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Relation between *in utero* arsenic exposure and growth during the first year of life in a New Hampshire pregnancy cohort

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Abstract

Background—We have previously reported that *in utero* arsenic exposure is associated with increased length and other anthropometric outcomes at birth in a U.S. cohort. However, it is unknown whether these anthropometric differences persist through early life.

Objectives—We assessed *in utero* arsenic exposure in relation to attained anthropometry and growth trajectories through the first year of life.

Methods—Among 760 mother-infant pairs from the New Hampshire Birth Cohort Study, we assessed *in utero* arsenic exposure using maternal second trimester urinary arsenic and assessed infant growth from medical records.

Results—Median maternal second trimester total urinary arsenic (tAs; inorganic arsenic + monomethylarsonic acid + dimethylarsinic acid) was 3.96 µg/L (IQR: 2.02, 6.72). In adjusted linear mixed effects models, each doubling of maternal urinary tAs was associated with a 0.05 increase in length WHO Z score (95% CI: 0, 0.09) over the first year of life which corresponds to

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Competing financial interests declaration

The authors declare they have no actual or potential competing financial interests.

Appendix A. Supplementary data

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an approximately 0.12 cm increase in males and 0.13 cm increase in females at 12 months. No associations were observed between urinary tAs and attained weight, weight-for-length, or head circumference. In adjusted piecewise linear mixed effects models, each doubling of urinary tAs was associated with a 0.07 (95% CI: 0.02, 0.12) cm per month decreased length growth rate through 3.5 months with no evidence of an association thereafter. No associations were observed between urinary tAs and infant weight gain or change in weight-for-length and head circumference through one year.

Conclusions—On average, infants exposed to higher *in utero* arsenic attained modestly longer length during the first year, despite having slower linear growth in the first 3.5 months of life. This suggests that the previously demonstrated arsenic-associated longer length among study infants at birth persists through the first year of life. No other anthropometric associations with *in utero* arsenic exposure were observed across the full study population.

Keywords

Arsenic; *In utero* exposure; Anthropometry; Infant growth

1. Introduction

Environmental exposures during the sensitive period of fetal development may have long-lasting effects on child health (Swanson et al., 2009). One environmental exposure of concern is arsenic, a naturally occurring metalloid that people are commonly exposed to through drinking water (Smedley and Kinniburgh, 2002) and consumption of rice and other foods (Gilbert-Diamond et al., 2011; Meharg and Rahman, 2003). It is estimated that at least 140 million individuals worldwide have been exposed to drinking water arsenic in excess of World Health Organization (WHO) guidelines of 10 µg/L (WHO, 2018). In New Hampshire, more than 10% of private wells are estimated to have water with arsenic concentrations in excess of these guidelines (Karagas et al., 1998).

Arsenic can be ingested in inorganic (iAs) and methylated forms. iAs is known to be highly toxic (Hughes, 2002), and has been associated with numerous health conditions including skin lesions (Ahsan et al., 2000; Haque et al., 2003), heart disease (Chen et al., 1996; James et al., 2015; Tseng et al., 2003), type 2 diabetes (Lai et al., 1994; Tseng et al., 2000), and some cancers (Hopenhayn-Rich et al., 1996, 1998; Smith et al., 1998). After ingestion, iAs goes through a series of methylation and reduction steps (Vahter, 2002). iAs can be methylated into monomethylarsonic acid (MMA^V) which then can be reduced to monomethylarsonous acid (MMA^{III}). MMA^{III} subsequently can be further methylated into dimethylarsinic acid (DMA^V) and then further be reduced to dimethylarsinous acid (DMA^{III}). The biotransformation of ingested iAs is incomplete and iAs, monomethylarsonic acid (MMA^V), and dimethylarsinic acid (DMA^V) are all excreted in urine (Francesconi et al., 2002; Watanabe and Hirano, 2013). In addition, MMA^{III} and DMA^{III} have also been found in the urine of people highly exposed to iAs (Mandal et al., 2001; Valenzuela et al., 2005), though not in the urine of people with low-level arsenic exposure (Lindberg et al., 2006; Rivera-Núñez et al., 2012). While the methylation of iAs to MMA and DMA is generally considered a detoxification process (Gebel, 2002; Moore et al., 1997), studies suggest that MMA^{III} and DMA^{III} may be more toxic than iAs with MMA^{III} being the most

toxic arsenic species (Vahter, 2002). This biotransformation is thought to be increased in pregnant women, with one study in a native Andean population finding that, during pregnancy, on average greater than 85% of arsenic excreted in urine is in the form of DMA (Concha et al., 1998). Arsenic (including iAs and its methylated forms) crosses the placenta (Concha et al., 1998; Punshon et al., 2015), and thus biomarkers of maternal exposure to arsenic during pregnancy, such as urine, are thought to reflect *in utero* arsenic exposure (Vahter, 2009).

Several studies have examined the association between prenatal arsenic exposure and birth anthropometric outcomes (Claus Henn et al., 2016; Gilbert-Diamond et al., 2016; Hopenhayn et al., 2003; Kwok et al., 2006; Laine et al., 2015; Myers et al., 2010; Rahman et al., 2009; Yang et al., 2003). While most of these studies were conducted in populations with high average levels of inorganic arsenic in drinking water (e.g., > 50 µg/L) (Hopenhayn et al., 2003; Kwok et al., 2006; Laine et al., 2015; Myers et al., 2010; Rahman et al., 2009; Yang et al., 2003); Claus Henn et al. (2016), and our group (Gilbert-Diamond et al., 2016) examined how prenatal arsenic exposure related to anthropometry at birth in U.S. populations with predominately lower levels of inorganic arsenic in drinking water (e.g., < 10 µg/L). In both of these studies, prenatal arsenic exposure was related to smaller head circumference at birth. Results varied between the two U.S. studies for other birth anthropometric outcomes. For example, Claus Henn et al. identified a negative association between *in utero* arsenic exposure and birth weight across all infants while in our cohort this association was seen only in females born to overweight and obese mothers (Gilbert-Diamond et al., 2016). In our cohort, there was also a positive association between *in utero* arsenic exposure and length at birth and a negative association between *in utero* arsenic exposure and adiposity at birth (assessed as ponderal index) in the overall study population (Gilbert-Diamond et al., 2016).

In addition, three published papers have previously reported on the association between prenatal arsenic exposure and early childhood growth (Agay-Shay et al., 2015; Gardner et al., 2013; Saha et al., 2012). In the Maternal and Infant Nutrition Interventions in Matlab (MINIMat) trial in the arsenic endemic region of Matlab, Bangladesh, prenatal arsenic, assessed as maternal total urinary arsenic, was negatively associated with attained weight and length in female infants at 3–24 months, but those associations largely disappeared after multivariable adjustment (Saha et al., 2012). In the same cohort, no association was identified between prenatal arsenic and child anthropometry at 5 years (Gardner et al., 2013). Similarly, the Environment and Childhood Project (INMA) in Sabadell (Catalonia, Spain) did not find any associations between total prenatal urinary arsenic concentrations (which included arsenobetaine, a nontoxic, unmetabolized form of arsenic found in fish and seafood) and weight at 7 years of age (Agay-Shay et al., 2015).

The aim of this study was to determine whether prenatal arsenic exposure was associated with differences in child anthropometric indicators through the first year of life in our U.S. population with generally low levels of arsenic exposure. We further sought to study whether any associations were modified by child sex or maternal pre-pregnancy weight status due to previous research suggesting effect modification by these factors on the association between *in utero* arsenic exposure and anthropometry at birth (Gilbert-Diamond et al., 2016) and by

child sex on the association between postnatal arsenic exposure and infant growth (Saha et al., 2012).

2. Methods

2.1. Source population

The New Hampshire Birth Cohort Study (NHBCS) is a prospective study that aims to examine the associations between environmental exposures and other factors and maternal-child health outcomes (Gilbert-Diamond et al., 2011). Beginning in January 2009, pregnant women between 24 and 28 weeks of gestation were recruited from prenatal clinics in New Hampshire. Eligibility criteria included age of 18–45 years old, English literacy, the use of a private, unregulated water system (e.g., private well) at home, not planning to move, and a singleton pregnancy. The study focused on New Hampshire residents using unregulated private water supplies, because it is estimated that more than 10% of homes in the state that use private wells have water arsenic concentrations that exceed the Environmental Protection Agency's recommended maximum of 10 µg/L (Karagas et al., 1998). At the time of the analysis there were 1,758 mother-child dyads enrolled in the New Hampshire Birth Cohort Study. Of those, maternal second trimester spot urine samples had been analyzed for speciated arsenic exposure for 1,260 women. Anthropometric data were available from medical record review at 2 weeks, 1 month, 2 months, 4 months, 6 months, 9 months, and 1 year for 686, 362, 744, 722, 720, 691, and 691 children, respectively. In total, 760 mother-child dyads had both speciated arsenic concentrations measured in maternal second trimester spot urine samples and anthropometry data from birth and at least one postnatal well child visit up to age 1 year. Participants provided written informed consent and all study procedures were approved by the Institutional Review Board at Dartmouth College.

2.2. Primary outcomes: anthropometric measures

Infant head circumference (cm), weight (g), and length (cm) were abstracted by trained study staff from medical records at birth and well child visits from 2-weeks to 12-months of age. We used the World Health Organization (WHO) reference curves to calculate sex- and age- standardized head circumference, weight, length, and weight-for-length Z-scores (WHO Multicentre Growth Reference Study Group, 2006).

2.3. Primary exposure: In utero arsenic exposure

We collected and analyzed maternal second trimester urinary arsenic using previously described methods (Gilbert-Diamond et al., 2011). In brief, women provided a spot urine sample collected at approximately 24–28 weeks of pregnancy. Samples were analyzed for iAs (As^{III} and As^V), MMA^V, and DMA^V using a high-performance liquid chromatography (HPLC) ICP-MS system (Larsen et al., 1993). The average limits of detection (LOD) for iAs, MMA^V, and DMA^V were 0.167, 0.065, and 0.061 µg/L, respectively. For each arsenic species, measurements below the detection limit were set to the LOD divided by the square root of two. There were 270 samples below the LOD for iAs, 177 samples below the LOD for MMA, 3 samples below the LOD for DMA, and 2 samples were below the LOD for all 3 arsenic species. We calculated total urinary arsenic concentrations (tAs) as the sum of iAs, MMA, and DMA. Arsenobetaine was also measured in all urine samples via HPLC but was

not included in the calculation of total urinary arsenic as it is considered a nontoxic, unmetabolized arsenic species (Francesconi et al., 2002). To assess urinary dilution, we also measured urinary creatinine using a colorimetric assay (Assay #500701; Cayman Chemical, Ann Arbor, MI). At the time of this analysis, urinary creatinine had been measured for 646 of the 760 urine samples.

2.4. Maternal weight status

Maternal usual weight prior to pregnancy was assessed via self-report as part of the enrollment questionnaire. We then combined the reported weight with height abstracted from the medical records to compute pre-pregnancy BMI. Pre-pregnancy weight status was categorized as normal weight ($18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$), overweight ($25 \leq \text{BMI} < 30 \text{ kg/m}^2$), or obese ($\geq 30 \text{ kg/m}^2$) (WHO, 2000). Due to previous research suggesting that underweight mothers have an increased risk of giving birth to low birth weight infants (Han et al., 2011) and the low prevalence of underweight mothers in our study population, women with a pre-pregnancy BMI of $< 18.5 \text{ kg/m}^2$ ($n = 28$) were excluded from this analysis.

2.5. Other measures

Women self-reported demographics, lifestyle characteristics, and medical history via prenatal and postpartum questionnaires. Trained study staff also conducted a medical record review to collect maternal weight throughout pregnancy. Gestational weight gain was calculated as the difference between the final reported weight from pregnancy and the self-reported pre-pregnancy weight. Gestational weight gain was then categorized as inadequate, adequate, or excessive according to Institute of Medicine (IOM) guidelines (Rasmussen and Yatkine, 2009).

Duration of breastfeeding was obtained via repeated telephone questionnaires, conducted when the infant was 4, 8, and 12 months of age, in which women were asked whether they were still breastfeeding and, if they were not, the date or the age of the infant when they had stopped breastfeeding. Additionally, if they were still breastfeeding, they were subsequently asked if they had ever fed their baby anything other than breast milk to establish whether a child had been exclusively breast fed up until that point. For statistical analyses, a breastfeeding variable was derived as the total number of months an infant was breastfed. In regression analyses, this variable was set to the lesser of the following two values: the total number of months the infant was breast fed and the age of the infant when the anthropometry values were collected.

2.6. Statistical analyses

All analyses were completed using R: A Language and Environment for Statistical Computing, version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria). A threshold of $p < 0.05$ was used to define main effects as statistically significant. To improve sensitivity to identify potential effect modification, a threshold of $p < 0.10$ was used to identify interactions for further consideration. We assessed distributions and univariate statistics of baseline characteristics, maternal urinary arsenic concentrations, and anthropometric measures at various ages.

After initial univariate analysis, we used natural log-transformed tAs as the exposure for all analyses because tAs was right-skewed. We then assessed the linearity of each dose-response relationship between tAs and each outcome through visual inspection of scatter plots of the data. We did not find evidence of any non-linear dose-response relationships between ln-transformed maternal urinary tAs (Fig. S1) and each outcome.

We used a series of linear regression models to fit each anthropometric outcome at each time period on ln-transformed tAs. Models were fit in the overall sample and then stratified by maternal pre-pregnancy weight status (normal weight vs. overweight and obese) or infant sex. In all models, variables associated with maternal urinary tAs or any anthropometric outcome at the $p < 0.10$ level in bivariate analyses were included as covariates to increase sensitivity to identify potential confounders of the association. The adjusted non-stratified linear regression models included maternal pre-pregnancy BMI (continuous), gestational weight gain (categorical; insufficient, sufficient, or excessive), maternal education (ordinal, with the four categories listed in Table 1 assigned values of 1–4, respectively), maternal smoking status (binary; ever smoked or never smoked), maternal parity (ordinal with parity of 3 or more set to 3), infant sex (binary), infant gestational age at delivery (continuous), and months breastfed (continuous). Additional variables that were considered but that did not achieve the stated threshold for inclusion in subsequent models included maternal age (continuous) and delivery mode (binary; vaginal delivery or cesarean section). Models stratified by maternal pre-pregnancy weight status did not adjust for maternal pre-pregnancy BMI. Models stratified by infant sex did not adjust for infant sex. Missing values for maternal pre-pregnancy BMI ($n = 30$) were assigned the study population mean (26.11 kg/m^2). Missing values for months breast fed ($n = 123$) were assigned the study population median (7.98 months). Missing values for maternal education ($n = 66$), maternal smoking status ($n = 69$), and gestational weight gain category ($n = 36$) were treated with a missing variable indicator. These methods assume that the missingness of a given covariate is not related to the exposure of interest, the violation of which could lead to biased estimates (Groenwold et al., 2012). This assumption is valid in these analyses as the missingness of these values is not associated with arsenic exposure (data not shown).

Models with multiplicative interaction terms between the ln-transformed tAs levels and either maternal pre-pregnancy weight status or infant sex were used to formally assess effect modification by those variables; a likelihood ratio test was used to determine statistical significance of the multiplicative terms. As an exploratory analysis, for anthropometry outcomes for which the likelihood ratio test was suggestive ($p < 0.10$) of effect modification by either maternal weight status or infant sex, we estimated the associations with tAs exposure stratified by both maternal weight status and infant sex. To test for the significance of a 3-way interaction between maternal weight status, infant sex, and tAs exposure, we fit a multivariable regression with main effect terms, 2-way multiplicative interaction terms, and a 3-way multiplicative interaction term, adjusted for covariates; we assessed the statistical significance of the 3-way multiplicative interaction by comparing the model with a 3-way multiplicative interaction term to a nested model without a 3-way multiplicative interaction term using a likelihood ratio test.

In addition, we fit the longitudinal age- and sex-adjusted Z-score data for weight, length, weight-for-length, and head circumference collected at birth, 2 weeks, 1 month, 2 months, 4 months, 6 months, 9 months, and one year in linear mixed effects models adjusted for the same covariates described above. Models were fit using the lme4 package (version 1.1–13) in R (Bates et al., 2015) and included fixed effects for ln-transformed tAs levels and covariates as well as a random intercept term to account for subject-specific anthropometric variability.

Change in growth trajectory was assessed by fitting piecewise linear mixed effects models for weight, length, weight-for-length, and head circumference measures collected at 2 weeks, 1 month, 2 months, 4 months, 6 months, 9 months, and one year adjusted for the same covariates described above. Raw anthropometry measures were used due to the non-linear association between WHO Z scores and age over the first year in our study population (Fig. S2). Models included fixed effects for anthropometry at birth (continuous), ln-transformed tAs (continuous), and covariates as well as random intercept and slope terms to account for subject-specific anthropometric variability. Interaction terms between infant sex and infant age as well as between breast feeding duration and infant age were included to allow for varying growth trajectories based on sex and breastfeeding status. Piecewise models were used due to a visually observed change in slope in the first year of life (Fig. S3). Change points were selected based on the age (assessed at ½ month intervals) that minimized the residual sums of squares (Bai, 1997) for unadjusted models, however selected change points did not differ when adjusting for all covariates used for the longitudinal model. Unadjusted piecewise models stratified by infant sex were used to obtain the mean growth trajectories for both segments of the model for both sexes in the study population.

Anthropometric outcomes that were identified as having a significant association with ln-transformed tAs levels were also tested for an association with maternal urinary inorganic arsenic (iAs), MMA, DMA, and tAs on a categorical scale with 3 levels. Due to the large number of subjects with iAs and MMA below the LOD, these exposures were categorized with all subjects below the LOD being assigned to the lowest level of exposure (35.5% and 23.3%, respectively), all subjects below the median of exposure for subjects above the LOD being assigned the second level of exposure, and all subjects at or above the median exposure for subjects above the LOD being assigned the highest level of exposure. For DMA and tAs, levels of exposure were established based on exposure < 33rd percentile, 33rd percentile and < 67th percentile, and 67th percentile. Models with arsenic exposure treated as three ordered quantiles (approximating tertiles) used the same covariates described above for models with arsenic exposure treated as continuous ln-transformed tAs.

Several sensitivity analyses were completed to assess the robustness of the results. Given that the metabolism of arsenolipids and arsenosugars from seafood consumption can contribute to measured levels of DMA and, subsequently, tAs (Francesconi et al., 2002; Raml et al., 2005; Taylor et al., 2017), multivariable regression models assessing associations of maternal urinary tAs with infant anthropometry were repeated 1) restricting to women who did not report any seafood intake within the two days prior to the urine sample collection (n = 653) and 2) adjusting for log-transformed maternal second trimester urinary arsenobetaine concentration (n = 760) to assess possible confounding of observed

results by maternal seafood consumption. Multivariable regression models assessing associations of maternal urinary tAs with infant anthropometry were also repeated: 1) restricting to women who did not report any rice intake within the two days prior to the urine sample collection ($n = 525$), and 2) adjusting for creatinine for the subset of women with urinary creatinine concentrations available ($n = 646$), 3) restricting to infants who were exclusively breastfed at 6 weeks ($n = 270$), 4) restricting to infants who were not large for gestational age (at or above the 90th percentile per Fenton and Kim 2013 growth curves (Fenton and Kim, 2013); $n = 691$), 5) restricting to infants who were born at a minimum of 37 weeks gestation and who were not small for gestational age (at or below the 10th percentile (Fenton and Kim, 2013); $n = 693$), 6) adjusting for whether or not rice cereal (a post-natal source of arsenic exposure) had been introduced at the time of the well child visit when anthropometry data were collected for the subset of infants with completed questionnaire data on the introduction of rice cereal ($n = 342$), and 7) restricting to women who did not have gestational diabetes during this pregnancy, defined as a 1-hr glucose challenge test (GCT) result ≥ 200 mg/dL or failing the 1-hr GCT (140–199 mg/dL) with two or more high values on the oral glucose tolerance test (OGTT) based on the American Diabetes Association criteria for a normal OGTT of blood glucose ≤ 95 mg/dL at baseline, 180 mg/dL at 1 h, ≤ 155 mg/dL at 2 h, and ≤ 140 mg/dL at 3 h ($n = 703$). Analyses testing the association between maternal urinary tAs and attained anthropometry were conducted with and without adjustment for anthropometry at birth in order to help elucidate potential mediation of associations by birth anthropometry. In addition, adjusting for baseline measurements when assessing change in measurements over time can introduce bias when the exposure and baseline measurement are associated (Glymour et al., 2005), so we also compared growth trajectory analysis results with and without adjusting for anthropometry at birth.

3. Results

In total, 760 mother-infant pairs had both second trimester urinary arsenic and anthropometry measurements at birth and during some or all of the first year of life available. Table 1 presents summary statistics for subject background characteristics and birth outcomes for the study population. Over 45% of mothers were classified as overweight or obese based on their pre-pregnancy BMI. The median second trimester urinary total arsenic (tAs) concentration for the 760 mothers included in the analysis was 3.96 $\mu\text{g/L}$ with DMA accounting for greater than 80% of urinary tAs in more than 50% of the samples (Table 2). When comparing women who were included in this study to the entire population-based cohort, women in this study had statistically significantly higher gestational weight gain and infants had statistically significantly higher gestational age, length WHO Z score, and weight WHO Z score at birth (Table S1).

In the overall study population, natural log-transformed maternal second trimester urinary tAs concentration was positively associated with infant length such that each doubling of urinary tAs was associated with a 0.05 (95% CI: 0, 0.09; $p = 0.044$) higher length WHO Z score over the first year of life (Table 3). In analyses assessing the association between tAs and attained length at each time point, each doubling of urinary tAs was associated with a

0.07 (95% CI: 0.01, 0.13; $p = 0.025$) higher length WHO Z score at 2 weeks but no statistically significant association was observed at subsequent timepoints.

In analyses that assessed *in utero* arsenic exposure by three ordered quantiles of specific arsenic species, individuals in DMA quantile 3 had, on average, a 0.24 increase (95% CI: 0.09, 0.39; $p_{trend} = 0.0019$) in attained length WHO Z score compared to those in quantile 1 when examining the relationship in repeated measures analysis as well as at several timepoints during the first year of life (Table S2). There was also a statistically significant trend for the positive association with iAs quantile with length Z score at 2 weeks of age ($p_{trend} = 0.045$), but not thereafter. There were no significant associations between MMA quantiles and attained length.

There was no statistically significant interaction identified between urinary tAs and maternal pre-pregnancy weight status ($p = 0.35$; Table S3), nor between urinary tAs and infant sex ($p = 0.77$; Table 4) in relation to infant length over the first year of life.

Maternal second trimester urinary tAs concentration was not related to infant attained weight, weight-for-length, or head circumference during the first year of life in the full sample (Table 3). No evidence was found of an interaction between urinary tAs and infant sex with respect to attained weight or head circumference over the first year of life. However, in analyses stratified by infant sex, urinary tAs was negatively associated with weight-for-length Z score over the first year of life exclusively in males, but not females (Table 4). In males, every doubling of urinary tAs was associated with a 0.07 decrease (95% CI: -0.13, 0; $p = 0.041$) in weight-for-length Z score over the first year of life ($p_{interaction} = 0.063$); among females this was 0 (95% CI: -0.05, 0.06; $p = 0.91$).

When assessing *in utero* arsenic exposure by arsenic species, the negative association between maternal urinary arsenic and male attained weight-for-length Z score was strongest when assessing arsenic exposure as MMA quantiles with quantile 3 being associated with a 0.22 decrease (95% CI: -0.45, 0; $p_{trend} = 0.039$) in weight-for-length Z score relative to quantile 1 over the first year of life (Table S4). Weak to null associations were observed between male attained weight-for-length Z score and iAs ($p_{trend} = 0.36$) or DMA ($p_{trend} = 0.15$) quantiles over the first year of life.

Further analyses failed to identify evidence of a three-way multiplicative interaction between urinary tAs, infant sex, and maternal pre-pregnancy weight status with respect to weight-for-length Z score over the first year of life ($p_{interaction} = 0.23$; Table S5). No evidence was found of an interaction between urinary tAs and maternal pre-pregnancy weight status with respect to attained weight, weight-for-length, or head circumference over the first year of life (Table S3).

In the study population, the average growth rate over the first 3.5 months of life was 3.50 cm per month in females and 3.76 cm per month in males (Table S6). In adjusted piecewise linear mixed effects models assessing the association between maternal urinary second trimester tAs concentration and infant growth trajectory, urinary tAs was negatively associated with change in length for the first 3.5 months of life (Table 5). Overall, each doubling of maternal urinary tAs was associated with a 0.07 cm per month lower length

growth (95% CI: -0.12 , -0.02 ; $p = 0.0051$) over the first 3.5 months of life. No association was observed between change in length and urinary tAs after 3.5 months ($p = 0.26$). There was no evidence of an interaction between urinary tAs and infant sex ($p_{\text{interaction}} = 0.18$) or maternal pre-pregnancy weight status ($p_{\text{interaction}} = 0.73$; Table S7) in relation to change in length over the first 3.5 months of life.

When comparing infant length growth during the first 3.5 months of life for those in the 3rd vs. 1st quantile of *in utero* arsenic exposure, iAs and MMA were both associated with decreased growth (Table S8); for iAs, the decrease was 0.12 cm per month (95% CI: -0.22 , -0.02 ; $p_{\text{trend}} = 0.013$) and for MMA it was 0.13 cm per month (95% CI: -0.24 , -0.02 ; $p_{\text{trend}} = 0.0097$). This negative association with infant length growth was not observed when assessing exposure by DMA quantiles ($p_{\text{trend}} = 0.10$).

Over the first 3.5 months of life, females in this study gained, on average, 848.23 g per month and males gained, on average, 1013.23 g per month (Table S6). There was evidence of an interaction between urinary tAs and infant sex with respect to change in weight over the first 3.5 months of life (Table 5; $p_{\text{interaction}} = 0.035$). Adjusted longitudinal analyses stratified by infant sex demonstrated that urinary tAs was positively associated with change in weight in females, but not in males ($p = 0.13$). Among females, every doubling of urinary tAs concentration was associated with a 19.27 (95% CI: 3.12, 35.41; $p = 0.019$) g per month increase in weight gain over the first 3.5 months of life. There was no evidence of an association between weight gain and tAs after 3.5 months among either females ($p = 0.45$) or males ($p = 0.72$).

When assessing weight gain during the first 3.5 months of life in relation to *in utero* arsenic exposure quantiles in females, being in the 3rd vs 1st quantile of MMA was associated with a 53.03 g per month increase in weight gain (95% CI: 12.05, 94.01; $p_{\text{trend}} = 0.0091$) and being in the 3rd vs. 1st quantile of DMA was associated with a 43.20 g per month increase in weight gain (95% CI: 5.88, 80.53; $p_{\text{trend}} = 0.02$) (Table S9). This positive association with infant weight gain was not observed when assessing exposure by iAs quantiles ($p_{\text{trend}} = 0.32$).

All findings were consistent in analyses restricted to women who had not eaten seafood in the two days prior to urine collection ($n = 653$; Tables S10–11), adjusting for log-transformed maternal second trimester urinary arsenobetaine concentration ($n = 760$; Tables S12–13), restricted to women who had not eaten rice in the two days prior to urine collection ($n = 525$; Tables S14–15), restricted to women who did not have gestational diabetes during this pregnancy ($n = 703$; Tables S16–17), restricted to infants who were not large for gestational age ($n = 691$; Tables S18–19), restricted to infants who were born after at least 37 weeks gestation and were not small for gestational age ($n = 693$; Tables S20–21), and restricted to infants who were exclusively breast feed at 6 weeks ($n = 270$; Tables S22–23). Findings were also consistent when adjusting for maternal urinary creatinine concentrations ($n = 646$; Tables S24–25) and adjusting for whether rice cereal had been introduced at the time anthropometry measurements were collected ($n = 342$; Tables S26–27). Attained anthropometry analyses were consistent but attenuated in analyses adjusting for

anthropometry at birth (Table S28). Growth trajectory findings were consistent in analyses that did not adjust for anthropometry at birth (Table S29).

4. Discussion

Within this sample of 760 mother-infant pairs in New Hampshire, we found modest associations between *in utero* arsenic exposure, as measured by maternal second trimester urinary tAs concentrations, and infant anthropometry WHO Z scores and growth trajectory over the first year of life. An overall modest positive association was observed between maternal pregnancy urine tAs levels and infant length, as assessed by WHO Z scores, throughout the entire first year of life. A 0.05 increase in Z score corresponds to an approximately 0.12 cm increase in males and 0.13 cm increase in females at 12 months. This association was attenuated after adjusting for length WHO Z score at birth, suggesting that the observed association may be mediated by anthropometry at birth. As this association only achieved statistical significance at 2 weeks in timepoint specific models, it is possible that the association observed in the repeated measures analysis is primarily driven by this single timepoint.

Higher maternal urinary tAs levels were also negatively associated with change in length over the first 3.5 months of life, but not thereafter. This negative association with length growth trajectory may represent a true effect of arsenic exposure on early growth or, given previous findings associating biomarkers of *in utero* arsenic exposure with longer birth length in this population (Gilbert-Diamond et al., 2016), this may reflect “regression to the mean”, the statistical tendency for values that are more extreme to be followed by values that are more moderate (Barnett et al., 2004). It is important to note that given the large number of statistical tests being conducted and the use of a nominal threshold of statistical significance of $p < 0.05$, it is possible that identified associations may be spurious and due to chance.

Interestingly, observed associations between *in utero* arsenic exposure and infant length were not found to be exclusively driven by DMA, the arsenic metabolite that accounted for over 80% of urinary tAs in more than 50% of participants in this study. This suggests that exposure to iAs and MMA may be more important for some anthropometric outcomes than total arsenic exposure (iAs and its metabolites). Further work is needed to better understand the association between *in utero* exposure to specific arsenic species and subsequent anthropometric outcomes.

In assessing possible effect modification by infant sex, we identified a persistent negative association between maternal urinary total arsenic levels and weight-for-length over the entire first year of life among male infants only. This decreased adiposity may be due to arsenic-associated greater length. Interestingly, in females, there was a positive association between urine total arsenic levels and the rate of weight gain over the first 3.5 months of life, but this did not translate into any statistically significant differences in weight or weight-for-length WHO Z scores over the first year of life. Previous studies have observed sex-specific associations between arsenic and growth (Gilbert-Diamond et al., 2016; Saha et al., 2012). One possible explanation for these sex-specific associations is mediation by the placental

expression of *AQP9*, a gene encoding a transporter involved in cellular uptake of arsenic that has been reported to vary with arsenic exposure in a sex-specific manner (Winterbottom et al., 2017).

Growth during infancy has been associated with risk of metabolic disease during adulthood. Therefore, altered infant growth related to *in utero* arsenic exposure may have long-term health consequences. Persistently lowered BMI throughout infancy ($< 15 \text{ kg/m}^2$) has been associated with an increased risk of impaired glucose tolerance in early adulthood (Bhargava et al., 2004), and when that lowered BMI is followed by a rapid increase in BMI during childhood it has been associated with type 2 diabetes in later adulthood (Eriksson et al., 2015). Decreased change in length in the first 3 months of infancy has also been associated with an increased risk of type 2 diabetes in adulthood in a dose dependent fashion among infants with birth weights above 3.5 kg, particularly when followed by a rapid increase in BMI after 2 years of age (Eriksson et al., 2003). Given that our study observed very modest changes in infant length (a 0.07 cm per month decrease) relative to those studied in Eriksson et al. where differences in growth rate were assessed in 1 cm per month increments, our observed deviations in growth trajectory may not be substantially associated with metabolic outcomes in adulthood.

Saha et al. (2012) identified a weak negative association between *in utero* arsenic exposure and infant weight and length over the first year of life. These disparate findings may be due to differences in study population characteristics. For example, our studies differed greatly in terms of maternal BMI (average of 20.1 kg/m^2 in the Saha study compared to 26.3 kg/m^2 in our study population). In addition, the median urine tAs concentration was much higher in the Bangladeshi study population examined by Saha et al. ($84.0 \text{ } \mu\text{g/L}$ compared to $3.83 \text{ } \mu\text{g/L}$ in our study population). The notion that arsenic exposure may have a differential relationship with growth dependent on dose is supported by previous *in vitro* research on cultured osteoblasts which are critical to bone formation. Research by Xu et al. reported that, in an *in vitro* model, lower levels of arsenic trioxide (ATO) exposure (0.25 , 0.5 , and $1 \text{ } \mu\text{M}$) enhance osteoblast viability in culture while higher levels of ATO exposure (5 , 10 , and $20 \text{ } \mu\text{M}$) reduce osteoblast viability in culture (Xu et al., 2014). However, it is currently unknown how arsenic trioxide exposure relates to tAs exposure or how this threshold effect might translate to a threshold of total arsenic concentration in urine. As the lower levels of total urinary arsenic concentrations seen in our study population encompass those commonly seen throughout the United States, our findings may be more relevant to the United States population than those from heavily exposed Bangladeshi populations.

Other studies relating high dose prenatal arsenic exposure to postnatal growth at 5 and 7 years of age (Agay-Shay et al., 2015; Gardner et al., 2013) did not identify an association between *in utero* arsenic exposure and child anthropometry. It will therefore be important to assess the association between prenatal arsenic exposure and later childhood growth in our population with relatively lower doses of *in utero* arsenic exposure.

Our study strengths include having speciated measures of arsenic exposure: urinary inorganic arsenic and its metabolites which act as sensitive biomarkers of toxicologically relevant *in utero* arsenic exposure. Our study was also strengthened by having access to

clinical anthropometry measurements collected at multiple time points across the first year of infancy. However, clinical measures of infant length may be prone to error due to variability in measurement techniques across health care providers (Wood et al., 2013). In addition, instruments (for example, scales) from multiple clinical practices are not standardized nor uniformly calibrated as would be the case in a research setting. Given that our study relied on clinical measurements obtained from medical record review of infant well child visits, added variability around anthropometric measurements may have diminished our power to detect an association between biomarkers of *in utero* arsenic exposure and infant growth.

Our study was limited by arsenic exposure only being measured at one time during pregnancy; however one study conducted in Native American populations with relatively low levels of arsenic exposure suggests that measures of urinary arsenic are relatively stable over time (Navas-Acien et al., 2009). Our study was also limited by not assessing biomarkers of postnatal arsenic exposure in infants, however our findings were robust in sensitivity analyses restricted to infants who were exclusively breast fed, a subgroup without demonstrable postnatal arsenic exposure (Carignan et al., 2015, 2016; Fångström et al., 2008). As women have been shown to underestimate their pre-pregnancy weight via self-report, causing some overweight mothers to be misclassified as normal weight prior to pregnancy (Han et al., 2016), our reliance on self-reported maternal pre-pregnancy weight may have led to some subjects being misclassified with regards to pre-pregnancy weight status. Such misclassification may have obscured potential differences between women of normal as compared to overweight and obese pre-pregnancy weight statuses, thus limiting our ability to test for modification by pre-pregnancy weight status. Our study was also limited by sample size, particularly in analyses stratified by infant sex and/ or maternal pre-pregnancy weight status. Given the limited number of infants in each group following stratification, we may have been underpowered to detect effect modification by these factors.

5. Conclusions

Our findings suggest that, on average, infants exposed to higher *in utero* arsenic attained slightly longer length through the first 12 months of life, despite having slower linear growth in the first 3.5 months after birth. This suggests that the previously reported positive association between *in utero* arsenic exposure and birth length among study infants persists through the first year of life. We did not observe any other statistically significant associations between *in utero* arsenic exposure and child anthropometry across the full study population. Future studies in our cohort are needed to better understand how both prenatal and postnatal arsenic exposure may continue to affect anthropometry and growth trajectories throughout infancy and into childhood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

As	arsenic
tAs	total arsenic
iAs	inorganic arsenic
MMA	monomethylarsonic acid
DMA	dimethylarsinic acid
WHO	World Health Organization
BMI	body mass index
LOD	limit of detection
IOM	Institute of Medicine

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Table 1

Selected subject characteristics.

Variable	All Participants (n = 760)	Missing Values (n)
Pre-pregnancy BMI (kg/m ²) [mean (sd)]	26.11 (5.52)	30
Maternal pre-pregnancy weight status [n (%)]		30
Normal (18.5 ≤ BMI < 25)	388 (53.2)	
Overweight (25 ≤ BMI < 30)	200 (27.4)	
Obese (BMI ≥ 30)	142 (19.5)	
Missing	30 (3.9)	
Maternal age (yrs) [mean (sd)]	31.09 (4.84)	0
Maternal education level [n (%)]		66
High school graduate or lower	78 (11.2)	
Some college	135 (19.5)	
College graduate	289 (41.6)	
Postgraduate schooling	192 (27.7)	
Missing	66 (8.7)	
Previous pregnancies [n (%)]		0
0	301 (39.6)	
1	290 (38.2)	
2	107 (14.1)	
3	62 (8.2)	
Maternal Smoking Status [n (%)]		69
Never smoker	591 (85.5)	
Ever smoker	100 (14.5)	
Missing	69 (9.1)	
Gestational weight gain (lbs) [mean (sd)]	35.15 (14.88)	33
IOM gestational weight gain category [n (%)]		63
Adequate	196 (27.1)	
Inadequate	79 (10.9)	
Excessive	449 (62.0)	
Missing	36 (4.7)	
Infant delivery mode [n (%)]		0
Vaginal	515 (67.8)	
Cesarean section	245 (32.2)	
Infant Sex [n (%)]		0
Female	379 (49.9)	
Male	381 (50.1)	
Birth Outcomes [mean (sd)]		
Gestational age (wks)	39.55 (1.39)	0
Length WHO Z score	0.78 (1.31)	0
Weight WHO Z score	0.35 (0.97)	0
Weight-for-Length (WFL) WHO Z score	-0.38 (1.42)	0

Variable	All Participants (n = 760)	Missing Values (n)
Head circumference WHO Z score	0.41 (1.18)	4
Duration of breast feeding (mo) (median [IQR])	7.98 [3.00, 12.16]	123

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Table 2

Distribution of arsenic exposure for 760 mother-infant pairs.

Arsenic Measure	Concentration (µg/L) Median [IQR]	Proportion of tAs Median [IQR]	Below LOD ^a n (%)
iAs ^b	0.36 [0.16, 0.81]	0.10 [0.06, 0.17]	270 (35.5)
MMA	0.34 [0.13, 0.66]	0.08 [0.05, 0.12]	177 (23.3)
DMA	2.84 [1.39, 5.07]	0.81 [0.70, 0.86]	3 (0.4)
tAs ^c	3.96 [2.02, 6.72]	1.00 [1.00, 1.00]	2 (0.3)

^aNumber of samples below the limit of detection (LOD).^biAs reflects the sum of AsIII and AsV measured in each sample where the number of samples below the LOD reflects the number of samples in which both AsIII and AsV were below the LOD.^ctAs reflects the sum of iAs (AsIII + AsV), MMA, and DMA measured in each sample where the number of samples below the LOD reflects the number of samples in which AsIII, AsV, MMA, and DMA were all below the LOD.

Table 3

Adjusted parameter estimates (95% confidence interval) for the change in anthropometry WHO Z scores with each doubling of total maternal second trimester urinary arsenic for all participants.

Outcome	Timepoint	Overall ^a		
		n	Beta (95% CI)	p
Weight	2 weeks	686	0.02 (−0.02, 0.06)	0.36
	2 months	744	0.02 (−0.03, 0.07)	0.45
	4 months	722	0.01 (−0.04, 0.06)	0.63
	6 months	720	0.01 (−0.04, 0.06)	0.70
	9 months	691	0.02 (−0.03, 0.07)	0.51
	12 months	691	0.01 (−0.04, 0.06)	0.67
	Repeated Measures ^b	760 (5,376)	0.01 (−0.03, 0.05)	0.52
Length	2 weeks	585	0.07 (0.01, 0.13)	0.025
	2 months	741	0.04 (−0.01, 0.10)	0.11
	4 months	722	0.02 (−0.04, 0.07)	0.50
	6 months	717	0.02 (−0.03, 0.08)	0.40
	9 months	688	0.04 (−0.02, 0.09)	0.24
	12 months	688	0.05 (−0.01, 0.11)	0.10
	Repeated Measures ^b	760 (5,238)	0.05 (0.00, 0.09)	0.044
WFL	2 weeks	584	−0.04 (−0.11, 0.02)	0.20
	2 months	738	−0.03 (−0.10, 0.03)	0.32
	4 months	722	0.00 (−0.06, 0.06)	1.00
	6 months	717	0.00 (−0.06, 0.06)	0.90
	9 months	688	0.00 (−0.06, 0.05)	0.97
	12 months	688	−0.02 (−0.07, 0.03)	0.51
	Repeated Measures ^b	760 (5,234)	−0.03 (−0.07, 0.02)	0.22
HC	2 weeks	577	−0.03 (−0.09, 0.03)	0.29
	2 months	727	0.01 (−0.04, 0.06)	0.80
	4 months	704	0.00 (−0.05, 0.05)	0.90
	6 months	697	−0.01 (−0.06, 0.04)	0.69
	9 months	667	0.01 (−0.05, 0.06)	0.83
	12 months	663	−0.01 (−0.07, 0.04)	0.62
	Repeated Measures ^b	756 (5,109)	−0.01 (−0.05, 0.04)	0.80

^aResults are from linear regression models fitting weight, length, weight-for-length (WFL), and head circumference (HC) WHO Z scores (WHO Multicentre Growth Reference Study Group, 2006) on log transformed maternal second trimester urinary tAs. Models are adjusted for gestational age (continuous), infant sex (binary), maternal pre-pregnancy BMI (continuous), IOM gestational weight gain category (Rasmussen and Yatkine, 2009) (categorical), maternal education level (ordinal with 4 levels listed in Table 1), parity (ordinal with parity 3 grouped together), duration of breast feeding up to the time of anthropometry measurement (continuous), and maternal smoking status (binary; ever or never).

^bResults are from a linear mixed effects model fitting a random intercept for each infant. Sample size reflects the total number of infants included in the analysis and, in parentheses, the total number of measurements included in the model. Each infant contributed between 2 and 8 measurements (collected at birth, 2 weeks, 1 month, 2 months, 4 months, 6 months, 9 months, and/or 12 months).

Table 4

Adjusted parameter estimates (95% confidence interval) for the change in anthropometry WHO Z scores with each doubling of total maternal second trimester urinary arsenic stratified by infant sex.

Outcome	Timepoint	Female ^a		Male ^a		^b <i>p</i> _{int}	
		n	Beta (95% CI)	n	Beta (95% CI)	<i>p</i>	
Weight	2 weeks	342	0.02 (−0.04, 0.08)	344	0.00 (−0.06, 0.07)	0.88	0.70
	2 months	369	0.02 (−0.04, 0.08)	375	0.02 (−0.06, 0.10)	0.60	0.98
	4 months	356	0.04 (−0.02, 0.10)	366	−0.01 (−0.10, 0.07)	0.72	0.25
	6 months	357	0.05 (−0.02, 0.11)	363	−0.03 (−0.11, 0.05)	0.43	0.10
	9 months	343	0.05 (−0.02, 0.11)	348	−0.02 (−0.09, 0.06)	0.65	0.16
	12 months	344	0.03 (−0.03, 0.09)	347	−0.01 (−0.09, 0.06)	0.73	0.32
Repeated Measures ^c		379 (2,670)	0.03 (−0.02, 0.08)	381 (2,706)	−0.01 (−0.07, 0.05)	0.82	0.31
Length	2 weeks	289	0.04 (−0.05, 0.12)	296	0.10 (0.01, 0.18)	0.022	0.19
	2 months	367	0.05 (−0.03, 0.13)	374	0.05 (−0.04, 0.13)	0.27	0.96
	4 months	356	0.01 (−0.07, 0.09)	366	0.02 (−0.06, 0.10)	0.55	0.74
	6 months	355	0.02 (−0.05, 0.10)	362	0.03 (−0.06, 0.11)	0.53	0.91
	9 months	340	0.04 (−0.05, 0.12)	348	0.04 (−0.05, 0.12)	0.41	0.95
	12 months	341	0.07 (−0.01, 0.15)	347	0.04 (−0.05, 0.13)	0.41	0.65
Repeated Measures ^c		379 (2,594)	0.05 (−0.02, 0.11)	381 (2,644)	0.05 (−0.01, 0.12)	0.12	0.77
WFL	2 weeks	289	−0.04 (−0.13, 0.05)	295	−0.09 (−0.19, 0.01)	0.068	0.27
	2 months	367	−0.03 (−0.12, 0.05)	371	−0.04 (−0.13, 0.06)	0.45	0.82
	4 months	356	0.04 (−0.03, 0.12)	366	−0.04 (−0.13, 0.05)	0.36	0.12
	6 months	355	0.04 (−0.03, 0.12)	362	−0.06 (−0.15, 0.03)	0.19	0.056
	9 months	340	0.04 (−0.03, 0.12)	348	−0.05 (−0.13, 0.03)	0.23	0.069
	12 months	341	0.00 (−0.07, 0.07)	347	−0.04 (−0.12, 0.04)	0.31	0.36
Repeated Measures ^c		379 (2,594)	0.00 (−0.05, 0.06)	381 (2,640)	−0.07 (−0.13, 0.00)	0.041	0.063
HC	2 weeks	285	−0.07 (−0.15, 0.01)	292	−0.02 (−0.10, 0.07)	0.69	0.45
	2 months	358	−0.01 (−0.08, 0.05)	369	0.03 (−0.04, 0.10)	0.42	0.46
	4 months	345	−0.02 (−0.09, 0.05)	359	0.02 (−0.05, 0.10)	0.58	0.56
	6 months	343	0.01 (−0.06, 0.08)	354	−0.02 (−0.10, 0.05)	0.55	0.42

Outcome	Timepoint	Female ^a		Male ^a		^b <i>p</i> _{int}	
		n	Beta (95% CI)	p	n	Beta (95% CI)	p
	9 months	331	0.03 (−0.05, 0.10)	0.51	336	0.00 (−0.08, 0.07)	0.92
	12 months	330	0.02 (−0.06, 0.10)	0.59	333	−0.04 (−0.12, 0.04)	0.28
	Repeated Measures ^c	376 (2,527)	0.00 (−0.06, 0.06)	0.99	380 (2,582)	0.00 (−0.07, 0.06)	0.89
							0.81

^aResults are from linear regression models fitting weight, length, weight-for-length (WFL), and head circumference (HC) WHO Z scores (WHO Multicentre Growth Reference Study Group, 2006) on log transformed maternal second trimester urinary (As and stratified by infant sex. Models are adjusted for gestational age (continuous), maternal pre-pregnancy BMI (continuous), IOM gestational weight gain category (Rasmussen and Yaktine, 2009) (categorical), maternal education level (ordinal with 4 levels listed in Table 1), parity (ordinal with parity 3 grouped together), duration of breast feeding up to the time of anthropometry measurement (continuous), and maternal smoking status (binary; ever or never).

^bP values reflect the p value from a likelihood ratio test comparing a model with an interaction between maternal arsenic and infant sex to a nested model with no interaction term.

^cResults are from a linear mixed effects model fitting a random intercept for each infant. Sample size reflects the total number of infants included in the analysis and, in parentheses, the total number of measurements included in the model. Each infant contributed between 2 and 8 measurements (collected at birth, 2 weeks, 1 month, 2 months, 4 months, 6 months, 9 months, and/or 12 months).

Table 5

Adjusted parameter estimates (95% confidence interval) for the change in growth trajectory associated with each doubling of total maternal second trimester urinary arsenic, overall and by infant sex.

Outcome	Age (months)	Overall (n = 760) ^a		Female (n = 379) ^b		Male (n = 381) ^b		P _{int} ^c
		Beta	(95% CI)	P	Beta	(95% CI)	P	
Weight (g/mo)	0–3.5	2.52	(−9.68, 14.71)	0.69	19.27	(3.12, 35.41)	0.019	0.13
	3.5–12	1.06	(−6.15, 8.28)	0.77	3.58	(−5.74, 12.90)	0.45	0.72
Length (cm/mo)	0–3.5	−0.07	(−0.12, −0.02)	0.0051	−0.03	(−0.10, 0.03)	0.30	0.0039
	3.5–12	0.01	(−0.01, 0.03)	0.26	0.02	(−0.01, 0.05)	0.16	0.79
WFL (g/cm/mo)	0–3	0.17	(−0.06, 0.40)	0.15	0.33	(0.02, 0.64)	0.036	0.83
	3–12	−0.01	(−0.10, 0.08)	0.84	0.01	(−0.11, 0.13)	0.90	0.61
HC (cm/mo)	0–3.5	0.01	(−0.02, 0.04)	0.56	0.01	(−0.03, 0.05)	0.63	0.64
	3.5–12	0.00	(−0.01, 0.01)	0.69	0.01	(−0.01, 0.02)	0.29	0.062

^aResults are from piecewise linear mixed effects models fitting each anthropometry measure on log transformed maternal second trimester urinary tAs. Parameters reflect the association between tAs and anthropometry growth trajectory, as longitudinally modeled by the multiplicative term between infant age and tAs exposure. Models are adjusted for anthropometry measurement at birth (continuous), gestational age (continuous), infant sex (with an additional interaction term between infant sex and infant age), maternal pre-pregnancy BMI (continuous), IOM gestational weight gain category (categorical), maternal education level (ordinal with 4 levels listed in Table 1), parity (ordinal with parity = 3 grouped together), duration of breast feeding up to the time of anthropometry measurement (continuous, with an additional interaction term between duration of breast feeding and infant age), and maternal smoking status. The changepoint for the piecewise model was selected based on the age (assessed at ½ month intervals) that minimized the residual sums of squares for unadjusted models.

^bResults are from piecewise linear mixed effects models fitting each anthropometry measure on log transformed maternal second trimester urinary tAs and stratified by infant sex. Models are adjusted for all variables described in footnote a with the exception of infant sex.

^cP value from a likelihood ratio test comparing a model with all the covariates and interaction terms described in footnote a as well as a 3-way interaction term between maternal arsenic, infant age, and infant sex and a 2-way interaction term between maternal arsenic and infant sex to a nested model with no 3-way interaction term and no 2-way interaction term between maternal arsenic and infant sex.