Environment International 108 (2017) 32–40

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

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

Mohammad L. Rahman[a], Linda Valeri[b], Molly L. Kile[c], Maitreyi Mazumdar[a], Golam Mostofa[d], Qazi Qamruzzaman[d], Mahmudur Rahman[d], Andrea Baccarelli[e], Liming Liang[f], Russ Hauser[a,g], David C. Christiani[a,g,*]

[a] Harvard T.H. Chan School of Public Health, Department of Environmental Health, Boston, MA, USA
[b] McLean Hospital, Belmont, Massachusetts, USA, Harvard Medical School, Boston, MA, USA
[c] Oregon State University, College of Public Health and Human Sciences, Corvallis, OR, USA
[d] Dhaka Community Hospital Trust, Dhaka, Bangladesh
[e] Columbia University, Mailman School of Public Health, Department of Environmental Health, New York, NY, USA
[f] Harvard T.H. Chan School of Public Health, Department of Biostatistics, Boston, MA, USA
[g] Harvard T.H. Chan School of Public Health, Department of Epidemiology, Boston, MA, USA

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 = 1182) collected at enrollment and maternal toenails (n = 1104) collected ≤ 1-month postpartum using inductively coupled plasma mass spectrometry. Gestational age was determined using ultrasound at ≤ 16 weeks' gestation. Demographic information was collected using a structured questionnaire.

Results: Of 1184 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: below 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 = − 19.7 g [95% CI: − 26.7, − 13.3] to 90th percentile = − 10.9 g [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 = − 28.0 g [95% CI: − 43.8, − 9.9] to 20th percentile = − 14.9 g [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 (Wilcox, 2001). Each year, an estimated 21 million infants are born with low birthweight worldwide, more than half of them are in South Asia (WHO and UNICEF, 2004). In Bangladesh, the incidence of low birthweight is estimated to be 22%, which is among

Abbreviations: IUGR, intrauterine growth restriction; LOD, limit of detection

* Corresponding author at: Department of Environmental Health, Harvard T. H. Chan School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA.
E-mail address: dchris@hsph.harvard.edu (D.C. Christiani).

http://dx.doi.org/10.1016/j.envint.2017.07.026
Received 31 January 2017; Received in revised form 3 June 2017; Accepted 30 July 2017
Available online 05 August 2017

the highest in the world (Lee et al., 2013), and in rural areas the estimates are as high as 31–47% (Hosain et al., 2006). 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) (Lee et al., 2013). These components of low birthweight generally differ in their etiologies and risks of mortality, morbidity and impaired growth (Kline et al., 1989; Kramer, 1987); therefore, it is important to distinguish between them in order to identify true causal determinants of low birthweight and develop effective public health interventions (Kramer, 1987).

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 (Uddin and Huda, 2011). 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 (Loewenberg, 2016). In rural areas, where 70% of the total population live (The World Bank, 2014), the problem is much more highly prevalent, as 97% of them relies on groundwater for drinking purposes (Flanagan et al., 2012).

Arsenic can cross the placenta readily(Concha et al., 1998), and prenatal arsenic exposure has been associated with spontaneous abortion, (Rahman et al., 2010; Milton et al., 2005; He et al., 2007), preterm birth (Ahmad et al., 2001; Chakraborti et al., 2003; Yang et al., 2003), and intrauterine growth restriction (Thomas et al., 2015; Kippler et al., 2012; Llanos and Ronco, 2009; Claus Henn et al., 2016). However, the epidemiological evidence for an association between prenatal arsenic exposure and birthweight is less consistent. While ten studies (Ahamed et al., 2006; Chakraborti et al., 2004; Gelmann et al., 2013; Kwok et al., 2006; Mukherjee et al., 2005; Myers et al., 2010; Shirai et al., 2010; Vall et al., 2012; Hu et al., 2015) reported a null or positive associations between arsenic exposure and birthweight, 14 other studies (Chakraborti et al., 2003; Yang et al., 2003; Llanos and Ronco, 2009; Claus Henn et al., 2016; Bloom et al., 2016; Guan et al., 2012; Hopenhayn et al., 2003; Huyck et al., 2007; Kile et al., 2016; Rahman et al., 2009; Xu et al., 2011; Fei et al., 2013; Gilbert-Diamond et al., 2016; McDermott et al., 2014; Laine et al., 2015), 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 (Yang et al., 2003; Hopenhayn et al., 2003; Kile et al., 2016), maternal urine (Rahman et al., 2009; Fei et al., 2013; Gilbert-Diamond et al., 2016; Laine et al., 2015), toenail (Kile et al., 2016), hair (Huyck et al., 2007), whole blood (Claus Henn et al., 2016; Guan et al., 2012; Xu et al., 2011), soil around the residence (McDermott et al., 2014), and placental tissue (Llanos and Ronco, 2009). 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 (Huyck et al., 2007; Kile et al., 2016; Rahman et al., 2009), India (Chakraborti et al., 2003), Chile (Hopenhayn et al., 2003), and Taiwan (Yang et al., 2003), several recent studies in the United States (Claus Henn et al., 2016; Fei et al., 2013; Gilbert-Diamond et al., 2016) and China (Guan et al., 2012; Xu et al., 2011) 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 (Valeri and Vanderweele, 2013). 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 (Kile et al., 2016), 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 (Rodosthenous et al., 2016). Both arsenic and lead has been implicated in hypoxia (Ahamed and Siddiqui, 2007; Flora et al., 2012) and generating oxidative stress (Ahamed and Siddiqui, 2007; Ahmed et al., 2011), which have been linked with the disruption of normal placentation, leading to adverse fetal growth outcomes (Jauniaux and Burton, 2016; Jauniaux et al., 2006). Built upon these researches, we investigated whether prenatal arsenic exposure disproportionately affects 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 (Koenker, 2005). 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 (Barker et al., 2002), 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 (Koenker, 2005). 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) (Imai et al., 2010). This method has been demonstrated previously in social science research (Shen et al., 2014). 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.