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# Arsenic in drinking water and adverse birth outcomes in Ohio

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ABSTRACT

*Background:* Arsenic in drinking water has been associated with adverse reproductive outcomes in areas with high levels of naturally occurring arsenic. Less is known about the reproductive effects of arsenic at lower levels.
*Objectives:* This research examined the association between low-level arsenic in drinking water and small for gestational age (SGA), term low birth weight (term LBW), very low birth weight (VLBW), preterm birth (PTB), and very preterm birth (VPTB) in the state of Ohio.
*Methods:* Exposure was defined as the mean annual arsenic concentration in drinking water in each county in Ohio from 2006 to 2008 using Safe Drinking Water Information System data. Birth outcomes were ascertained from the birth certificate records of 428,804 births in Ohio from the same time period. Multivariable generalized estimating equation logistic regression models were used to assess the relationship between arsenic and each birth outcome separately. Sensitivity analyses were performed to examine the roles of private well use and prenatal care utilization in these associations.
*Results:* Arsenic in drinking water was associated with increased odds of VLBW (AOR 1.14 per μg/L increase; 95% CI 1.04, 1.24) and PTB (AOR 1.10; 95% CI 1.06, 1.15) among singleton births in counties where < 10% of the population used private wells. No significant association was observed between arsenic and SGA, or VPTB, but a suggestive association was observed between arsenic and term LBW.
*Conclusions:* Arsenic in drinking water was positively associated with VLBW and PTB in a population where nearly all (> 99%) of the population was exposed under the current maximum contaminant level of 10 μg/L. Current regulatory standards may not be protective against reproductive effects of prenatal exposure to arsenic.

## 1. Introduction

Arsenic is the 20th most common element in the Earth's crust and is a naturally occurring water contaminant in many regions of the world (IARC, 2004). The primary route of human exposure to arsenic is through contaminated drinking water, with additional contributions from contaminated food and air (Vahter, 2009; World Health Organization (WHO), 2011). While arsenic in drinking water has been classified as a Group 1 (known) carcinogen to humans (IARC, 2004) for bladder, lung, and skin cancers; the effect of chronic arsenic exposure through drinking water on fetal development is less well understood. Arsenic and its metabolites readily cross the placental barrier, and arsenic levels in cord blood are nearly as high as in maternal blood, demonstrating biologic plausibility for an association between exposure and fetal development (Concha et al., 1998; Hall et al., 2007). Currently, the maximum contaminant level (MCL) in drinking water set by the WHO and the USEPA is 10 μg/L, based on risk of cancers, cardiovascular diseases, and neurologic effects (40 C.F.R. § 141.62).

A growing body of epidemiologic research from regions with elevated arsenic levels in drinking water suggests that arsenic exposure during pregnancy is associated with reduced birth weight. In a cross-sectional study of pregnant women in Taiwan, women residing in areas

*Abbreviations:* AOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; CFR, Code of Federal Regulations; CWS, community water system; GEE, generalized estimating equations; IARC, International Agency for Research on Cancer; LMP, last menstrual period; LOD, limit of detection; MCL, maximum contaminant level; NHLBI, National Heart, Lung, and Blood Institute; ODH, Ohio Department of Health; PNC, prenatal care; PTB, preterm birth; SDWIS, Safe Drinking Water Information System; SES, socio-economic status; SGA, small for gestational age; term LBW, term low birth weight; USEPA, United States Environmental Protection Agency; USGS, United States Geological Survey; VLBW, very low birth weight; VPTB, very preterm birth; WHO, World Health Organization; WIC, Women, Infants, and Children

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of high drinking water arsenic (range, 0.15–590 μg/L) delivered infants with significantly lower mean birth weight than women in low arsenic areas (< 0.15 μg/L) (Yang et al., 2003). Similarly, a prospective cohort study comparing birth outcomes between two Chilean cities, one with a mean arsenic concentration in drinking water of 42 μg/L and one with an average arsenic concentration < 1 μg/L, found increased arsenic levels were associated with a 57 g reduction in birth weight (Hopenhayn et al., 2003). In a cohort of pregnant Bangladeshi women, a significant dose-response relationship between arsenic and birth weight, head circumference, and chest circumference was observed only for women with lower arsenic exposure (< 100 μg/L in urine) compared to those with higher arsenic exposures (≥100 μg/L) (Rahman et al., 2009). In a study of mothers and infants in Oklahoma, USA, Claus Henn et al. (2016) found that maternal urinary arsenic concentrations (median 0.3 μg/L) were significantly inversely related to birth weight and gestational length, although the fetal arsenic exposure was not solely from drinking water. In a cohort of 706 women and their infants in New Hampshire, USA, Gilbert-Diamond et al. (2016) found a significant decrease in birth weight from arsenic in drinking water and diet only among female infants born to overweight or obese mothers. The specific exposure window during pregnancy in which the fetus is most susceptible to the effects of arsenic is unknown, but one study of pregnant women in Bangladesh found a significant decrease in birthweight among women with higher arsenic exposure early in pregnancy (Huyck et al., 2007). Kwok et al. (2006), however, found no association between drinking water arsenic and birthweight among term infants born to women residing in three regions of Bangladesh with a range of exposures to arsenic through drinking water. In a prospective study of 122 pregnant women in Romania, Bloom et al. (2015) found a significant negative relationship between arsenic in drinking water and birthweight only among smokers.

Epidemiologic evidence of an association between arsenic in drinking water and preterm birth is inconsistent (Bloom et al., 2014). In a cross-sectional study of birth outcomes in Bangladesh, women who lived in an arsenic-affected village (mean arsenic in drinking water 240 μg/L, range 200–1371 μg/L) had significantly increased rates of spontaneous abortions, stillbirths, and preterm births compared to those in a "non-exposed" village (≤20 μg/L in drinking water) (Ahmad et al., 2001). Yang et al. (2003) found a non-significant increase in the odds of preterm birth among women in a high drinking water arsenic region compared to those in a low arsenic region. A study of adverse birth outcomes in Inner Mongolia did not detect an association of drinking water arsenic levels > 50 μg/L with preterm birth (Myers et al., 2010). In a sample of Chinese male infants, gestational age was significantly inversely related to arsenic in maternal blood (Xu et al., 2011). Preterm birth and reduced birthweight were spatially associated with higher levels of groundwater arsenic in New Hampshire, USA (Shi et al., 2015).

The majority of data on arsenic and birth outcomes are from populations with very high exposure, such as Bangladesh, West Bengal, China, and Argentina. Associations and dose-response relationships observed at high levels of exposure may not accurately reflect those at lower exposure. Less is known about reproductive health effects at low arsenic exposures (Quansah et al., 2015), such as those found in the Midwestern United States. The objective of this research was to examine the association between arsenic in drinking water and five birth outcomes; small for gestational age, term low birth weight, very low birth weight, preterm birth, and very preterm birth; in the state of Ohio where arsenic levels are relatively low.

## 2. Methods

### 2.1. Study population

This study used birth certificate data (from the 2003 revision of the U.S. Certificate of Live Birth) for births occurring in the state of Ohio between 2006 and 2008. Individual-level, de-identified birth certificate data for children born in Ohio was provided by the Ohio Department of Health (ODH).

### 2.2. Birth outcomes

The primary outcomes of interest in the study were small for gestational age (SGA), term low birth weight (term LBW), very low birth weight (VLBW), preterm birth (PTB), and very preterm birth (VPTB). SGA was defined as the smallest 10% of infants, according to birth weight, at each gestational age in the population (Wilcox, 2010). SGA status was calculated using sex- and gestational age-specific national birth weight references developed by Duryea et al. (2014). Term LBW was defined as an infant weighing < 2500 g at time of delivery among term infants (≥37 weeks gestation). An infant was considered VLBW if it weighed < 1500 g at time of delivery, regardless of gestational age. Preterm and very preterm births were defined as infants delivered prior to 37 and 32 weeks gestation, respectively. Gestational age was based on the reported last normal menstrual period (LMP). If the LMP was unknown, a clinical estimate of gestation was used. All birth outcomes were either reported directly on or were calculated from variables reported on the birth certificates.

### 2.3. Exposure assessment

The USEPA defines the legal limits of water contaminants and water testing schedules, as mandated in the Safe Drinking Water Act. The MCL for arsenic in drinking water is 10 μg/L (40 C.F.R. § 141.62). Public drinking water systems are required to monitor for arsenic every three years when using groundwater and annually when using surface water sources (40 C.F.R. § 141.23).

A total of 2968 arsenic measurements from 975 community water systems (CWS) in Ohio from 2006 to 2008 were obtained from the Ohio EPA Safe Drinking Water Information System (SDWIS). An annual measure of arsenic in drinking water was calculated for each of the 88 counties in Ohio as follows. First all measurements in each CWS providing drinking water in a county in a year were averaged, giving a CWS-year mean. Second, the CWS-year means in each county were averaged, weighted by the population served to control for the variable distribution network sizes of CWSs within a county. The resulting county-year mean was used as the exposure measure. The median number of CWSs in each county was 11, with a range from 3 to 54. The exposure measure assumed that each CWS serves only residents in the county in which the CWS office is located (Jones et al., 2014). The limits of detection (LODs) varied, but were typically 0.5 μg/L, and measurements below the LOD were equated with LOD/2. County-level population percentages of those using private well water were obtained from the Unites States Geological Survey (USGS) (USGS, 2015).

The arsenic exposure measures were linked with birth outcomes by the county and year(s) of gestation. If an infant's entire gestation fell within one calendar year, the county-year arsenic measure was assigned to the birth. If an infant's gestation spanned two calendar years, an average of the two annual estimates of arsenic was assigned to that birth, weighted by gestational months in each calendar year.

### 2.4. Covariates

The individual-level covariates were ascertained from the birth certificates and included infant sex, maternal age at birth, mother's race/ethnicity, maternal educational attainment, marital status, prenatal care (PNC) utilization, socioeconomic status, parity, cigarette use, and maternal pre-pregnancy body mass index (BMI). Maternal age was categorized as 10–19, 20–29, 30–39, and ≥40 years of age. Maternal race/ethnicity was defined as non-Hispanic white, non-Hispanic black, Hispanic, and other/unknown. Maternal educational attainment was categorized as less than a high school degree, high school degree, some

**Table 1**
Summary of mean annual arsenic concentrations reported in finished[a] public drinking water samples for all Ohio counties (N = 88) between 2000 and 2008.

| Year | Mean ± SD (μg/L) | Median concentration (μg/L) | Minimum concentration (μg/L) | Maximum concentration (μg/L) | Percent Missing[b] (%) |
|---|---|---|---|---|---|
| 2006 | 2.04 ± 1.42 | 1.51 | 0.74 | 10.51 | 5 |
| 2007 | 2.33 ± 2.08 | 1.50 | 0.74 | 12.17 | 10 |
| 2008 | 1.84 ± 0.98 | 1.50 | 0.50 | 6.28 | 7 |

Data source: Ohio EPA Safe Drinking Water Information System.
[a] Finished water refers to treated water.
[b] Percentage of counties missing an annual mean arsenic concentration.

college, and college degree or higher. Marital status was dichotomized as married or not married. The Kotelchuck index was used to define adequate PNC utilization. The Kotelchuck index classifies the adequacy of PNC utilization based on the month of entry into PNC and total number of PNC visits adjusted for gestational age when care began (Kotelchuck, 1994). Maternal smoking was dichotomized as smoker versus non-smoker. The cigarette use data was non-specific to the window of time including pregnancy. Whether or not the mother was enrolled in the Women, Infant, and Children (WIC) supplemental nutrition program was used as a proxy for low socioeconomic status (SES). Maternal pre-pregnancy BMI was categorized according to the National Heart, Lung, and Blood Institute (NHLBI) definitions of underweight, normal, overweight, and obese (NHLBI, 1998). Parity was categorized as having had 0, 1, 2, or ≥3 previous live births.

### 2.5. Data analysis

We explored bivariate relationships between arsenic concentrations and each outcome using *t*-tests. Additionally, we examined bivariate relationships between annual concentrations of arsenic and each covariate as well as each covariate and each outcome using *t*-tests for continuous variables, Rao-Scott Chi-Square tests for dichotomous variables, and ANOVA test for covariates with > 2 categories. Potential confounders were considered as those variables that were associated with both the exposure measures and outcome measures and were not in the causal pathway. Maternal age, maternal race/ethnicity, and infant sex were included in modeling based on *a priori* knowledge.

We developed generalized estimating equation (GEE) logistic regression models, with an exchangeable working correlation structure and robust standard errors, to estimate the association between arsenic in drinking water and dichotomous birth outcomes, including SGA, term LBW, VLBW, PTB, and VPTB while accounting for clustering at the county level. Arsenic exposure was treated as a continuous variable in the models. Confounding was indicated if the effect estimate for the exposure variable changed by more than 10% with the addition of the potential confounder into the model. Between 9% and 10% of observations were not used due to missing data on covariates, exposure, or outcome status. All analyses were performed using SAS®, Version 9.4 (SAS Institute, Inc., 2002). Based on the findings of Bloom et al. (2015), multiplicative interaction between arsenic in drinking water and prenatal smoking status was assessed through the use of a product term in the modeling process.

Two sets of sensitivity analyses were performed to better understand the relationship between arsenic and the birth outcomes of interest. The study lacks estimates of arsenic in private well water, therefore sensitivity analyses were performed which restrict the arsenic analyses *a priori* to counties with < 20% (N = 31) and < 10% (N = 20) of county residents using private well water to explore the exposure-outcome relationship in those counties with the least exposure misclassification. The mean percentage of private well use in Ohio counties was 31% (range 0–81%). Twenty-six percent of birth certificates for singleton births in Ohio were missing either the month of entry into PNC or the number of PNC visits attended which resulted in a missing Kotlechuck index score of PNC utilization. To better understand the role of this important covariate, we examined the association between arsenic and each outcome across three sets of models: (1) full sample analyses as described above, without controlling for PNC; (2) complete case analyses of those with non-missing PNC data, but not controlling for PNC; and (3) complete case analyses of those with non-missing PNC data, controlling for PNC.

## 3. Results

### 3.1. Descriptive statistics

County-year mean arsenic concentrations ranged from 0.50 to 12.2 μg/L during 2006–2008 (Table 1). County-year mean concentrations were missing in 5%, 10%, and 7% of counties in 2006, 2007, and 2008 respectively, such that < 4% of births in each year did not have an exposure measure. Annual concentrations of arsenic did not exceed the MCL of 10 μg/L among counties with < 20% of the population receiving drinking water from private wells.

There were 428,804 live singleton births in Ohio between 2006 and 2008, of which 51% were male (Table 2). The majority of the births were born to mothers who were non-Hispanic white (76%), between 20 and 29 years old (56%), had completed more than a high-school degree (54%), were married (58%), and parous (59%). Only 38% of mothers reported intermediate or adequate PNC utilization, but 26% had an unknown level of PNC utilization. There was a high prevalence of obesity (25%), WIC use (42%), and reported cigarette use (26%) in this population. Among live singleton births, 10.6% were SGA, 1.2% were very low birth weight, 10.9% were preterm, and 1.8% very preterm. Among singleton term births, 2.9% were term LBW. With the exception of PNC utilization, there were low levels of missing data on covariates. Less than 1% of births were missing data on maternal age (N = 1536), education (N = 3460), and cigarette use (N = 44). Between 2% and 3% of births were missing data on parity (N = 11,173), pre-pregnancy BMI (14,374), and WIC status (12,309).

Nearly all covariates were significantly associated with each of the five outcomes examined in bivariate analyses (Table 2). A slightly higher proportion of female infants were SGA and term LBW compared to male infants. Conversely, a higher proportion of male infants were preterm or very preterm than female infants. Non-Hispanic black mothers had the highest prevalence of all adverse outcomes. With the exception of SGA, all adverse outcomes were more likely among the youngest and oldest maternal age categories. All outcomes were inversely related to maternal education. The proportions of mothers with any adverse outcome was significantly higher among smokers compared to non-smokers, among WIC users compared to non-WIC users, and among unmarried mothers compared to married mothers. Nulliparous mothers as well as mothers who had ≥3 previous births demonstrated elevated proportions of term LBW, VLBW, preterm, and very preterm births compared to mothers with 1–2 previous births. SGA was most common among nulliparous women. Women with intermediate or adequate PNC utilization had the lowest proportion of adverse outcomes, with the exception of SGA. VLBW, PTB, and VPTB exhibited a U-shaped relationship with maternal BMI, with the highest prevalence among underweight and obese women.

**Table 2**
Distribution of demographic and economic covariates across the sample population and by outcome for all live singleton births in Ohio 2006–2008 (N = 428,804).

| Variable | N (%) | SGA % | Term LBW % | VLBW % | PTB % | VPTB % |
|---|---|---|---|---|---|---|
| **Gender** | | | | | | |
| Male | 209,617 (51) | 10.5 | 2.3 | 1.2[b] | 11.3 | 1.8 |
| Female | 219,187 (49) | 10.8 | 3.4 | 1.2[b] | 10.4 | 1.7 |
| **Race/Ethnicity** | | | | | | |
| Non-Hispanic white | 327,343 (76) | 9.2 | 2.4 | 0.9 | 9.8 | 1.4 |
| Non-Hispanic black | 69,325 (16) | 16.8 | 5.2 | 2.7 | 16.0 | 3.5 |
| Hispanic | 19,631 (5) | 1.6 | 2.7 | 1.1 | 11.9 | 1.8 |
| Other | 12,505 (3) | 13.9 | 3.7 | 1.3 | 10.7 | 1.8 |
| **Maternal Age at Birth** | | | | | | |
| 10–19 | 47,544 (11) | 15.5 | 4.2 | 1.8 | 13.5 | 2.7 |
| 20–29 | 239,250 (56) | 11.2 | 2.9 | 1.2 | 10.6 | 1.7 |
| 30–39 | 132,021 (31) | 8.0 | 2.2 | 1.1 | 10.2 | 1.5 |
| 40 + | 8453 (2) | 9.2 | 3.5 | 1.8 | 13.7 | 2.5 |
| **Maternal Education** | | | | | | |
| < High School | 14,851 (4) | 11.3 | 2.9 | 1.1 | 10.6 | 1.8 |
| High School | 178,980 (42) | 13.7 | 3.9 | 1.5 | 12.8 | 2.2 |
| Some College/Degree | 195,754 (46) | 8.4 | 2.1 | 1.0 | 9.5 | 1.4 |
| > College Degree | 35,759 (8) | 6.9 | 1.6 | 0.8 | 7.8 | 1.1 |
| **Maternal Smoking** | | | | | | |
| Yes | 113,552 (26) | 15.5 | 4.7 | 1.5 | 12.5 | 2.2 |
| No | 315,208 (74) | 8.9 | 2.2 | 1.2 | 10.3 | 1.6 |
| **Prenatal Care Utilization** | | | | | | |
| Inadequate | 58,850 (14) | 14.4 | 4.5 | 1.5 | 11.9 | 2.0 |
| Intermediate | 40,854 (10) | 11.1 | 2.2 | 0.3 | 3.9 | 0.3 |
| Adequate | 120,563 (28) | 10.0 | 1.9 | 0.3 | 3.3 | 0.4 |
| Adequate Plus | 94,803 (22) | 8.7 | 3.3 | 1.8 | 20.8 | 2.9 |
| Unknown | 113,734 (26) | 10.8 | 3.0 | 2.0 | 12.7 | 2.7 |
| **WIC use** | | | | | | |
| Yes | 175,604 (42) | 13.6 | 3.8 | 1.3 | 12.1 | 1.9 |
| No | 240,891 (58) | 8.4 | 2.1 | 1.1 | 9.8 | 1.6 |
| **Prepregnancy BMI** | | | | | | |
| Underweight | 18,811 (4) | 18.7 | 6.2 | 1.6 | 14.2 | 2.2 |
| Normal | 197,071 (48) | 11.1 | 2.9 | 1.0 | 10.3 | 1.5 |
| Overweight | 94,621 (23) | 9.4 | 2.3 | 1.1 | 10.3 | 1.6 |
| Obese | 103,927 (25) | 9.2 | 2.5 | 1.6 | 11.5 | 2.1 |
| **Parity** | | | | | | |
| 0 | 170,155 (41) | 12.9 | 3.3 | 1.5 | 10.9 | 2.0 |
| 1 | 131,510 (31) | 8.8 | 2.2 | 0.9 | 9.6 | 1.4 |
| 2 | 68,891 (17) | 9.0 | 2.5 | 1.0 | 10.9 | 1.6 |
| ≥3 | 47,075 (11) | 9.8 | 3.1 | 1.2 | 13.2 | 2.0 |
| **Marital Status** | | | | | | |
| Married | 247,516 (58) | 7.9 | 2.0 | 0.9 | 9.0 | 1.2 |
| Unmarried[a] | 181,288 (42) | 14.4 | 4.1 | 1.8 | 13.5 | 2.5 |

[a] Not married category includes mothers who responded single, widowed, or divorced.
[b] All comparisons in table are significant ($\chi 2$ p-value < 0.05) except as indicated.

### 3.2. Regression analyses

#### 3.2.1. Small for gestational age

We found no evidence of an association between annual measures of arsenic and SGA in either crude or fully covariate-adjusted models (AOR 1.00, 95% CI 0.98, 1.01) (Table 3). Similarly, we observed no association between arsenic and the odds of SGA when we restricted the analysis to those residing in counties with < 20 and < 10% private well use. We found no evidence of multiplicative interaction between arsenic concentration and maternal smoking status in the SGA analyses.

#### 3.2.2. Term low birth weight and very low birth weight

Similar to the SGA analyses, we observed no association between county-year measures of arsenic in drinking water and term LBW in crude or adjusted models of all Ohio counties (AOR 0.99, 95% CI 0.98, 1.01) (Table 3). We did observe a significant increase in the odds of term LBW with increasing arsenic in crude models restricted to those counties with < 20 and < 10% private well use, but these associations were attenuated after controlling for covariates ($AOR_{<20}$ 1.07, 95% CI 1.00, 1.14; $AOR_{<10}$ 1.06, 95% CI 0.98, 1.15).

We found no association between arsenic in drinking water and VLBW in models of all counties in Ohio (AOR 0.99, 95% CI 0.96, 1.03) (Table 3). The odds of VLBW births increased significantly with increasing arsenic concentrations in drinking water in counties with < 10% of the populations using private well water in adjusted models ($AOR_{<10}$ 1.14, 95% CI 1.04, 1.24). We found no evidence of multiplicative interaction between arsenic concentration and maternal smoking status in the term LBW or VLBW analyses.

#### 3.2.3. Preterm birth and very preterm birth

While the odds of preterm birth did not significantly increase with increasing arsenic levels across the entire state (AOR 0.99, 95% CI 0.98, 1.01), we observed a significant 8 − 10% increase in the odds of PTB per 1 μg/L increase in arsenic in drinking water for counties with < 20% and < 10% private well use in both crude and covariate-adjusted models ($AOR_{<20}$ 1.08, 95% CI 1.02, 1.14; $AOR_{<10}$ 1.10, 95% CI 1.06, 1.15) (Table 4).

We observed no association between VPTB and county-year arsenic in drinking water when using all counties in Ohio (Table 4). In models restricted to those counties with < 20% and < 10% private well use, we observed a non-significant increase in odds of VPTB with increasing arsenic levels in crude and covariate-adjusted models ($AOR_{<20}$ 1.07, 95% CI 0.89, 1.28; $AOR_{<10}$ 1.12, 95% CI 0.96, 1.31). We found no evidence of higher odds of PTB or VPTB with increasing arsenic concentrations among smokers compared with non-smokers.

### 3.3. Prenatal care utilization sensitivity analyses

Among all live singleton births in Ohio, 17% of observations were missing data on the month of entry into PNC. Another 11% were missing data on the total number of PNC visits attended, which resulted in 26% with an unknown Kotelchuck index of PNC utilization. PNC utilization is a confounder in the associations observed above, therefore we performed analyses of these data controlling for PNC, but dropping those individuals with a missing Kotelchuck index score.

Similar to the initial models (Table 3), we observed no association between arsenic and SGA in adjusted models (Table 5). We found that annual county-year measures of arsenic exposure were significantly associated with term LBW among infants with known PNC utilization in counties with < 20 and < 10% private well use ($AOR_{<20}$ 1.07, 95% CI 1.01, 1.13; $AOR_{<10}$ 1.06, 95% CI 1.00, 1.13). We observed no association between arsenic and VLBW among births with known PNC utilization.

Unlike in the models which did not control for PNC, we observed a significant elevation in the odds of PTB in counties with < 10% private well use in models that were restricted to those births with a known PNC utilization ($AOR_{<10}$ 1.10, 95% CI 1.00, 1.21) (Table 6). Similar to the initial models of VPTB (Table 4), we observed no significant associations between VPTB and arsenic, however, the odds of VPTB were elevated in counties with < 20 or < 10% private well use.

## 4. Discussion

Previous studies from regions of high endemic arsenic concentrations in drinking water show strong associations with adverse reproductive outcomes. In this study, we examined the relationship between arsenic in drinking water and several adverse reproductive outcomes in a geographic region with relatively low arsenic concentrations, the state of Ohio in the United States. Our analyses of all live singleton births in the state showed no association between arsenic in drinking water, measured as an annual county-level average, and any of the birth outcomes assessed, but over 50% of these counties had a substantial percentage of private well users (30–81%), thereby introducing considerable exposure misclassification. When we assessed this relationship in a subset of the population for which exposure was most

**Table 3**
Associations[a] between mean annual arsenic exposure (μg/l) and SGA, term LBW, and VLBW in Ohio counties, 2006–2008.

| Outcome | Model | Well restriction (%) | N (Counties) | N (Births) | OR[e] (95% CI) | P-value |
|---|---|---|---|---|---|---|
| SGA[b] | Crude | | 88 | 385,833 | 1.00 (0.98, 1.01) | 0.755 |
| | Adjusted | | 88 | 385,833 | 1.00 (0.98, 1.01) | 0.551 |
| | Crude | < 20 | 31 | 241,905 | 1.00 (0.97, 1.03) | 0.944 |
| | Adjusted | < 20 | 31 | 241,905 | 1.01 (0.99, 1.03) | 0.577 |
| | Crude | < 10 | 20 | 216,240 | 1.00 (0.97, 1.04) | 0.803 |
| | Adjusted | < 10 | 20 | 216,240 | 1.01 (0.99, 1.03) | 0.224 |
| Term LBW[c] | Crude | | 88 | 345,030 | 0.99 (0.96, 1.01) | 0.252 |
| | Adjusted | | 88 | 345,030 | 0.99 (0.98, 1.01) | 0.360 |
| | Crude | < 20 | 31 | 215,394 | 1.08 (1.03, 1.14) | 0.001 |
| | Adjusted | < 20 | 31 | 215,394 | 1.07 (1.00, 1.14) | 0.056 |
| | Crude | < 10 | 20 | 192,236 | 1.09 (1.03, 1.15) | 0.003 |
| | Adjusted | < 10 | 20 | 192,236 | 1.06 (0.98, 1.15) | 0.137 |
| VLBW[d] | Crude | | 88 | 385,833 | 1.01 (0.95, 1.08) | 0.656 |
| | Adjusted | | 88 | 385,833 | 0.99 (0.96, 1.03) | 0.672 |
| | Crude | < 20 | 31 | 241,905 | 1.08 (0.85, 1.39) | 0.523 |
| | Adjusted | < 20 | 31 | 241,905 | 1.10 (0.96, 1.25) | 0.160 |
| | Crude | < 10 | 20 | 216,240 | 1.13 (0.91, 1.40) | 0.253 |
| | Adjusted | < 10 | 20 | 216,240 | 1.14 (1.04, 1.24) | 0.005 |

[a] Models controlled for year, infant sex, maternal race/ethnicity, maternal age, maternal education, marital status, cigarette use during pregnancy, pre-pregnancy BMI, WIC use, and parity.
[b] Small for gestational age (SGA) defined as the smallest 10% of infants, according to birth weight, at each gestational age in the population.
[c] Term low birth weight (term LBW) defined as < 2500 g among term births (≥37 weeks gestation).
[d] Very low birth weight (VLBW) defined as < 1500 g at time of delivery.
[e] Odds ratios reflect increase in odds per 1 μg/L increase in arsenic in drinking water.

**Table 4**
Associations[a] between mean annual arsenic exposure (μg/L) and PTB and VPTB in Ohio counties, 2006–2008.

| Outcome | Model | Well restriction (%) | N (Counties) | N (Births) | OR[d] (95% CI) | P-value |
|---|---|---|---|---|---|---|
| Preterm birth[b] | Crude | | 88 | 386,164 | 1.00 (0.98, 1.02) | 0.921 |
| | Adjusted | | 88 | 386,164 | 0.99 (0.98, 1.01) | 0.455 |
| | Crude | < 20 | 31 | 242,152 | 1.08 (1.01, 1.15) | 0.018 |
| | Adjusted | < 20 | 31 | 242,152 | 1.08 (1.02, 1.14) | 0.005 |
| | Crude | < 10 | 20 | 216,465 | 1.11 (1.06, 1.16) | < 0.0001 |
| | Adjusted | < 10 | 20 | 216,465 | 1.10 (1.06, 1.15) | < 0.0001 |
| Very preterm birth[c] | Crude | | 88 | 386,164 | 0.99 (0.94, 1.04) | 0.735 |
| | Adjusted | | 88 | 386,164 | 0.99 (0.96, 1.02) | 0.572 |
| | Crude | < 20 | 31 | 242,152 | 1.06 (0.82, 1.37) | 0.669 |
| | Adjusted | < 20 | 31 | 242,152 | 1.07 (0.89, 1.28) | 0.471 |
| | Crude | < 10 | 20 | 216,465 | 1.11 (0.88, 1.40) | 0.381 |
| | Adjusted | < 10 | 20 | 216,465 | 1.12 (0.96, 1.31) | 0.151 |

[a] Models controlled for year, infant sex, maternal race/ethnicity, maternal age, maternal education, marital status, cigarette use during pregnancy, pre-pregnancy BMI, WIC use, and parity.
[b] Preterm births defined as infants delivered before 37 weeks gestation.
[c] Very preterm births defined as infants delivered before 32 weeks gestation.
[d] Odds ratios reflect increase in odds per 1 μg/L increase in arsenic in drinking water.

accurately defined − those counties in which less than 10 or 20% of the households used private wells as their drinking water source − we found a significant increase in the odds of VLBW and PTB among live singleton births with increasing arsenic exposure. We were not able to assess the shape of the dose-response relationship between arsenic concentrations in drinking water and these outcomes, but it may be nonlinear. We observed no association between arsenic and either SGA or VPTB, but we did observe a suggestive association between arsenic and term LBW in this population. Furthermore, we did not observe the same interaction between arsenic exposure and smoking that was reported by Bloom et al. (2015).

The mechanism by which arsenic may affect birth weight and gestational age at delivery is uncertain. Arsenic intoxication as well as chronic arsenic exposure at lower levels has been associated with anemia among pregnant women (Hopenhayn et al., 2006; Kyle and Pease, 1965; Surdu et al., 2015; Taheri et al., 2015; Westhoff et al., 1975). Anemia during pregnancy has been found to be associated with low birthweight and preterm delivery (Bondevik et al., 2001). Fei et al. (2013) identified a target gene for arsenic which may lead to functional impairment of the placenta, thereby affecting fetal growth and leading to reduced birthweight. There is growing evidence that arsenic exposure increases general inflammation in chronically exposed individuals (Wu et al., 2003) and well as inflammatory markers in newborns exposed *in utero* (Ahmed et al., 2011; Fry et al., 2007). Inflammation is associated with preterm birth, through such mechanisms as ripening of cervix and rupture of membranes (Challis et al., 2009). Other possible mechanisms by which arsenic is toxic for fetal growth and development likely result from direct toxic effects on enzyme production and activity which alter DNA repair enzymes, oxidative stress, hormone interactions, and the one-carbon metabolism pathway (Vahter, 2009).

This study is one of the largest of its kind, and among the first to integrate data from environmental regulatory agencies and state vital statistics departments to examine the relationship between drinking

**Table 5**
Associations[a] between mean annual arsenic exposure (μg/L) and SGA, term LBW, and VLBW in Ohio counties, 2006–2008, controlling for prenatal care utilization.

| Outcome | Model | Well restriction (%) | N (Counties) | N (Births) | OR[e] (95% CI) | P-value |
|---|---|---|---|---|---|---|
| SGA[b] | Crude | | 88 | 289,091 | 0.99 (0.98, 1.01) | 0.363 |
| | Adjusted | | 88 | 289,091 | 0.99 (0.98, 1.00) | 0.189 |
| | Crude | < 20 | 31 | 172,907 | 1.02 (0.99, 1.04) | 0.138 |
| | Adjusted | < 20 | 31 | 172,907 | 1.01 (0.99, 1.03) | 0.213 |
| | Crude | < 10 | 20 | 155,115 | 1.02 (1.00, 1.04) | 0.016 |
| | Adjusted | < 10 | 20 | 155,115 | 1.01 (0.99, 1.03) | 0.162 |
| Term | Crude | | 88 | 260,060 | 0.98 (0.96, 1.01) | 0.246 |
| | Adjusted | | 88 | 260,060 | 0.99 (0.97, 1.01) | 0.193 |
| | Crude | < 20 | 31 | 154,503 | 1.09 (1.06, 1.13) | < 0.0001 |
| LBW[c] | Adjusted | < 20 | 31 | 154,503 | 1.07 (1.01, 1.13) | 0.022 |
| | Crude | < 10 | 20 | 138,429 | 1.11 (1.08, 1.13) | < 0.0001 |
| | Adjusted | < 10 | 20 | 138,429 | 1.06 (1.00, 1.13) | 0.047 |
| VLBW[d] | Crude | | 88 | 289,091 | 1.02 (0.94, 1.10) | 0.616 |
| | Adjusted | | 88 | 289,091 | 0.99 (0.94, 1.05) | 0.828 |
| | Crude | < 20 | 31 | 172,907 | 1.01 (0.72, 1.41) | 0.952 |
| | Adjusted | < 20 | 31 | 172,907 | 1.01 (0.79, 1.29) | 0.940 |
| | Crude | < 10 | 20 | 155,115 | 1.05 (0.78, 1.41) | 0.740 |
| | Adjusted | < 10 | 20 | 155,115 | 1.03 (0.82, 1.30) | 0.792 |

[a] Models controlled for year, infant sex, maternal race/ethnicity, maternal age, maternal education, marital status, cigarette use during pregnancy, pre-pregnancy BMI, WIC use, PNC utilization, and parity.
[b] Small for gestational age (SGA) defined as the smallest 10% of infants, according to birth weight, at each gestational age in the population.
[c] Term low birth weight (term LBW) defined as < 2500 g among term births (≥37 weeks gestation).
[d] Very low birth weight (VLBW) defined as < 1500 g at time of delivery.
[e] Odds ratios reflect increase in odds per 1 μg/L increase in arsenic in drinking water.

water arsenic and adverse birth outcomes. The robust sample size of 428,804 births in Ohio from 2006 to 2008 allowed for greater statistical power to detect small increases in risks than prior studies. This study also benefited from individual-level data on important covariates with relatively little missing data.

This study had several limitations originating from the data sources used. Both the exposure and outcome data for this study were from secondary data sources, meaning that these data were collected for purposes other than research. While meeting the regulatory requirements for arsenic testing, the counties in this study had relatively infrequent arsenic measurements from 2006 to 2008. The infrequent monitoring schedules meant that not all CWSs in each county contributed to the county-year exposure measure in all years, and some county-year exposure measures were missing. These limitations were exacerbated in more refined time scales (i.e., monthly or trimester-specific exposure measures), prompting use of an annual exposure measure. Monthly mean values of arsenic were originally calculated, but between 47% and 55% of counties were missing a monthly estimate due to the infrequent sampling requirements under current regulations. Furthermore, the monthly estimates did not show significant variation by month, therefore annual estimates were used in analysis. Potential exposure measurement error is another limitation of these data. Furthermore, we evaluated only one exposure, arsenic, in drinking water and did not consider co-exposures in this population, however, a recent study of arsenic exposure and fetal growth in Oklahoma found an inverse relationship between arsenic and birth weight and gestational length, controlling for lead and manganese levels (Claus Henn et al., 2016).

The exposure measure was aggregated from the CWS to the county level because we were unable to link individual births to the CWS that served as their mother's primary drinking water source during pregnancy, which introduced some exposure misclassification at the in-

**Table 6**
Associations[a] between mean annual arsenic exposure (μg/L) and PTB and VPTB in Ohio counties, 2006–2008, controlling for prenatal care utilization.

| Outcome | Model | Well restriction (%) | N (Counties) | N (Births) | OR[d] (95% CI) | P-value |
|---|---|---|---|---|---|---|
| Preterm birth[b] | Crude | | 88 | 289,303 | 1.00 (0.98, 1.02) | 0.813 |
| | Adjusted | | 88 | 289,303 | 1.00 (0.98, 1.02) | 0.912 |
| | Crude | < 20 | 31 | 173,062 | 1.07 (1.01, 1.14) | 0.026 |
| | Adjusted | < 20 | 31 | 173,062 | 1.09 (0.99, 1.19) | 0.087 |
| | Crude | < 10 | 20 | 155,257 | 1.10 (1.07, 1.13) | < 0.0001 |
| | Adjusted | < 10 | 20 | 155,257 | 1.10 (1.00, 1.21) | 0.056 |
| Very preterm birth[c] | Crude | | 88 | 289,303 | 0.99 (0.93, 1.05) | 0.675 |
| | Adjusted | | 88 | 289,303 | 0.98 (0.94, 1.03) | 0.445 |
| | Crude | < 20 | 31 | 173,062 | 1.05 (0.82, 1.36) | 0.686 |
| | Adjusted | < 20 | 31 | 173,062 | 1.09 (0.89, 1.34) | 0.400 |
| | Crude | < 10 | 20 | 155,257 | 1.08 (0.85, 1.37) | 0.512 |
| | Adjusted | < 10 | 20 | 155,257 | 1.11 (0.91, 1.36) | 0.306 |

[a] Models controlled for year, infant sex, maternal race/ethnicity, maternal age, maternal education, marital status, cigarette use during pregnancy, pre-pregnancy BMI, WIC use, PNC utilization, and parity.
[b] Preterm births defined as infants delivered before 37 weeks gestation
[c] Very preterm births defined as infants delivered before 32 weeks gestation.
[d] Odds ratios reflect increase in odds per 1 μg/L increase in arsenic in drinking water.

dividual level. This aggregation of exposure reduced the variability in the exposure estimates, as infants were assigned their county's (N = 88) mean annual arsenic level.

We used public drinking water data to calculate the exposure measures, thereby introducing exposure misclassification in those counties in which a large percentage of the population was using private well water. Any such misclassification was likely non-differential with respect to the outcome. We attempted to reduce exposure misclassification by restricting analyses to those counties with limited private well use. A further limitation is that we lacked information on drinking water consumption habits for this study population.

We used birth certificate data to ascertain all outcomes and covariates examined in this study, however, the reliability of birth certificate data varies widely by data element. Demographic variables on the birth certificate about the mother, including maternal age, race/ethnicity, and marital status are highly accurate (DiGiuseppe et al., 2002; Querec, 1980; Reichman and Hade, 2001; Schoendorf et al., 1993; Zollinger et al., 2006). There is also high agreement between birth certificates and medical records for variables including infant gender, birth weight, plurality, number of previous live births, and prenatal care received (DiGiuseppe et al., 2002; Green et al., 1998; Northam and Knapp, 2006; Querec, 1980; Roohan et al., 2003; Schoendorf et al., 1993; Zollinger et al., 2006). Gestational age, parental education, paternal demographics show moderate agreement, but maternal weight gain during pregnancy, maternal medical risk factors (e.g., chronic hypertension, previous LBW or preterm birth), tobacco and alcohol use, and number of prenatal care visits have very low reliability (DiGiuseppe et al., 2002; Dobie et al., 1998; Northam and Knapp, 2006; Querec, 1980; Reichman and Hade, 2001; Roohan et al., 2003; Zollinger et al., 2006). In particular, information on maternal smoking was not specific to the window of pregnancy and we lacked data on environmental tobacco smoke exposure potentially resulting in residual and/or unmeasured confounding in these analyses.

Furthermore, we lacked information on whether or not the mothers of the infants in these analyses had moved at any point during their pregnancy. Rates of pregnancy mobility are estimated between 12–32% (Canfield et al., 2006; Fell et al., 2004; Miller et al., 2010; Zender et al., 2001), and vary by geography and demographic factors. We were unable to account for those women who moved during pregnancy and assumed that the residence listed on the birth certificate was the residence throughout the entire pregnancy.

## 5. Conclusions

To our knowledge, this study is the first of its kind to explore the association between arsenic in drinking water and multiple birth outcomes in a region of relatively low arsenic exposure; specifically, 99% of births in this study were estimated to be exposed to arsenic in drinking water below the current MCL of 10 μg/L. In fact, annual concentrations of arsenic in drinking water did not exceed the MCL in all models in which we observed a significant association between arsenic concentration in drinking water and adverse birth outcomes. In models with the least potential for exposure misclassification (e.g., low use of private drinking water wells), we found that the risk of VLBW and preterm birth increased with increasing levels of arsenic in drinking water. These findings suggest that the current MCL may not be sufficiently protective against these adverse birth outcomes. Further epidemiologic research is needed to explore these associations at low levels of arsenic exposure with individual exposure measurements or biomarkers of exposure.

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## Conflicts of interest

The authors of this manuscript have no conflicts of interest to report.

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