the associations were stronger among smaller infants (Figure 2: A1, B1), suggesting a shift in the birthweight distribution curve toward the left. For instance, among infants with birthweight <2300g (i.e.10th percentile), a unit increase in natural log water arsenic exposure was associated with 19.7g (95%CI: −26.7, −13.3) lower birthweight mediated via gestational age, while among infants born with birthweight >3250g (i.e. 90th percentile), for the same exposure the change in birthweight was −10.9g (95% CI: −18.5, −5.9) (Supplemental Table 1). Similar association was observed for maternal toenail arsenic (Supplemental Table 2).

The direct effect of arsenic exposure on birthweight through pathways independent of gestational age and hemoglobin level across birthweight percentiles were heterogeneous and bidirectional (Figure 2: A2, B2). For instance, via direct pathways, each unit increase in

natural log water arsenic exposure was associated with 28.0 g (95%CI: −63.1, −29.4) lower birthweight among infants with birthweight <2300g (10^{th} percentile), whereas the reduction was 14.9 g (95%CI: −30.3, −1.7) among infants with birthweight around 2520g (20^{th} percentile) (Supplemental Table 1). On the contrary, water arsenic exposure showed positive associations with birthweight among the heavier infants (>50^{th} percentile), although the associations were not statistically significant. Similar pattern of associations were observed for maternal toenail arsenic, although none of the direct effect associations were statistically significant. This paradoxical change in birthweight in response to prenatal arsenic exposure via pathways independent of gestational age was supported by the shift in the birthweight-for-gestational age z-score (birthweight in units of standard deviation within strata of gestational age) curve away from the mean in arsenic exposure above the median compared to that in arsenic exposure bellow the median in our cohort (Figure 3: A2, B2).

The direct and indirect effects were summed to obtain the total effects of arsenic exposure on birthweight. As predicted, our results showed marked heterogeneity in the total effects of arsenic exposure on birthweight across birthweight percentiles (Figure 2: A3, B3), Overall, water arsenic exposure was negatively associated with birthweight among infants <40^{th} percentile of birthweight distribution, while the associations were strongest among the smaller infants (Supplemental Table 1). For instance, each unit increase in natural log water arsenic exposure was associated with 47.7g (95%CI: −63.1, −29.4) lower birthweight among infants with birthweight <2300g (10^{th} percentile) compared to 18.7g (95% CI: −31.4, −5.5) decrease in birthweight among infants with birthweight around 2800g (40^{th} percentile). The proportion of the total effects mediated by gestational age (PM%) also showed marked heterogeneity; where the contribution of the indirect pathway in overall reduction of birthweight steadily increased as birthweight percentiles increased up to 40^{th} percentile ($PM_{10th\ percentile}$ = 41.2% vs $PM_{40th\ percentile}$ = 83.4%) (Supplemental Table 1). Similar patterns were observed for maternal toenails arsenic exposure, but the total effect associations were significant for infants at 20^{th} and 30^{th} percentiles of birthweight distribution (Supplemental Table 2). The overall effect of arsenic exposure on birthweight appeared to be positive among the heavier infants, but the associations were not statistically significant. These results are supported by the shift in the birthweight distribution curves away from the mean with a heavier lower tail in arsenic exposure above the median compared to that in arsenic exposure bellow the median in our study cohort (Figure 3: A1, B1).

4. DISCUSSION

This prospective cohort study was built upon our previous research that linked prenatal arsenic exposure with lower birthweight, primarily via shortening of gestational age. In this study, we expanded our previous analysis to investigate the causal relation between arsenic exposure and birthweight, and whether the susceptibility of arsenic exposure varies by infant birth sizes by implementing quantile causal mediation modeling technique. Our analyses revealed that prenatal arsenic exposure was negatively associated with birthweight, and that the magnitude of the association varied across birthweight percentiles, suggesting heightened susceptibility to arsenic exposure among smaller infants. The association between arsenic exposure and birthweight involved pathways mediated via gestational age as

well as pathways independent of gestational age, indicating possible role of shortening of gestation and intrauterine growth restriction, the two main causal processes underlying low birthweight, in explaining this complex exposure-outcome relation. The negative association between arsenic and birthweight via shortening of gestation was observed among all infants irrespective of birth sizes, whereas the negative association between arsenic and birthweight via pathways independent of gestational age was observed only among the smallest infants and for drinking water arsenic exposure.

Our findings are consistent with previous epidemiological studies that also report that prenatal arsenic exposure is negatively associated with birthweight (33–37) and positively associated with preterm delivery,(15–17) and fetal growth restriction (18–20). These associations were observed in populations with very high exposure (15–17), relatively lower levels of exposure (21, 31, 37), and exposure comparable to our study population (33–36), suggesting that there is likely no safe threshold for the embryotoxic effect of arsenic. Corroborating with our study, prospective cohort studies in Bangladesh (34–36) and Chile (33) have also observed a dose-dependent relationship between arsenic exposure and birthweight. Additionally, our quantile causal mediation analysis results were fairly consistent in magnitude and direction with mean regression analysis in the same cohort (35), but captured additional shift in birthweight distribution in response to prenatal arsenic exposure. For instance, Kile et. al. previously estimated in this cohort that a unit increase in natural log drinking water and maternal toenail arsenic exposure was associated with 17.4 g (−22.8, −12.0) and 13.6 g (−22.1, −5.1) lower birthweight, respectively via shortening of gestational age (35), which were comparable to the estimates we obtained at 50^{th} percentile of birthweight distribution (median regression) with larger sample size for drinking water (n=1,140 vs 1,181) and toenail (n= 624 vs 1,104) arsenic exposure. Additionally, our analyses revealed a significant negative association between drinking water arsenic and birthweight among the smallest infants (e.g. $<20^{th}$ percentile) via pathways independent of gestational age that was not captured by OLS regression technique used by Kile et al (35). This difference is likely due to the assumption of homogenous arsenic-birthweight relation made by Kile et al (35). While the heterogeneity in the associations between arsenic exposure and birthweight were identified in previous studies based on smoking,(31) infant genders,(37, 39) and maternal prepregnancy BMI status,(39) we observed disparities based on infant birth sizes. Overall, our results suggested that prenatal arsenic exposure was associated with a shift in the birthweight distribution curve away from the mean with a heavier lower tail, corresponding to a higher percentage of small preterm infants (≈9.2%) in our cohort (1). The proportion of small preterm infants in a population, which typically ranges between 2–5%, is an indicator of perinatal risk in that population (1, 59). Our findings emphasized the importance of arsenic mitigation to improve perinatal outcomes in Bangladesh.

Known biologic effects of inorganic arsenic exposure support the biological plausibility of our findings. Arsenic can generate reactive oxygen species and deplete antioxidant enzymes (e.g. glutathione) leading to oxidative stress (60). Oxidative damage in early pregnancy can disrupt placental development, function and remodeling (47), which in turn can hamper oxygen and nutrient supply to the growing fetus and production and metabolism of fetal growth regulating hormones leading to preterm delivery and IUGR (61, 62). Another

plausible explanation is epigenetic alterations. Prenatal arsenic exposure has been found associated with deregulation of microRNA expression profiles in umbilical cord blood (63) and DNA methylation status in maternal and umbilical cord blood (64). MicroRNAs have important role in normal placental development; and alteration of microRNA expression profiles have been associated with abnormal placentation, preeclampsia, eclampsia, and SGA births (65, 66).

Our study has some limitations. The observed positive associations between arsenic exposure and birthweight among the heavier infants in our cohort could partly because of inadequate adjustment for maternal perinatal nutritional status. Individual's micronutrient status (e.g. folate, antioxidants) plays an important role in arsenic detoxification, where adequate nutrition may ameliorate individual's vulnerability to arsenic toxicity (67), resulting in heavier infants. Therefore, inadequate adjustment for perinatal nutritional status will lead to an underestimation of the negative associations between arsenic and birthweight, and the underestimation will be larger for heavier infants. Future studies to explore potential interactions between arsenic exposure and maternal nutritional status during pregnancy in relation to birthweight will be useful. Future analysis using dietary exposure as predictors of arsenic exposure will also be beneficial to estimate the relative contribution of dietary arsenic given the modest correlation ($\sigma_{spearman}$=0.48; 95% CI: 0.44–0.53) between drinking water and maternal toenail arsenic exposure in this population.

Hence, it is possible that there is error in our estimates due to unmeasured confounders. We selected a priori list of covariates that were previously found to be associated with birthweight and/or gestational age. All women were provided with free prenatal multivitamins including 400 μg of folic acid and the same level of health care during pregnancy by our community health clinics, which were among the few of healthcare providers in the catchment area. Folate supplementation has been shown to reduce blood arsenic concentration as well as the toxic effect of arsenic by increasing arsenic methylation efficiency, particularly in population with folate deficiency (68–70), and thereby may reduce the risk of embryotoxic effect of arsenic (71). The compliance of regular multivitamins intake was reported to be 99% in our cohort. Therefore, any bias associated with multivitamin supplementation for the association between arsenic exposure and birthweight will likely be non-differential and towards the null. We did not collect detail pregnancy history to adequately control for other factors that could confound our results, such as pregnancy spacing or history of adverse birth outcomes in past pregnancies. Furthermore, we were not able to test the robustness of our estimated direct and indirect effects in presence of unmeasured confounders because no such method had yet been developed for quantile causal mediation analyses technique.

It is likely that our collected toenail clippings were not in the same length for all study participants, where longer clippings would have a higher absolute arsenic concentration and reflect a greater duration of exposure (and potentially greater variability in exposure). We collected toenail clippings from all available toes and pooled them together for analysis, which would give an estimate of participant's average duration of exposure. Furthermore, the concentrations reported in this analysis were per gram of nail, and we excluded any samples that had a toenail mass ≤ 5mg. So, we agree that there could be exposure

misclassification resulting from a mixture of people with different toenail lengths (e.g. duration of exposures); however, it would likely to be non-differential.

Few women in our cohort were able to recall their date of last menstrual period (LMP), which led us to solely rely on ultrasound measurements to estimate gestational age. Pregnancy dating using ultrasound technique is considered gold standard if used in early pregnancy, but the estimations are increasingly inaccurate after the end of 1st trimester [70]. Hence, we agree that there could be some misclassification in gestational age, as we were not able to use LMP information in conjunction with ultrasound to validate pregnancy duration. In a previously published study from the same cohort [29], we demonstrated that arsenic exposure was not associated with the timing of enrollment; thus, it is likely that any misclassification of gestational age introduced by increasing variability of ultrasound measurements for women enrolled between 13–16 weeks of gestation is non-differential. Thus, this error is likely to just decrease the precision of our observed associations.

Strengths of our study include its prospective design, where we collected birth outcome data from a fairly large number of pregnant mothers. We measured arsenic exposure in drinking water that pregnant mothers identified as their primary water source early in pregnancy. Previous studies in Bangladesh demonstrated that arsenic exposure measured in drinking water show little temporal variability (72) and serve as an adequate marker for long-term exposure when collected from participant's main water source (73). We also measured arsenic exposure in maternal toenails as a biomarker of internal dose and observed similar pattern of association. Our previous analysis demonstrated that toenail sample collected <1 month postpartum represents individual's cumulative exposure over the past 9–12 months (74), which essentially correspond to the entire pregnancy. Our study participants also provided a toenail sample at the time of enrollment (≤ 16 weeks of gestation); hence, we are fairly confident that arsenic concentrations measured in maternal toenails collected within one-month post-partum reflects gestational exposure. Therefore, our proposed temporal relation for the causal mediation framework between the exposure, mediator and outcome is valid. Additionally, the wide range of arsenic exposure in drinking water ranging from below the LOD to 1400 μg/L in our cohort enables our study findings to be applicable to other population where exposure is modest. Moreover, our quantile causal mediation analysis technique helped us to address methodological challenges involved in the investigation of potential heterogeneous association between prenatal arsenic exposure and birthweight in relation to shortening of gestation and intrauterine growth restriction, the two main causal processes underlying low birthweight, and enabled us to identify susceptible sub-population to arsenic toxicity.

5. CONCLUSIONS

Our results showed that prenatal arsenic exposure was associated with lower birthweight, which involved shortening of gestation and possibly intrauterine growth restriction in the causal pathways and that the magnitude of the association varied across birthweight percentiles. Smaller infants, who are already at higher risk of perinatal mortality and morbidity, are more susceptible to the toxic effects of arsenic on birthweight. Thus,

minimizing maternal arsenic exposure during pregnancy may significantly improve perinatal health outcomes in Bangladesh.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

IUGR	Intrauterine Growth Restriction
LOD	Limit of Detection

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Highlights

- We investigated the causal relation between prenatal arsenic exposure and birthweight
- Smaller infants were more susceptible to arsenic exposure.
- Both shortened gestation and IUGR likely to play important role in explaining arsenic-birthweight relation.
- Minimizing prenatal arsenic exposure may improve perinatal outcomes in Bangladesh

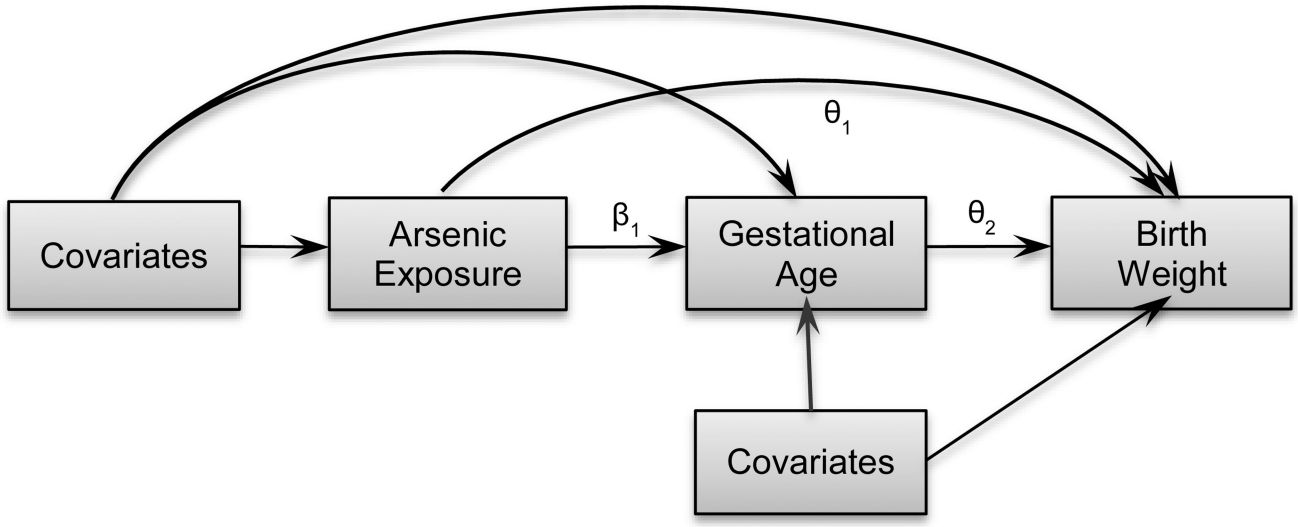

Figure 1.

Conceptual model for causal mediation analysis showing the relation between arsenic exposure and birthweight considering gestational age a mediator. Covariates include maternal age, education, enrollment BMI, number of past pregnancies, blood hemoglobin, secondhand smoking, and infant gender. Respective path co-efficient for the association between arsenic-birthweight, gestational age-birthweight, and arsenic-gestational age are given by θ_1, θ_2, and β_1, respectively.

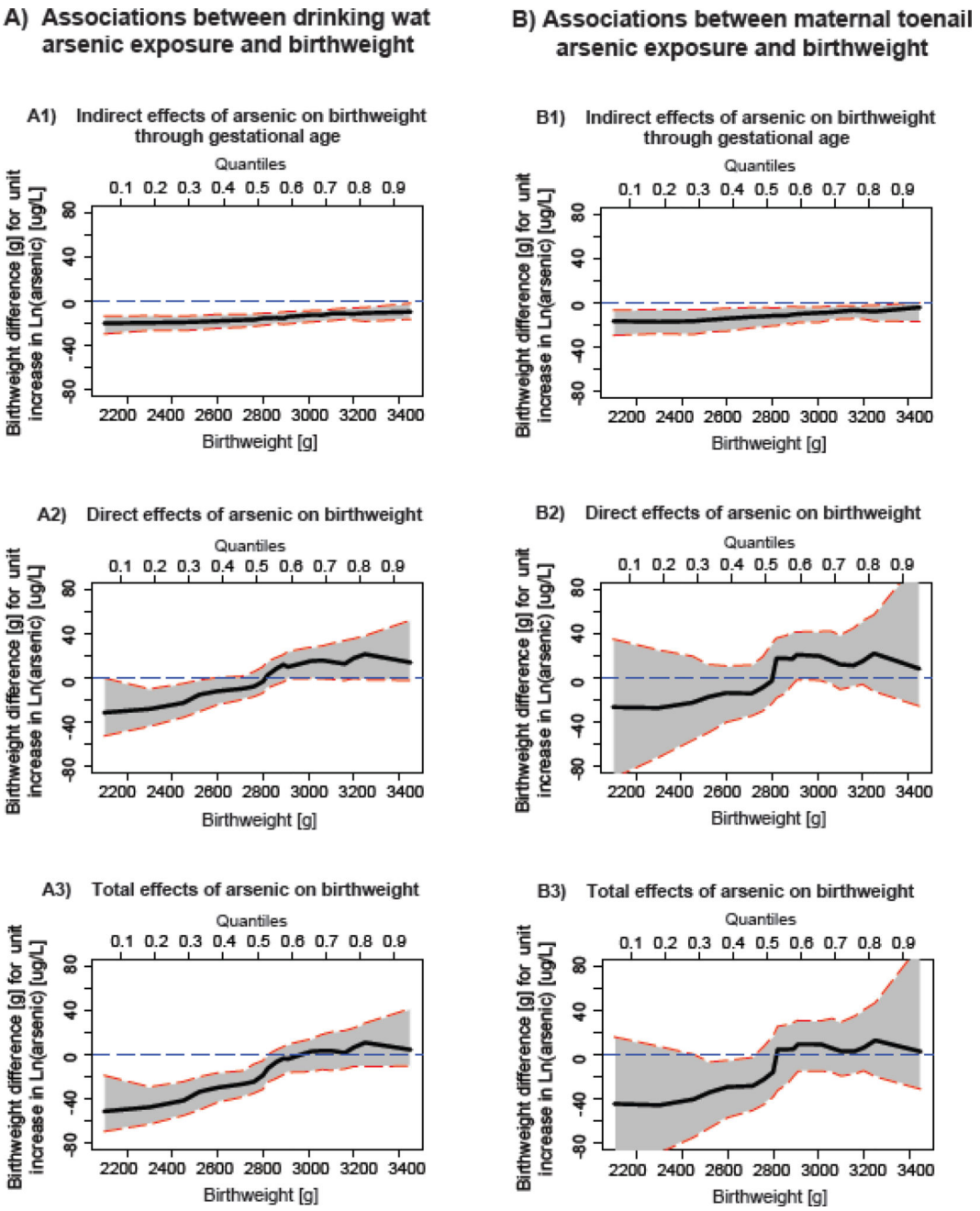

Figure 2.

Indirect, direct, and total effects of prenatal exposure to inorganic arsenic in drinking water (A1–A3) and maternal toenails (B1–B3) on birthweight considering gestational age a mediator, adjusting for maternal age, education, number of past pregnancies, secondhand smoking, enrollment BMI, blood hemoglobin level and infant gender. Solid black lines sorrounded by shadded areas represent effect estimates and 95% confidence intervals across birthweight percentiles. Horizontal blue dashed lines show reference values.

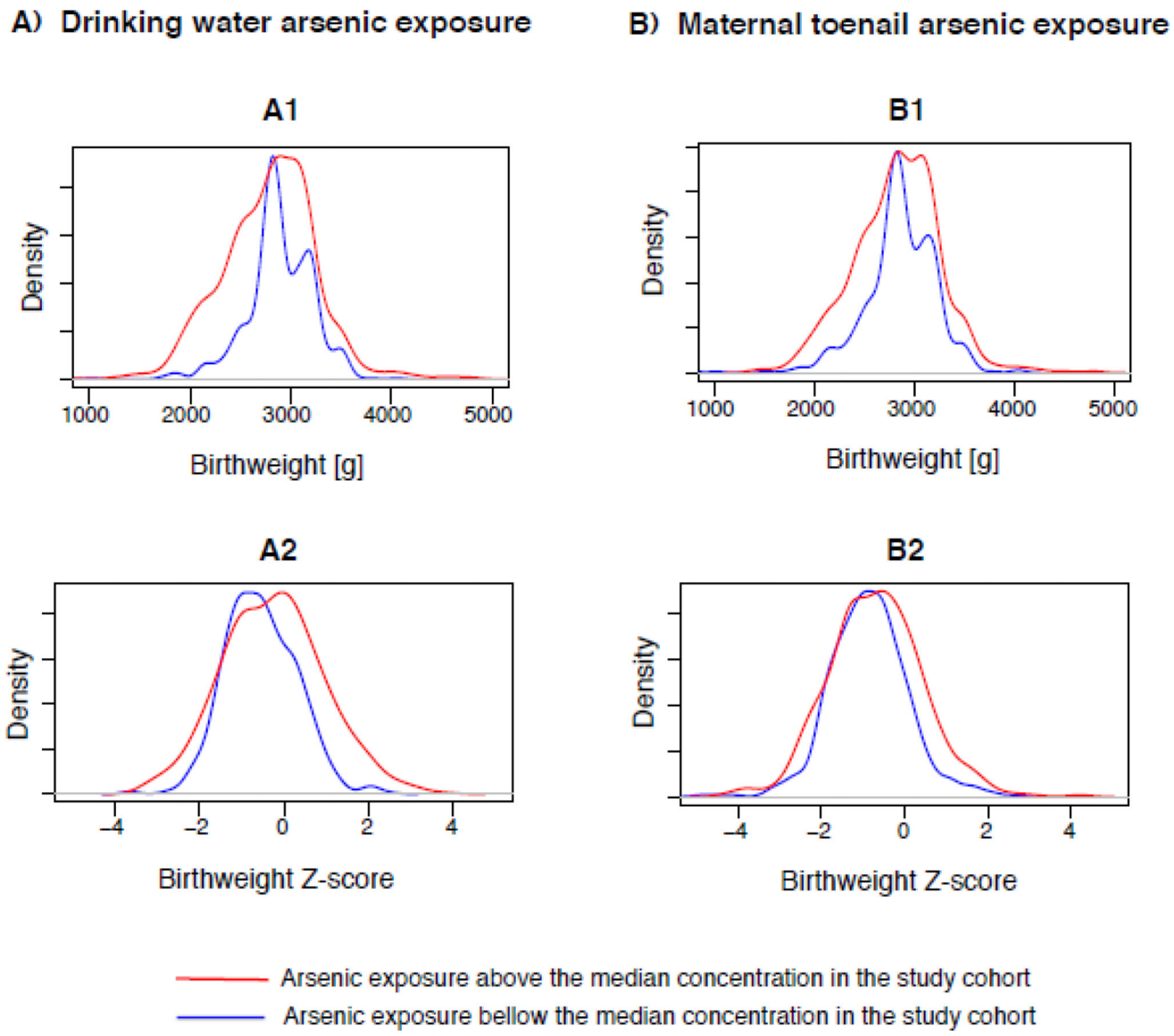

Figure 3.

The distributions of birthweight and birthweight-for-gestational age Z-score by prenatal arsenic exposure measured in drinking water (A1–A2) and maternal toenails (B1–B2) bellow the median concentration (blue) and above the median concentration (red) in the study cohort

Table 1

Distribution of selected characteristics of study participants and their bivariate associations with birthweight [g]

Characteristic	n (%)[a]	Co-efficient (95% CI)	P-value
Maternal age, years (mean ± SD)	23.0 ± 4.2	−1.3 (−6.8, 4.2)	0.75
Gestational Age, weeks (mean ± SD)	38.0 ± 1.8	82.5 (71.5, 93.4)	<0.001
Enrollment BMI, kg/m^2			
≤18·5	335 (28.4)	−63.3 (−115.5, −11.1)	0.02
>18·5 to ≤25.0	738 (62.5)	Reference	-
>25.0	108 (9.1)	175.0 (93.4, 256.7)	<0.001
Infant Sex			
Male	598 (50.6)	73.8 (27.3, 120.2)	0.002
Female	583 (49.4)	Reference	-
No. of past pregnancies			
0	475 (40.2)	Reference	-
1	353 (29.9)	−4.0 (−60.2, 52.1)	0.90
≥2	353 (29.9)	−68.9 (−125.1, −12.8)	0.02
Maternal education			
No formal education	172 (14.6)	−154.6 (−223.0, −86.2)	<0.001
Primary education	380 (32.2)	−22.2 (−73.9, 29.4)	0.40
Secondary or higher	629 (53.2)	Reference	-
Secondhand smoke			
Yes	495 (41.9)	−73.7 (−120.8, −26.6)	0.002
No	685 (56.1)	Reference	-
Blood hemoglobin, gm/L			
7.9–10.2	298 (25.2)	−47.7 (−115.1, 19.7)	0.17
>10.2–11.2	396 (33.5)	−106.2 (−169.6, −42.8)	0.001
>11.2–12.0	223 (18.9)	−13.5 (−86.0, 59.1)	0.72
>12.0–16.3	264 (22.4)	Reference	-
Drinking water arsenic, μg/L			
<LOD–<10	718 (60.8)	Reference	-
10–<50	202 (17.1)	−115.4 (−178.8, −52.0)	<0.001
50–1400	261 (22.1)	−80.1 (−137.7, −22.6)	0.006
Toenail arsenic, μg/g			
<LOD–<1.2	544 (49.8)	Reference	-
1.2–<2.3	216 (19.8)	−76.2 (−139.4, −13.0)	0.02
2.3–46.5	333 (30.4)	−4.7 (−59.4, 50.0)	0.87

[a] Values are n (%) except where indicated

Abbreviations: SD= Standard deviation; LOD= Limit of detection