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Accessibility
Infant Infections and Respiratory Symptoms in Relation to in Utero Arsenic Exposure in a U.S. Cohort

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BACKGROUND: Arsenic has been linked to disrupted immune function and greater infection susceptibility in highly exposed populations. Well arsenic levels above the U.S. EPA limit occur in our U.S. study area and are of particular concern for pregnant women and infants.

OBJECTIVES: We investigated whether in utero arsenic exposure affects the risk of infections and respiratory symptoms over the first year of life.

METHODS: We prospectively obtained information on infant infections and symptoms, including their duration and treatment (n = 412) at 4, 8, and 12 months using a parental telephone survey. Using generalized estimating equation models adjusted for potential confounders, we evaluated the association between maternal pregnancy urinary arsenic and infant infections and symptoms over the first year.

RESULTS: Each doubling of maternal urinary arsenic was related to increases in the total number of infections requiring prescription medication in the first year (relative risk (RR) = 1.1; 95% CI: 1.0, 1.2). Urinary arsenic was related specifically to respiratory symptoms (difficulty breathing, wheezing, and cough) lasting ≥2 days or requiring prescription medication (RR = 1.1; 95% CI: 1.0, 1.2; and RR = 1.2; 95% CI: 1.0, 1.5, respectively), and wheezing lasting ≥2 days, resulting in a doctor visit or prescription medication treatment (RR = 1.3; 95% CI: 1.0, 1.7; RR = 1.3; 95% CI: 1.0, 1.8, and RR = 1.5; 95% CI: 1.0, 2.2, respectively). Associations also were observed with diarrhea (RR = 1.4; 95% CI: 1.1, 1.9) and fever resulting in a doctor visit (RR = 1.2; 95% CI: 1.0, 1.5).

CONCLUSIONS: In utero arsenic exposure was associated with a higher risk of infection during the first year of life. We extend this work, we sought to investigate the extent to which in utero arsenic exposure may be associated with infections and other evidence of impaired immune function including early respiratory symptoms, which may indicate later-life risk of allergy and atopy (e.g., wheeze) (Ly et al. 2006; Wright 2002), among infants during their entire first year of life.

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Prenatal arsenic exposure and infant infections

Methods
We began recruiting 18- to 45-year-old pregnant women receiving prenatal care at study clinics in New Hampshire (USA) in January 2009, as previously described (Farzan et al. 2013b; Gilbert-Diamond et al. 2011). Briefly, women were screened for eligibility at an initial prenatal care visit and enrolled around 24–28 weeks gestation if they reported using water from a private, unregulated well in their home since their last menstrual period and were not planning a change in residence before delivery. Only singleton births were included in the cohort. All protocols were approved by the Dartmouth College Institutional Review Board. Participants provided written informed consent upon enrollment.

Participants were asked to complete a medical history and lifestyle questionnaire upon enrollment, which ascertained socio-demographic factors (age, race/ethnicity, marital status, education), reproductive history (previous pregnancies, complications, birth outcomes), and health history. Women were asked about habits, including tobacco and alcohol use, along with their home water source and consumption. At 2 weeks post-partum, mothers were sent a follow-up questionnaire to obtain additional information about pregnancy, delivery, and changes in key exposures. Participants also consented to a medical record review, which allowed additional information to be recorded about prenatal infections, medication use, birth outcomes, and delivery details and general health of the women and their infants after birth.

During the infant’s first year of life, parents were contacted to participate in three telephone surveys administered at 4, 8, and 12 months postpartum. In each survey, parents were asked a series of questions to determine whether their child had any infections (e.g., influenza, otitis media) or symptoms of infections (e.g., fever, cough, wheeze) in the preceding 4 months of life. We asked about 12 types of common infections, including colds/runny or stuffed nose, strep throat, ear infections, eye infections, whooping cough, pneumonia, bronchitis, respiratory syncytial virus (RSV), and influenza, as well as 5 types of symptoms, including cough, wheezing, diarrhea, and fever. For each type of infection or symptom we asked whether in the past 4 months “has [name of child] had a [infection/symptom]?” If the parent responded positively, we then asked “Did the [infection/symptom] last more than 2 days?” and “Did [name of child] see a doctor for this [infection/symptom]?” If the child had seen a doctor for the infection, we then asked “Did [name of child] receive a prescription medication for this [infection/symptom]?” The parental telephone survey responses were validated against pediatric medical records in the first year of life for a subset of the children ($n = 153$). Preliminary comparisons between the prevalence of infections involving a doctor visit obtained from pediatric medical record review were similar to those from parental interviews (data not shown).

A spot urine sample was collected from participants upon enrollment (~24–28 weeks gestation) and stored as previously described (Farzan et al. 2013b; Gilbert-Diamond et al. 2011). Urines were analyzed for arsenite (iAsIII), arsenate (iAs V), monomethylarsonic acid (MMA), dimethylarsinic acid (DMA), and arsenobetaine by high-performance liquid chromatography (HPLC) inductively coupled plasma mass spectrometry (ICP-MS) at the University of Arizona Hazard Identification Core (Larsen et al. 1993; Le et al. 2000; Wei et al. 2001). Detection limits were 0.07–0.17 μg/L for individual species, and samples that registered below the detection limit were assigned a value equal to the detection limit divided by the square root of 2. Our primary exposure measure was total urinary arsenic during pregnancy, calculated by summing inorganic (iAs = iAsIII + iAs V) and organic (DMA, MMA) metabolites, as previously reported (Farzan et al. 2013b; Gilbert-Diamond et al. 2011). We excluded arsenobetaine from the total arsenic calculation, because it is thought to be nontoxic and to pass through the body unmetabolized (Tseng 2009). Participants also collected home water samples at the time of enrollment, which were analyzed by ICP-MS at the Dartmouth Trace Element Analysis Core, as described (Farzan et al. 2013b; Gilbert-Diamond et al. 2011).

Using natural log (ln)–transformed total urinary arsenic during pregnancy (treated as a continuous variable) as our measure of in utero exposure, we tested for associations with total infant infections overall, lasting ≥ 2 days, resulting in a doctor visit, or treated with prescription medication over the first year of life. We used generalized estimating equation (GEE) models (Fitzmaurice et al. 1993; Levy 2005) by summing inorganic (iAs = iAsIII + iAs V) and organic (DMA, MMA) metabolites, as previously reported (Farzan et al. 2013b; Gilbert-Diamond et al. 2011). In a secondary analysis, we used the same modeling strategy as above, except with an independence working correlation matrix, to assess the relation between ln-transformed maternal pregnancy urinary arsenic and common types of infections as separate outcomes within each time interval (i.e., 0–4, 5–8, and 9–12 months), similar to methods in prior work (Farzan et al. 2013b). We evaluated the relation between ln-transformed maternal urinary arsenic and total number of infections reported within each time interval, as well as those lasting ≥ 2 days, resulting in a doctor visit, or treated with a prescription medication.

Models included covariates that could influence infection risk based on a priori considerations, including age at enrollment (years), smoking during pregnancy (yes/no), relationship status (married, single, divorced/ widowed), education (≤ 11th grade, high school, some college, college, postgraduate), parity (0, 1–2, ≥ 3), delivery type (vaginal, cesarean), infant sex, birth weight (grams), gestational age (weeks), breastfeeding (ever, never in GEE models; yes/no during each interval for time specific models), and child care attendance (yes/no during each interval). Gestational age was calculated using first trimester ultrasound gestational age estimates or, if an ultrasound was unavailable, last menstrual period date. For maternal smoking and birth weight, which were missing for 29 and 15 individuals, respectively, due to incomplete records at the time of analysis, we applied the missing indicator method in our GEE analyses (Miettinen 1985).

Finally, we assessed nonlinear trends of the data for the total number of infections in the first year resulting in a doctor visit or treated with a prescription medication using a generalized additive model (GAM) with cubic regression splines.
Results

Of the 1,033 mothers enrolled in our study, 726 had infants who were at least 12 months of age at the time of analysis. Three hundred seven women either had not yet given birth or had yet to participate in an interval questionnaire. A total of 683 mothers had completed at least one follow-up questionnaire during the infant’s first 12 months, and 412 had maternal urinary arsenic measured at the time of these analyses. Mothers who had urinary arsenic results available did not significantly differ from those who did not (n = 271) in any key demographic or lifestyle characteristics, nor did mothers who completed at least one questionnaire differ from those who had not (n = 350) (data not shown).

Demographic data. The mean (± SD) participant age was 31.2 ± 4.9 years at the time of delivery (Table 1). Most (95%) reported that they did not smoke while pregnant and were not exposed to secondhand smoke (91%). Slightly more than half of infants were female (54%) and infants had a mean (± SD) birth weight of 3,438 ± 544 g. The average (± SD) gestational age at birth was 40 ± 2 weeks (Table 1). Most children (70%) were not in child care at 4 months, but the percentage of children receiving all care in the home decreased with age (63% at 8 months, 60% at 12 months). Forty-three percent of mothers reported exclusive breastfeeding at 4 months, and 36% were still breastfeeding their child at 12 months (Table 1).

Infections were common, with nearly all parents (94%) reporting at least one infection in the infant’s first year of life, of which 90% lasted ≥ 2 days (Table 2). More than half (51%) reported at least one infection that involved a doctor visit, and 41% reported at least one infection that was treated with prescription medicine. Upper respiratory infections were the most commonly reported type of infection (89% of infants during the first year).

Arsenic exposure. The median maternal total urinary arsenic concentration was 3.8 μg/L and the mean (± SD) was 5.7 ± 6.5 μg/L (range, 0.5–58.3 μg/L) (Table 1). The average drinking water arsenic concentration was 4.6 μg/L (range, 0.0–147.7 μg/L) (Table 1).

In utero arsenic exposure and infant infections. After adjustment for maternal age, parity, smoking, infant sex, gestational age, birth weight, breastfeeding, and child care attendance, each doubling of maternal urinary arsenic concentration during pregnancy on a micrograms per liter natural log scale was associated with an increased risk of any infection resulting in a doctor visit [relative risk (RR) = 1.1; 95% confidence interval (CI): 1.0, 1.2] (Table 3, Figure 1A) or that was treated with prescription medication (RR = 1.1; 95% CI: 1.0, 1.2) (Table 4, Figure 1B). We did not find evidence of nonlinearity (e.g., p-value for linearity = 0.73 for infections treated with prescription medication). Each doubling of maternal urinary arsenic was associated with increased risk of infections treated with prescription medication (Table 4), including upper respiratory (RR = 1.1; 95% CI: 1.0, 1.2), lower respiratory (RR = 1.2; 95% CI: 1.0, 1.5), and colds, or runny or stuffed noses (RR = 1.2; 95% CI: 1.0, 1.4). Maternal urinary arsenic was associated with greater risk of respiratory symptoms treated with prescription medication (RR = 1.2; 95% CI: 1.0, 1.5) (Table 4), as well as for those lasting ≥ 2 days (RR = 1.1; 95% CI: 1.0, 1.5) (Table 2). Maternal urinary arsenic was associated with an increased risk of wheezing lasting ≥ 2 days (RR = 1.3; 95% CI: 1.0, 1.7), resulting in a doctor visit (RR: 1.3, 95% CI: 1.0, 1.8).

Table 1. Selected sample characteristics for mothers and infants participating in the New Hampshire Birth Cohort Study (n = 412).

| Variable                          | Mean (range) or percent |
|----------------------------------|-------------------------|
| **Maternal variables**           |                         |
| Drinking-water arsenic           | 4.6 (0.0–147.7)         |
| Median (IQR)                     | 0.5 (3.1)               |
| Pregnancy urinary arsenic        | 5.7 (0.5–58.3)          |
| Median (IQR)                     | 3.8 (4.8)               |
| Age at enrollment (years)        |                         |
| < 20                             | 2                       |
| 20–29                            | 40                      |
| 30–35                            | 41                      |
| > 35                             | 17                      |
| Education level                 |                         |
| < 11th grade                     | 1                       |
| High school graduate, Ged        | 9                       |
| Junior college, some college, technical school | 21 |
| College graduate                 | 39                      |
| Postgraduate schooling           | 30                      |
| Relationship status              |                         |
| Single                           | 12                      |
| Married                          | 84                      |
| Separated, divorced              | 4                       |
| Smoking during pregnancy         |                         |
| Yes                              | 5                       |
| Secondhand smoke exposure        |                         |
| Yes                              | 9                       |
| Prepregnancy BMI                 | 25.1 (17.0–48.3)        |
| Parity                           |                         |
| Nulliparous                      | 43                      |
| 1–2                              | 50                      |
| ≥ 3                              | 7                       |
| Delivery type                    |                         |
| Vaginal (spontaneous or induced) | 67                      |
| Cesarean                         | 33                      |
| Infant variables                 |                         |
| Sex                              |                         |
| Male                             | 46                      |
| Birth weight (g)                 | 3438.3 (1380.0–5318.0)  |
| Gestational age (weeks)          | 39.5 (26.9–44.9)        |
| Child care setting               |                         |
| In child care at 4 months        | 30                      |
| In child care at 8 months        | 37                      |
| In child care at 12 months       | 40                      |
| Feeding                          |                         |
| Exclusively formula fed at 4 months | 7                  |
| Exclusively breastfed at 4 months | 43                      |
| Still breastfeeding at 6 months  | 56                      |
| Still breastfeeding at 12 months | 36                      |
| Infections within first 12 months of life |         |
| At least one infection           | 94                      |
| At least one infection lasting ≥ 2 days | 90               |
| At least one infection resulting in a doctor visit | 51 |
| At least one infection treated with prescription medication | 41 |

*Sum of subjects is less than total sample size due to missing values (25 subjects missing drinking-water arsenic, 33 missing education and relationship status, 28 missing smoking, 35 missing prepregnancy BMI and secondhand smoke exposure, 1 missing parity, 11 missing delivery type, 2 missing sex, 15 missing birth weight, and 10 missing gestational age).
or treatment with prescription medication (RR = 1.5; 95% CI: 1.0, 2.2) (Tables 2, 3, and 4). Additionally, diarrhea resulting in a doctor visit (RR = 1.4; 95% CI: 1.1, 1.9) in the first year was associated with arsenic exposure, as was fever resulting in a doctor visit (RR = 1.2; 95% CI: 1.0, 1.5) (Table 3).

In general, associations with arsenic exposure during pregnancy were stronger for infections at 4 months of age and weaker for infections or symptoms at 8 or 12 months. Over the first 4 months, maternal urinary arsenic was associated with an increased risk of infections among children in the first year of life, per doubling of urinary arsenic was associated with an increased risk of total infections resulting in a doctor visit (RR = 1.1; 95% CI: 1.0, 1.2) and wheezing lasting ≥ 2 days (RR = 1.6; 95% CI: 1.0, 2.4) (Tables 2 and 3). At 12 months of age, maternal urinary arsenic was related to an increased risk of respiratory symptoms treated with prescription medication (RR = 1.3; 95% CI: 1.0, 1.6) (Table 4), and cough lasting ≥ 2 days (RR = 1.2; 95% CI: 1.0, 1.5) (Table 5).

### Discussion

Prenatal arsenic exposure was associated with an increased risk of infections among children in the first year of life in our U.S.

#### Table 2. Relative risk estimates* (95% CI) for infant infections or symptoms lasting ≥ 2 days in the first year of life, per doubling of maternal − 24–28 weeks gestation urinary arsenic (n = 412).

| Infections                                      | 0–4 months | 5–8 months | 9–12 months | Over the first year |
|-------------------------------------------------|------------|------------|-------------|---------------------|
| Any infection lasting ≥ 2 days                  | 1.1 (1.0, 1.2) | 1.0 (0.9, 1.1) | 1.0 (0.9, 1.1) | 1.0 (0.9, 1.1) |
| Respiratory tract infections (RTI)              |            |            |             |                     |
| Any upper RTI                                   | 1.1 (1.0, 1.2) | 1.0 (0.9, 1.1) | 1.0 (0.9, 1.1) | 1.0 (1.0, 1.1) |
| Any lower RTI (i.e., bronchitis, pneumonia, bronchiolitis, RSV, pertussis) | 1.2 (0.8, 1.8) | 1.3 (0.9, 1.8) | 1.0 (0.6, 1.8) | 1.1 (0.9, 1.4) |
| Acute symptoms, conditions, illnesses          |            |            |             |                     |
| Any respiratory (i.e., cough, wheeze, difficulty breathing) | 1.2 (1.0, 1.4) | 1.0 (0.9, 1.2) | 1.2 (1.0, 1.5) | 1.1 (1.0, 1.5) |
| Wheezing                                        | 1.4 (0.9, 2.3) | 1.6 (1.0, 2.4) | 0.7 (0.4, 1.4) | 1.3 (1.0, 1.7) |
| Cough                                           | 1.2 (1.0, 1.5) | 1.0 (0.8, 1.2) | 1.2 (1.0, 1.5) | 1.1 (1.0, 1.2) |
| Difficulty breathing                            | 1.0 (0.6, 1.8) | 1.2 (0.8, 1.9) | 1.3 (0.7, 2.7) | 1.1 (0.8, 1.5) |
| Gastrointestinal (i.e., diarrhea)               | 1.6 (0.9, 2.9) | 1.3 (0.9, 2.0) | 1.1 (0.8, 1.5) | 1.2 (0.9, 1.6) |
| Fever                                           | 1.2 (0.6, 2.2) | 1.1 (0.8, 1.5) | 1.2 (0.9, 1.6) | 1.1 (0.9, 1.3) |

*Estimates after adjustment for maternal age, parity, smoking, infant sex, gestational age, birth weight, breastfeeding, and child care attendance. *Number of children with a report of at least one infection (for estimates over the first year, each child could contribute up to three reports, one per interval questionnaire, of any type of infection).

#### Table 3. Relative risk estimates* (95% CI) for infant infections or symptoms resulting in a doctor visit in the first year of life, per doubling of maternal − 24–28 weeks gestation urinary arsenic (n = 412).

| Infections                                      | 0–4 months | 5–8 months | 9–12 months | Over the first year |
|-------------------------------------------------|------------|------------|-------------|---------------------|
| Any infection resulting in a doctor visit       | 1.1 (1.0, 1.2) | 1.1 (1.0, 1.2) | 1.0 (0.9, 1.2) | 1.1 (1.0, 1.2) |
| Respiratory tract infections (RTI)              |            |            |             |                     |
| Any upper RTI                                   | 1.1 (1.0, 1.3) | 1.1 (0.9, 1.2) | 1.0 (0.9, 1.2) | 1.1 (1.0, 1.1) |
| Any lower RTI (i.e., bronchitis, pneumonia, bronchiolitis, RSV, pertussis) | 1.0 (0.7, 1.4) | 1.2 (0.9, 1.6) | 1.0 (0.6, 1.6) | 1.1 (0.9, 1.4) |
| Acute symptoms, conditions, illnesses          |            |            |             |                     |
| Any respiratory (i.e., cough, wheeze, difficulty breathing) | 1.2 (1.0, 1.4) | 1.0 (0.9, 1.2) | 1.1 (0.9, 1.4) | 1.1 (0.8, 1.3) |
| Wheezing                                        | 1.5 (0.9, 2.5) | 1.5 (0.9, 2.4) | 1.0 (0.6, 1.7) | 1.3 (1.0, 1.8) |
| Cough                                           | 1.2 (0.9, 1.6) | 0.9 (0.7, 1.2) | 1.2 (0.9, 1.7) | 1.0 (0.9, 1.2) |
| Difficulty breathing                            | 1.5 (0.9, 2.6) | 1.2 (0.8, 1.8) | 1.5 (0.8, 2.9) | 1.3 (0.9, 1.8) |
| Gastrointestinal (i.e., diarrhea)               | 1.9 (1.1, 4.8) | 1.5 (0.9, 2.5) | 1.3 (0.9, 1.9) | 1.4 (1.1, 1.9) |
| Fever                                           | 1.2 (0.7, 1.9) | 1.4 (1.0, 1.9) | 1.2 (0.9, 1.6) | 1.2 (1.0, 1.5) |

*Estimates after adjustment for maternal age, parity, smoking, infant sex, gestational age, birth weight, breastfeeding, and child care attendance. *Number of children with a report of at least one infection (for estimates over the first year, each child could contribute up to three reports, one per interval questionnaire, of any type of infection).
A larger cohort study (n = 1,552) in Bangladesh likewise found that higher levels of urinary arsenic in pregnancy were associated with increased risk of lower respiratory infections and diarrhea in infants over the first year of life (Rahman et al. 2011). In our earlier analysis of in utero arsenic exposure and infections and symptoms up to 4 months of age in a smaller subset of infants, we found that maternal urinary arsenic was related to total number of infections requiring a doctor visit or prescription medication, as well as respiratory infections and symptoms treated with prescription medication in the first 4 months (Farzan et al. 2013b). In the present study, in which we expanded our sample size and obtained multiple repeated measurements of infections through age 1 year, we found an association between maternal arsenic exposure during pregnancy and increased risks of total infections, fever, and diarrhea resulting in a doctor visit, as well as infections and symptoms treated with prescription medication, including respiratory infections, respiratory symptoms, and wheezing. Findings from the present study are consistent with

![Figure 1: Maternal arsenic exposure and mean total infections over the first year of life. The relation of ln-transformed maternal urinary arsenic at ~ 24–28 weeks gestation with mean total infections over the first year of life that resulted in a doctor visit (A) or treatment with prescription medication (B), based on Poisson models, adjusted for maternal age, parity, smoking, infant sex, gestational age, birth weight, breastfeeding, and child care attendance. p-values for linearity based on GAM were 0.39 and 0.73, respectively. Dotted lines represent the 95% CI.]

### Table 4. Relative risk estimates (95% CI) for infant infections or symptoms treated with prescription medication in the first year of life, per doubling of maternal (~ 24–28 weeks gestation) urinary arsenic (n = 412).

| Infections                                           | 0–4 months | 5–8 months | 9–12 months | Over the first year |
|------------------------------------------------------|------------|------------|-------------|---------------------|
| Any infection treated with prescription medication   | 1.3 (1.1, 1.5) | 1.0 (0.9, 1.2) | 1.1 (0.9, 1.2) | 1.1 (1.0, 1.2)      |
| Respiratory tract infections (RTI)                   |            |            |             |                     |
| Any upper RTI                                        | 1.2 (1.0, 1.5) | 1.0 (0.9, 1.2) | 1.1 (0.9, 1.2) | 1.1 (1.0, 1.2)      |
| Any lower RTI (i.e., bronchitis, pneumonia, bronchiolitis, RSV, pertussis) | 1.6 (1.1, 2.3) | 1.1 (0.8, 1.5) | 1.1 (0.7, 1.9) | 1.2 (1.0, 1.5)      |
| Acute symptoms, conditions, illnesses               |            |            |             |                     |
| Any respiratory (i.e., cough, wheeze, difficulty breathing) | 1.5 (1.1, 2.0) | 1.1 (0.9, 1.3) | 1.3 (1.0, 1.6) | 1.2 (1.0, 1.5)      |
| Wheezing                                             | 2.1 (1.0, 4.3) | 1.4 (0.8, 2.5) | 1.0 (0.5, 2.0) | 1.5 (1.0, 2.2)      |
| Cough                                                | 1.5 (0.8, 2.9) | 0.9 (0.6, 1.4) | 1.4 (0.8, 2.2) | 1.2 (0.9, 1.6)      |
| Difficulty breathing                                 | 1.6 (0.9, 1.3) | 1.2 (0.8, 1.8) | 1.5 (0.8, 2.9) | 1.2 (0.9, 1.6)      |
| Gastrointestinal (i.e., diarrhea)                    | 1.3 (0.7, 2.2) | 1.1 (0.7, 1.7) | 1.3 (0.8, 1.9) | 1.2 (0.8, 1.6)      |

--- too few observations to estimate.

*Estimates after adjustment for maternal age, parity, smoking, sex, gestational age, birth weight, breastfeeding, and child care. †Number of children with at least one reported infection (Over the first year, each child could contribute up to three reports, one per interval, for any infection).
the results of previous studies, which have consistently observed increases in similar types of infections in the first year of life, most frequently respiratory infections, across a range of exposure levels.

Although it is possible that associations between in utero arsenic exposure and early infections in our study population represent a transient effect, prenatal arsenic exposure has been associated with immune alterations that may indicate long-term impacts on immune functionality. These include decreased thymic size and function, enhanced inflammatory responses, increased oxidative stress and cytokine levels, and immune changes in the placenta (Ahmed et al. 2011, 2012; Dangleben et al. 2013; Fry et al. 2007; Rager et al. 2014; Raqib et al. 2009). Evidence suggests that arsenic exposure may fundamentally transform the immune response by altering developmental signaling pathways. Among newborns in the BEAR (Markers of Exposure to Arsenic) cohort in Mexico, prenatal arsenic exposure was associated with altered cord blood expression levels of 12 microRNAs and 334 mRNA transcripts (Rager et al. 2014). Pathway analysis and interaction mapping found that many of these molecules are involved in innate and adaptive immune response, as well as respiratory disease (Rager et al. 2014), similar to previously observed inflammatory and immune-related gene alterations in arsenic-exposed newborns in Thailand (Fry et al. 2007). Recent evidence indicates that even relatively low levels of in utero arsenic exposure can impair T-cell function and alter the fetal immune cell repertoire found in cord blood at birth, skewing it toward a pro-inflammatory Th2 (T-helper 2) phenotype (Nadeau et al. 2014), which could impact long-term immune response and allergy development (Belderbos et al. 2009). Although limited in number, these studies begin to indicate that prenatal arsenic exposure may impair healthy immune development, although further mechanistic data are needed, especially at lower exposure levels.

A growing body of evidence supports a connection between arsenic exposure and lung disease and impairment. In animal models, transplacental arsenic exposure affects lung development, by altering pulmonary structure and function (Lantz et al. 2009; Ramsey et al. 2013b), changing expression of lung morphogenesis and structurally important extracellular matrix genes (Petrick et al. 2009; Ramsey et al. 2013b), and increasing susceptibility to infection (Ramsey et al. 2013a). Studies from Bangladesh and West Bengal described increased incidence of respiratory disorders, chronic bronchitis, decreased lung function, and bronchiectasis among arsenic-exposed individuals, compared with unexposed adults (Mazumder et al. 2000, 2005; Milton et al. 2001; Milton and Rahman 2002; von Ehrenstein et al. 2005). In Antofagasta, Chile, where public water arsenic levels reached nearly 900 μg/L from 1958 to 1971, residents experienced increased rates of mortality from pulmonary tuberculosis (Smith et al. 2011), and those exposed to high arsenic levels in utero or during early life had higher mortality from lung cancer, bronchiectasis, and chronic lung disease, than residents of a nonexposed region (Smith et al. 2006).

Prospective work from Bangladesh found that well and urinary arsenic were related to increases in respiratory symptoms, including chronic cough and difficulty breathing, as well as significant lung function impairment (Farve et al. 2010, 2013). Similar associations between high-level early life arsenic exposure and respiratory impairment in children have also been reported. In Bangladesh, 7- to 17-year-olds exposed to > 500 μg/L water arsenic throughout childhood, and likely in utero as well, reported increased wheezing [odds ratio (OR) = 8.4; 95% CI: 1.7, 42.6] and shortness of breath [OR = 3.9; 95% CI: 1.1, 13.7], compared with children exposed to water with arsenic < 10 μg/L (Smith et al. 2013). A recent prospective study of 6- to 12-year-old Mexican children reported a relationship between in utero and early-life arsenic exposure and clinical indicators of decreased lung function (Recio-Vega et al. 2015). These studies indicate that arsenic exposure across life stages may adversely affect lung function and increase risk of lung disease. Although additional follow-up is needed, our findings of increased risk of wheezing or respiratory symptoms may signal later risk of lung disease (Ly et al. 2006; Wright 2002).

Our study has strengths and limitations. Our analyses used carefully collected prospective data, including repeated assessments of infection occurrence over the first year of life, as well as information on potential confounders, including detailed maternal medical and sociodemographic information. The study’s internal validity is strengthened by the prospective longitudinal design. Repeated-measures analyses can reveal changes in the frequency of common outcomes that may appear small on an individual basis, but are relevant to the population at large (Farrington 1991). Our exposure measure was maternal urinary arsenic, a biomarker of in utero exposure. However, we lacked sufficient information on postnatal infant exposure to arsenic (i.e., from food or water sources), which may contribute to overall exposure and health outcomes as these children age. The accuracy of parental recall is a potential source of bias, but we attempted to minimize misclassification and assess infection severity by focusing on infections requiring a doctor visit or prescription medicine. We cannot rule out the possibility that reporting inaccuracies may be related to maternal exposure status, potentially causing differential misclassification, or of nondifferential misclassification reducing our ability to observe associations.

Conclusions

Infectious diseases still remain a primary cause of mortality in young children, resulting in > 4 million deaths before the age of 5 each year (WHO 2010). All infants, even those born in developed countries, experience a high burden of infection-related morbidity and mortality, particularly in the first year of life and primarily from respiratory infections and diarrhea (Mehal et al. 2012; Tregoning and Schwarz 2010; Yorita et al. 2008). Early-life respiratory infections have been associated with wheezing symptoms, and may predict later-life asthma and atopic disease (Ly et al. 2006; Wright 2002). Incidence of these conditions has risen rapidly in recent years (Aberg et al. 1995; Heinrich et al. 2002), with approximately 300 million individuals worldwide affected at 20 years of age and approximately 30% of the population of industrialized countries affected by atopic conditions (Palomares et al. 2010; WHO 2007). Moreover, common rhinovirus infection was the strongest predictor of later-life wheezing among children at high risk of developing asthma (Lemanske et al. 2005). Although our current knowledge of the effects of arsenic exposure on childhood immunity is still very limited, our study is among the first to explore this issue in a population exposed at relatively common environmental levels. Millions worldwide are exposed to elevated arsenic concentrations in drinking water, and dietary sources may contribute to overall exposure; thus even small increases in infection morbidity or severity due to arsenic exposure could have broad public health impacts.

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