# Prenatal arsenic exposure, child marriage, and pregnancy weight gain: Associations with preterm birth in Bangladesh

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## ABSTRACT

*Background:* Preterm birth is a disease of multifactorial etiologies that has environmental, social, and maternal health components. Individual studies have shown that exposure to arsenic contaminated drinking water, child marriage, and low maternal weight gain during pregnancy contribute to preterm birth. These factors are highly prevalent and often co-exist in Bangladesh, a country in South Asia with one of the world's highest prevalences of preterm birth.

*Objective:* To evaluate the individual and interactive effects of prenatal arsenic exposure, child marriage, and pregnancy weight gain on preterm birth in a prospective birth cohort in Bangladesh.

*Methods:* During 2008–2011, we recruited 1613 pregnant women aged ≥ 18 years at ≤ 16 weeks of gestation and followed them until 1-month post-partum. We measured total arsenic in drinking water (n = 1184) and in maternal toenails (n = 1115) collected at enrollment and ≤ 1-month post-partum, respectively using inductively coupled plasma mass spectrometry. Child marriage (< 18 years old) was defined using self-report, and 2nd and 3rd trimester pregnancy weight gain was calculated using monthly records. Gestational age was determined at enrollment by ultrasound.

*Results:* In multivariate adjusted Poisson regression models, the risk ratios (RR) for preterm birth were 1.12 (95% CI: 1.07–1.18) for a unit change in natural log water arsenic exposure, 2.28 (95% CI: 1.76–2.95) for child marriage, and 0.64 (95% CI: 0.42–0.97) for a pound per week increase in maternal weight during the 2nd and 3rd trimesters. In stratified analysis by child marriage, pregnancy weight gain was inversely associated with preterm birth among women with a history of child marriage (RR = 0.58; 95% CI: 0.37–0.92), but not among women with no history of child marriage (RR = 86; 95% CI: 0.37–2.01). Mediation analysis revealed that both arsenic exposure and child marriage had small but significant associations with preterm birth via lowering pregnancy weight gain. Similar associations were observed when arsenic exposure was assessed using maternal toenail arsenic concentrations.

*Conclusions:* Reducing arsenic exposure and ending child marriage could reduce the risk of preterm birth in Bangladesh. Furthermore, enhancing nutritional support to ensure adequate weight gain during pregnancy may provide additional benefits especially for women with a history of child marriage.

## 1. Introduction

Preterm birth, defined as having a live birth < 37 weeks of gestation, is the leading cause of neonatal mortality and the second leading cause of mortality among children under five years of age; the surviving infants are at lifelong risk of neurological impairments and chronic lung diseases (Mwaniki et al., 2012). Worldwide, > 15 million babies are born prematurely each year, and more than a third of them are born in South Asia (Blencowe et al., 2012). In Bangladesh, the incidence of preterm birth is estimated to be 14% (Blencowe et al., 2012) and can be 19–22% in rural areas (Baqui et al., 2013; Shah et al., 2014). These represent one of the highest incidence rates of preterm birth in the world. Common risk factors for preterm birth in Bangladesh and other countries in South Asia include prenatal arsenic exposure (Ahmad et al., 2001; Chakraborti et al., 2003), child marriage (marriage < 18 years old) (Pandya and Bhanderi, 2015; Stewart et al., 2007), and poor maternal weight gain during pregnancy (Bhavadharini et al., 2017). These factors often co-exist in this region but have been studied independently from each other. Improving our understanding of how these common risk factors interact with each other in relation to preterm birth would provide useful information for both practitioners and policy makers who seek to reduce the prevalence of preterm birth – one of the priorities identified in the United Nations 2030 sustainable development agenda (UN, 2015).

With regards to arsenic-contaminated groundwater, an estimated 30–70 million people in Bangladesh (Kinniburgh and Smedley, 2001) and an additional 26 million in West Bengal (Chakraborti et al., 2009) are exposed to arsenic through contaminated drinking water that has levels that are higher than the World Health Organization (WHO) recommendation of < 10 μg/L. Arsenic can readily cross the placenta, and thereby pose a risk to the developing fetus (Concha et al., 1998; Rudge et al., 2009). Several studies have reported that higher prenatal arsenic exposure is associated with increased risk of adverse birth outcomes including spontaneous abortion (Milton et al., 2005), stillbirth (Milton et al., 2005; von Ehrenstein et al., 2006), low birth weight (Hopenhayn et al., 2003; Kile et al., 2015; M. L. Rahman et al., 2017), neonatal mortality (Hopenhayn-Rich et al., 2000; A. Rahman et al., 2007), and preterm birth (Ahmad et al., 2001; Almberg et al., 2017; Shi et al., 2015; Yang et al., 2003). However, the association between arsenic exposure and preterm birth measured as a dichotomous outcome, or as gestational age, which is a continuous outcome variable, was not consistently observed (Bloom et al., 2014; Claus Henn et al., 2016; Gilbert-Diamond et al., 2016; Kile et al., 2016; Laine et al., 2015; Vall et al., 2012). It is likely that the inconsistency in the association between arsenic exposure and preterm birth is due to differences in study design, the arsenic exposure level in the different populations, small sample size, or inadequate adjustment for confounders. This highlights the need for large prospective studies with individual-level exposure measurements that are relevant to prenatal exposure and accurate gestational age when assessing the association between arsenic and preterm birth (Bloom et al., 2014; Quansah et al., 2015).

An important social factor that affects maternal and child health in Bangladesh is child marriage. Child marriage is defined by the United Nations Children's Fund as marriage or in union for girls before age 18 years. Bangladesh has one of the world's highest prevalences of child marriage where 52% of girls are married before age 18 years and 18% are married before age 15 years (UNICEF, 2016). The prevalence of child marriage is also very high in many South Asian countries, including India (47%), Nepal (37%), Afghanistan (33%), and Pakistan (21%) (UNICEF, 2016). With approximately one in two girls married off before age 18 years, South Asia, as a region, has the highest prevalence of child marriage in the world (UNICEF, 2016). Child marriage often forces girls into pregnancy at a younger age because child brides have less control over their reproductive decision and are less likely to use contraception prior to first childbirth (Raj et al., 2009). Studies have shown that child brides experience higher risks of complications during pregnancy and childbirth, which is the 2nd leading cause of mortality among 15–19 year-old girls globally (UNFPA, 2012). Infants born to child brides are also at a higher risk of low birth weight, preterm birth, and neonatal death (Chen et al., 2007; Cunnington, 2001; Kumar et al., 2007). In addition to a child bride's biological immaturity, marriage at a young age is also related to socio-economic deprivation (Raj et al., 2014; Sayem and Nury, 2011), higher fertility and lower birth spacing (Godha et al., 2013; Raj et al., 2009), higher risk of perinatal infections (Nour, 2006), and lower quality and quantity of perinatal health care (Godha et al., 2013). Together, these social factors and access to medical care may compromise the reproductive and perinatal health of the mother and her infant.

Both prenatal arsenic exposure and child marriage impact maternal health status during pregnancy, resulting in inadequate pregnancy weight gain (Kile et al., 2016; Klein and American Academy of Pediatrics Committee on, 2005; Scholl and Hediger, 1993), which is an independent risk factor for preterm birth (Schieve et al., 2000). For instance, studies both in the developing and developed countries have reported higher risk of preterm birth among women who gain less total weight over the course of pregnancy, or who's weekly weight gain rate during the 2nd and 3rd trimesters is less (Dietz et al., 2006; Han et al., 2011; Schieve et al., 2000; Siega-Riz et al., 1996; Spinillo et al., 1998). These findings suggest that weight gain during pregnancy may act as a mediating or intermediate variable that could influence the effect of prenatal arsenic exposure and child marriage on preterm birth.

Therefore, we used mediation analysis to examine the relationship between prenatal arsenic exposure, child marriage, pregnancy weight gain, and preterm birth. We hypothesized that pregnancy weight gain would mediate the risk of arsenic exposure and child marriage on preterm birth. Using this modeling approach, we quantified the direct effects of prenatal arsenic exposure and child marriage on preterm birth as well as the indirect effects of these factors on preterm birth that is mediated via maternal weight gain during pregnancy (MacKinnon and Luecken, 2008).

## 2. Methods

### 2.1. Study participants

We used data from a prospective birth cohort established in Bangladesh during 2008–2011. The details of this study, including methods of recruitment and enrollment have been previously reported (M. L. Rahman et al., 2017). Briefly, women were eligible to participate if they were ≥ 18 years old with an ultrasound confirmed singleton pregnancy of ≤ 16 weeks' gestation; used a tube well as their primary source of drinking water; had been using the same drinking water source for > 6 months; and intended to live in her current residence throughout pregnancy. A total of 1613 pregnant women were recruited and followed until delivery (Fig. 1). At the end of follow-up, 1184 singleton livebirths were recorded. The reasons for loss to follow up included losing contact with participants who moved (n = 99), withdrawal (n = 121), miscarriage (n = 132), stillbirth (n = 72), and multiple pregnancies (n = 5). Missing data were reported for maternal toenail arsenic (n = 69) and secondhand smoke exposure (n = 1). Women who remained in the study were similar with those who dropped out in respect to age, age at marriage, exposure to secondhand smoke, number of past pregnancies, household income, education, and enrollment BMI and toenail arsenic exposure (data not shown).

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 the Bangladesh standard of < 50 μg/L (Flanagan et al., 2012). Prenatal care and multivitamins were provided to all participants through our community outreach clinics which were among the few healthcare providers in the catchment areas. All protocols were reviewed and approved by the Human Research Committees at Harvard T.H. Chan School of Public