Early life arsenic exposure, infant and child growth, and morbidity. A systematic review

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Abstract

Epidemiological studies have suggested a negative association between early life arsenic exposure and fetal size at birth, and subsequently with child morbidity and growth. However, our understanding of the relationship between arsenic exposure and morbidity and growth is limited. This paper aims to systematically review original human studies with an analytical epidemiological study design that have assessed arsenic exposure in fetal life or early childhood and evaluated the association with one or several of the following outcomes: fetal growth, birth weight or other birth anthropometry, infant and child growth, infectious disease morbidity in infancy and early childhood. A literature search was conducted in PubMed, TOXLINE, Web of Science, SciFinder and Scopus databases filtered for human studies. Based on the predefined eligibility criteria, two authors independently evaluated the studies. A total of 707 studies with morbidity outcomes were identified, of which six studies were eligible and included in this review. For the growth outcomes a total of 2,959 studies were found, and nine fulfilled the criteria and were included in the review. A majority of the papers (10/15) emanated from Bangladesh, three from the USA, one from Romania and one from Canada. All included studies on arsenic exposure and morbidity showed an increased risk of respiratory tract infections and diarrhea. The findings in the studies of arsenic exposure and fetal, infant and child growth were heterogeneous. Arsenic exposure was not associated with fetal growth. There was limited evidence of negative associations between arsenic exposures and birth weight and growth during early childhood. More studies from arsenic affected low- and middle-income countries are needed to support the generalizability of study findings.

Keywords: Arsenic, human studies, growth, morbidity, systematic review

Background

Arsenic concentration in groundwater exists in many parts of the world and is a major public health concern in these settings (Mukherjee et al. 2006; Ng et al. 2003). Millions of people are exposed through drinking water to arsenic concentrations above the World Health Organization guideline value of 10μg/L (Smith et al. 2000). However, the level of exposure is particularly great in Bangladesh and West Bengal, India. Arsenic is a potent toxicant and carcinogen. Epidemiological studies have reported an association between arsenic exposure and increased risks of various cancers and non-cancerous diseases. These include skin lesions (Rahman et al. 1999a; Tondel et al. 1999), hypertension (Rahman et al. 1999b), cardiovascular and respiratory diseases (Milton and Rahman 2002; Moon et al. 2013), diabetes mellitus (Navas-Acien et al. 2008) and malignancies of skin and internal organs (IARC 2004). Arsenic can easily pass through the placenta and poses a threat to early human development (Vahter 2009). A number of studies have reported an association between prenatal arsenic exposure and adverse pregnancy outcomes such as spontaneous abortions (Milton et al. 2005; Rahman et al. 2007), stillbirths (Milton et al. 2005; von Ehrenstein et al. 2006), low birth weight (Rahman et al. 2009), and infant mortality. All these adverse health outcomes may affect the progress of an overall health envisioned by the Sustainable Development Goals.

Bangladesh has shown significant achievements in the reduction of child mortality (NIPORT 2014; UNICEF 2015). However, the success has been limited in efforts to reduce morbidity and improve growth of fetuses and children. For example, recent studies have reported that the prevalence of small for gestational age at birth is 36% and stunting at five years of age is 45% (Mridha et al. 2016; Svefors et al. 2016). Morbidity and growth are interrelated and may

influence future development and survival of children. Epidemiological studies have suggested a negative association between early life arsenic exposure and fetal size at birth, and subsequently with morbidity and growth during childhood (Gardner et al. 2013; Rahman et al. 2009). However, our understanding of the relationship between arsenic exposures and morbidity and growth is limited. A previous systematic review evaluated the association between arsenic exposure and adverse pregnancy outcomes with a focus on spontaneous abortion, stillbirth, birth outcomes and mortality during infancy and childhood (Quansah et al. 2015). This paper aims at systematically review original human studies with an analytical epidemiological study design that measure arsenic exposure in fetal life or early childhood, and evaluates the association with one or several of the following outcomes: fetal growth, birth weight or other birth anthropometry, infant and child growth, infectious disease morbidity in infancy and early childhood.

Methods

A literature search was conducted 9-13 May 2016 in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), TOXLINE (https://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE), Web of Science (*https://webofknowledge.com),* SciFinder (http://www.cas.org/products/scifinder) and Scopus (https://www.scopus.com/) databases filtered for human studies. Keywords used were "arsenic", "fetal", "birth weight", "infant growth", "child growth", "infant morbidity" and "child morbidity". The term "arsenic" was combined with all of the other search terms. The articles were screened via title and abstract and excluded if not eligible. Two authors (CG, LÅP) evaluated the articles independently based on inclusion and exclusion criteria and articles included in this review fulfilled the following eligibility criteria a)

original study; b) case-control or cohort study design, i.e. a longitudinal design ascertaining that exposure came before outcome; c) human study; d) English language; e) arsenic exposure; f) one or more of the following outcomes: fetal growth, birthweight, infant growth, child growth, infant infectious morbidity, child infectious morbidity. Studies were excluded if being reviews or meta-analyses. Studies with an ecological design were not included.

Due to the differences in design, sources of arsenic exposure assessments (drinking water, urine, blood, hair, nails), classification of levels of exposure, outcome data collection and classification, and statistical analyses employed we did not include any meta analysis. The quality of the included studied was assessed according to the Newcastle-Ottawa Quality Assessment Scale for Case-Control or Cohort Studies (Wells et al. 2013). The results of the included studies were reviewed and discussed for the different outcomes as to the quality of studies, consistency of findings, contextual factors, and strength of associations.

Results

A total of 707 studies with morbidity outcomes were identified, of which six studies were eligible and included in this review (Figure 1). For the growth outcomes a total of 2,959 studies were found, and nine fulfilled the criteria and were included in the review (Figure 2). A majority of the papers (10/15) emanated from Bangladesh, and three were from the USA, one from Romania and one from Canada. Two of the morbidity studies (Rahman et al. 2011; Raqib et al. 2009) and four of the growth studies (Gardner et al. 2013; Kippler et al. 2012; Rahman et al. 2009; Saha et al. 2012) were based on the MINIMat trial and cohort (Maternal and Infant Nutrition Interventions, Matlab) in rural Bangladesh (Persson et al. 2012). Two of the US studies

of arsenic and child morbidity were also based on different selections of the same cohort (Farzan et al. 2013; Farzan et al. 2016).

Arsenic exposure and infant and child morbidity

All included studies, two US studies from the same cohort (Farzan et al. 2013; Farzan et al. 2016) as well as in the Bangladeshi studies (George et al. 2015; Rahman et al. 2011; Raqib et al. 2009; Smith et al. 2013), showed an increased morbidity risk when exposed to arsenic (Table 1). All papers addressed respiratory outcomes. In the Bangladeshi case-control study child urinary arsenic levels were associated with higher risk of pneumonia (George et al. 2015), and in the MINIMat cohort prenatal urinary arsenic was linked to an increased risk of lower respiratory tract infections (Rahman et al. 2011). Maternal urinary arsenic levels were associated with respiratory symptoms or upper respiratory tract infections demanding certain health service attention in the American as well as the Bangladeshi studies (Farzan et al. 2013; Farzan et al. 2016; Raqib et al. 2009). In another Bangladeshi cohort it was also shown that drinking water arsenic levels in pregnancy and childhood were associated with child wheezing and breathlessness (Smith et al. 2013). In the American as well as the MINIMat cohort in Bangladesh the prenatal urinary arsenic levels were associated with higher risk of childhood diarrhea (Farzan et al. 2016; Rahman et al. 2011).

Arsenic exposure and fetal, infant and child growth

There was only one study employing a longitudinal analysis of prenatal arsenic exposure and ultrasound-based fetal growth outcomes, Table 2 (Kippler et al. 2012). Six studies had an outcome with birth weight or other measurements of size at birth (Bloom et al. 2016; Gilbert-

Diamond et al. 2016; Huyck et al. 2007; Kile et al. 2016; Rahman et al. 2009; Thomas et al. 2015). Two studies, based on the MINIMat cohort, evaluated the association between arsenic exposure and infant or young child growth (Gardner et al. 2013; Saha et al. 2012).

There was no association between prenatal arsenic exposure assessed by urine samples and ultrasound assessment of fetal growth parameters from week 8 to 30 in rural Bangladesh, Table 2 (Kippler et al. 2012). In the same cohort maternal urinary arsenic in the range below 100 µg/L was negatively associated with birth weight, head, and chest circumference but not with birth length (Rahman et al. 2009). Above that level of exposure no further increase in the negative association was found. In another Bangladeshi cohort arsenic in maternal drinking water as well as in toenails was negatively associated with birth weight. A major part of that association was mediated over gestational age at birth (Kile et al. 2016). Another small Bangladesh pregnancy cohort showed a negative association between maternal hair arsenic levels and birth weight (Huyck et al. 2007). The studies from the US and Romania did not show any overall associations between prenatal arsenic exposure and birth weight. In the American study stratifications by maternal weight groups and infant sex showed that urinary arsenic of overweight mothers was positively associated with birth length in boys and negatively associated with birth weight in girls (Gilbert-Diamond et al. 2016). There were no adjustments done for other potential confounders. In the Romanian cohort study a negative association between prenatal drinking water arsenic levels and birth weight and length was only seen among smoking mothers (Bloom et al. 2016).

The growth follow-up of the MINIMat cohort to two years (Saha et al. 2012) and later to five years (Gardner et al. 2013) showed that the strongest negative association between arsenic exposure and growth (weight and height) was seen with the concurrent exposure and among girls. Even here the strongest association was seen in a lower range of exposure (Gardner et al. 2013).

Discussion

This systematic review has shown that arsenic exposure is associated with an increased risk of infant and child respiratory infections and diarrhea, and, less consistent, with impaired growth.

This review was based on a comprehensive search of articles, and two authors had independently reviewed and selected the articles based on predefined criteria. We also recognize the potential weakness of using the Newcastle-Ottawa Quality Assessment Scale, which may be prone to bias. Some studies have reported poor agreement between reviewers and authors of the reviewed articles when ranking the quality (Lo et al. 2014). In addition, the external validity and generalizability of the study findings were compromised due to the bulk of the studies conducted in Bangladesh. No studies regarding these outcomes are so far available from other arsenic-affected low- and middle-income countries.

The articles selected for this systematic review evaluated the association of early life arsenic exposures with morbidity limited to respiratory infections and diarrhea during infancy and childhood. The findings were more or less consistent, although the individual studies differed from each other in design, exposure and outcome assessments, and selection of study

participants. In the case-control study, physicians assessed the outcome based on criteria set by the World Health Organization (George et al. 2015), while the other high-ranked study defined the outcomes based on reported symptoms (Rahman et al. 2011). These high-ranked studies reported about two times increased risk of respiratory infections in the higher exposure levels in comparison with the low-level exposure. These studies also found mild to moderate risk of diarrhea based on reported symptoms. Overall, the findings suggest effects of arsenic on common childhood morbidity that are of public health importance. These infections are also among the main causes of under-five mortality (Liu et al. 2015).

The findings of consequences of arsenic exposure on fetal, infant, and child growth were not consistent. Two studies, which evaluated the effect on fetal growth and SGA at birth, did not show any association. Three studies from Bangladesh had reported negative associations with birthweight, while the studies in Romania and USA, respectively, only demonstrated an association in sub-groups of the study population. Thus, these studies provide no evidence of an association with fetal growth and limited evidence regarding effects on birthweight. The studies in Bangladesh, based on the MINIMat cohort, demonstrated a sex-dependent association with child growth; the possible effects were shown in girls.

The suggested associations between arsenic exposures and childhood morbidity may be mediated via immune suppression. In experimental studies, arsenic exposure has been found to suppress the immunoglobulin (Ig)M and IgG antibody-forming cell response (Selgrade 2007) and decrease interleukin-2 mRNA expression (Conde et al. 2007). Arsenic exposure during pregnancy has also been associated with fewer T-cells (CD3+ cells) in the placenta (Ahmed et al.

2011). The mechanisms by which arsenic exposure potentially affects fetal and early childhood growth are less clear. Arsenic is suggested to induce oxidative stress by producing free oxygen radicals or by perturbation of oxidative defense leading to placental insufficiency including intra-uterine growth retardation (Vahter 2007). Epidemiological studies have demonstrated associations between arsenic exposure and anemia. Growth impairment may also be a consequence of anemia in children (Gardner et al. 2013; Heck et al. 2008; Sazawal et al. 2010).

In conclusion, arsenic exposure is associated with an increased risk of childhood respiratory tract infections and diarrhea. The evidence is so far weak regarding associations between arsenic exposure and fetal growth, size at birth, and growth during childhood. Present results mostly emanate from studies conducted in Bangladesh. Millions of people are still exposed to arsenic, and pregnant women drink arsenic-contaminated water (Smith et al. 2000). The earlier demonstrated increased child mortality risk (Quansah et al. 2015), the increased risk of child infections, and the suggested impaired growth demonstrates the public health importance of this toxic exposure. Concerted actions and effective mitigation programs are needed in the affected countries, with priority given to women of reproductive age and their children.

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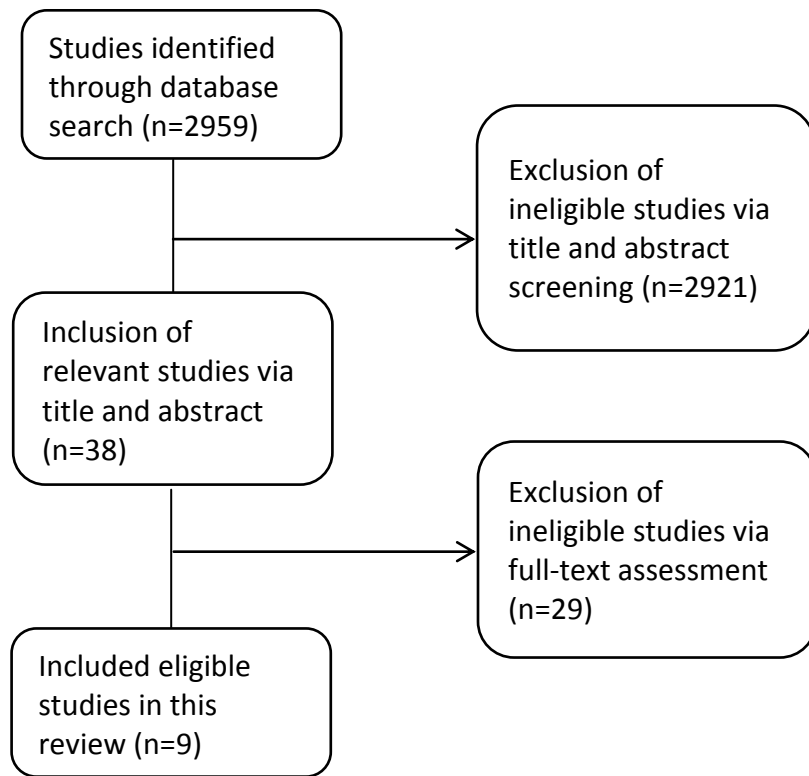   Bangladesh. Environ Health Perspect 120(8):1208-14 doi:10.1289/ehp.1003378

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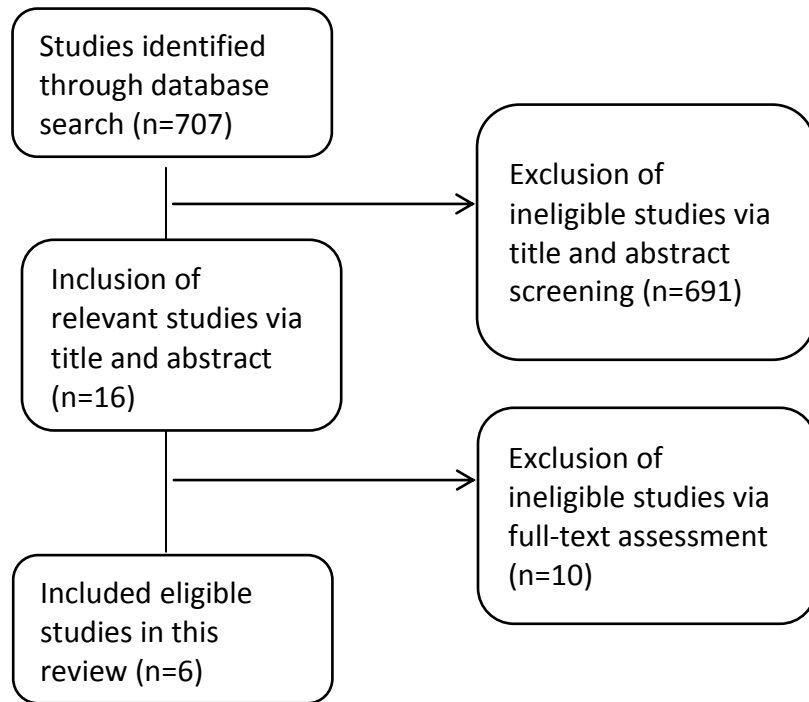
Figure 1. The study selection flow diagram, morbidity outcomes.

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│ Studies identified │
│ through database │
│ search (n=2959) │
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Figure 2. The study selection flow diagram, fetal growth, low birthweight and infant and child growth outcomes.

Table 1. Characteristics of studies with arsenic exposure and infant or child morbidity outcome

Author	Country	Study design	Study population	Exposure	Outcome	Adjustment for confounders	Results	Quality[a]
Farzan et al. (2016)	USA	Cohort	Mother-infant pairs, n=412	U-As during pregnancy	Respiratory infections, fever, diarrhea	Maternal age, parity, smoking, infant sex, gestational age, birth weight, breastfeeding, day care attendance	Doubling U-As associated with an increased risk of medical consultation for infection (RR 1.1; 95% CI 1.0, 1.2), respiratory symptoms >2 days (RR 1.1; 95% CI 1.0, 1.2). Also association with diarrhea (RR 1.4; 95% CI 1.1, 1.9) and fever resulting in doctor visit (RR 1.2; 95% CI 1.0, 1.5)	7/9
George et al. (2015)	Bangladesh	Case-control	Children, cases n=153, controls n=296	Child U-As. Lowest quartile <6 μg/L	Pneumonia	U-Creatinine, weight for height, breastfeeding, paternal age, education, household size	U-As associated with risk of pneumonia. OR for quartiles U-As: 1.00 (reference), 1.75 (95 % CI 0.90, 3.40), 2.11 (95 % CI 1.01, 4.34)), and 2.04 (95 % CI 0.92, 4.51).	9/9
Farzan et al. (2013)	USA	Cohort	Mother-infant pairs, n=214	U-As during pregnancy	Respiratory infections, diarrhea	Maternal age, parity, child sex, gestational age, birth weight, breastfeeding, day care attendance	U-As associated with any upper respiratory tract infection with prescribed treatment at 4 months (RR 1.6; 95% CI 1.0, 2.5), any lower respiratory tract infection treated with prescription (RR 1.6; 95% CI 1.0, 2.5)	6/9.
Smith et al. (2013)	Bangladesh	Cohort	Children, n=495	W-As in pregnancy and childhood	Pulmonary effects, asthma, wheezing	Age, gender, mother's education, father's education, father's smoking status, rooms in the house	W-As associated with wheezing (OR 8.41, 95% CI 1.66, 42.6), shortness of breath if walking on level ground (OR 3.86, 95% CI 1.09, 13.7) or walking fast or climbing (OR 3.19, 95% CI 1.22, 8.32). Reference category As exposure <10μg/l	6/9
Rahman et al.	Bangladesh	Cohort	Mother-infant	U-As during	Lower respiratory	Maternal education, household asset	Maternal U-As associated with the risk of LRTI (RR 1.69; 95% CI, 1.36, 2.09) and	8/9

(2011)			pairs, n=1552	pregnancy	tract infection (LRTI), diarrhea	scores, parity, body mass index, gestational age, infant sex	diarrhea (RR = 1.20; 95% CI, 1.21, 1.97) when comparing the highest and lowest exposure quintiles.	
Raqib et al. **(2009)**	Bangladesh	Cohort	Mother-infant pairs, n=140	U-As during pregnancy	Acute respiratory infections (ARI)	Child BMI SD score, maternal BMI, household asset score, child sex	U-As at week 30 of gestation significantly associated with days of ARI 0-12 months	6/9

[a]The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses (Wells et al. 2013)

Table 2. Characteristics of studies with arsenic exposure and fetal growth, size at birth and infant and child growth outcomes

Author	Country	Study design	Study population	Exposure	Outcome	Adjustment for confounders	Results	Quality [a]
Kippler et al. (2012)	Bangladesh	Cohort	Pregnant women, n=1929	U-As wk 8 and 30	Fetal size wk 8, 14, 30	Maternal BMI, household asset score, birth order, fetal sex	No association U-As and fetal size in adjusted longitudinal analysis	8/9
Gilbert-Diamond et al. (2016)	USA	Cohort	Mother-infant pairs, n=706	Maternal U-As in pregnancy	Size at birth	Stratification for maternal weight group, infant sex	U-As of overweight mothers positively associated with birth length in boys, negatively associated with birth weight in girls	7/9
Kile et al. (2016)	Bangladesh	Cohort	Mother-infant pairs, n=1140 (toenails n=624)	W-As in pregnancy and As in toenails	Birth weight	Mediation analyses gestational age, maternal weight gain. Adjustments infant sex, maternal education, indirect tobacco smoke, BMI, maternal age, birth type and location	W-As as well as toenail As negatively associated with birth weight; most mediated over gestational age at birth	7/9
Bloom at al. (2016)	Romania	Cohort	Mother-infant pairs, n=122	W-As in pregnancy	Size at birth	Maternal age, pre-pregnancy BMI, education	No association pregnancy W-As and size at birth. Smokers: higher W-As (Δ 10µg/L) negatively associated with birth weight and length	8/9
Thomas et al. (2015)	Canada	Cohort	Mother-infant pairs, n=1835	U-As and As in blood in pregnancy	SGA[2]	Maternal age, parity, pre-pregnancy BMI, smoking	No association between arsenic exposure and SGA	8/9
Rahman et al. (2009)	Bangladesh	Cohort	Mother-infant pairs, n=1578	U-As in pregnancy	Size at birth	Household asset score, maternal BMI, height, age and education, season, gestational age at birth, sex of infant	U-As below 100 µg/L negatively associated with birth weight, head and chest circumferences. Above this level no negative association	8/9

Huyck et al. (2007)	Bangla desh	Cohor t	Mother-infant pairs, n=43	W-As and As in toenail, hair	Birth weight	Gestational age at first prenatal visit, activity level, maternal weight gain, gestational age at birth	Maternal hair As negatively associated with birth weight	7/9
Saha et al. (2012)	Bangla desh	Cohor t	Children, n=2372	U-As in pregnancy and childhood	Weight and length up to 2 years of age	Age and sex of child, maternal BMI, household asset score	Maternal U-As inversely associated with length at 3 months. Child U-As at 18 months inversely associated with weight and height to 24 months, particularly in girls	8/9
Gardner et al. (2012)	Bangla desh	Cohor t	Mother-infant pairs, n=1505	U-As in pregnancy and childhood	Weight, height up to 5 years of age	Child's sex, season of birth, gestational age at birth, birth order, household asset score, maternal education, maternal height or body mass index, maternal tobacco-chewing, indoor cooking	U-As in pregnancy and childhood inversely associated with height and weight at age 5 years. The strongest association with concurrent exposure, among girls, and in the lower range of exposure	7/9

SGA Small for gestational age

[a]The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.