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Early life and adolescent arsenic exposure from drinking water and blood pressure in adolescence

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ABSTRACT

Objectives: Evidence of the association between inorganic arsenic (As) exposure, especially early-life exposure, and blood pressure (BP) in adolescence is limited. We examined the association of As exposure during early childhood, childhood, and adolescence with BP in adolescence.

Methods: We conducted a cross-sectional study of 726 adolescents aged 14–17 (mean 14.75) years whose mothers were participants in the Bangladesh Health Effects of Arsenic Longitudinal Study (HEALS). Adolescents' BP was measured at the time of their recruitment between December 2012 and December 2016. We considered maternal urinary As (UAs), repeatedly measured during childhood, as proxy measures of early childhood (< 5 years old, A1) and childhood (5–12 years old, A2) exposure. Adolescents' current UAs was collected at the time of recruitment (14–17 years of age, A3).

Results: Every doubling of UAs at A3 and maternal UAs at A1 was positively associated with a difference of 0.7-mmHg (95% confidence interval [CI]: 0.1, 1.3) and a 0.7-mmHg (95% CI: 0.05, 1.4) in SBP, respectively. These associations were stronger in adolescents with a BMI above the median (17.7 kg/m^2) than those with a BMI below the median (*P* for interaction = 0.03 and 0.03, respectively). There was no significant association between any of the exposure measures and DBP. The Weighted Quantile Sum (WQS) regression confirmed that adolescents' UAs at A3 and maternal UAs at A1 contributed the most to the overall effect of As exposure at three life stages on SBP. Mixture analyses using Bayesian Kernel Machine Regression identified UAs at A3 as a significant contributor to SBP and DBP independent of other concurrent blood levels of cadmium, lead, manganese, and selenium.

Conclusion: Our findings suggest an association of current exposure and early childhood exposure to As with higher BP in adolescents, which may be exacerbated by higher BMI at adolescence.

Abbreviations: As, arsenic; BAs, blood arsenic; BCd, blood cadmium; BKMR, Bayesian Kernel Machine Regression; BMI, body mass index; BMn, blood manganese; BP, blood pressure; BPb, blood lead; BSe, blood selenium; CVD, cardiovascular disease; DBP, diastolic blood pressure; HEALS, Health Effects of As Longitudinal Study; SBP, systolic blood pressure; UAs, urinary arsenic; UCr, urinary creatinine

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1. Introduction

Inorganic arsenic (As) occurs naturally in groundwater, exposing millions of people in the U.S. and worldwide. Evidence suggests a positive association of As exposure with cardiovascular disease (CVD) (Chen et al., 2011, 2013a, 2013b, 2013c; Jiang et al., 2015; Moon et al., 2012, 2013) and blood pressure (BP) in adults (Abhyankar et al., 2012; Chen et al., 2007; Jiang et al., 2015; Kwok et al., 2007). However, data on cardiovascular-related outcomes in children and adolescents are limited.

A growing body of evidence suggests effects of early-life exposure to As on cancer (Smith et al., 2006, 2012; Steinmaus et al., 2014), respiratory function (Dauphine et al., 2011; Smith et al., 2006), and neurological function (Goggin et al., 2012; Martinez-Finley et al., 2009; Martinez et al., 2008, 2011), including data among children (Hamadani et al., 2010; Hamadani et al., 2011; Parajuli et al., 2013; Rosado et al., 2007; Roy et al., 2011; Tsai et al., 2003; von Ehrenstein et al., 2007; Wasserman et al., 2007; Wasserman et al., 2004; Wasserman et al., 2011). BP has been shown to track from childhood and adolescence to adulthood, and those with elevated BP in adolescence have an increased risk of developing prehypertension and hypertension (Chen and Wang, 2008; Chiolero et al., 2013; Juhola et al., 2011; Lauer and Clarke, 1989; Toschke et al., 2010), as well as preclinical and clinical CVD in adulthood (Barker et al., 1989; Magnussen and Smith, 2016). Recent data suggest that early-life and *in utero* exposure to As can lead to increases in BP among young children (4–8 years of age) (Hawkesworth et al., 2013; Osorio-Yanez et al., 2015). However, no studies have examined the effects of early-life or current As exposure on BP in adolescents or have assessed whether the effects differ by other risk factors or exposures.

In 2000, we established the Health Effects of As Longitudinal Study (HEALS) in Bangladesh, a prospective cohort of 11,746 adult participants. In 2012–2016, we conducted a cross-sectional study of 726 adolescents aged 14–17 (mean 14.75) years whose mothers were participants in the HEALS with complete As exposure histories. We examined associations between As exposure and BP in adolescence, using urinary biomarkers of maternal (i.e., household) exposure over time, as well as concurrent adolescent urinary biomarker of As (UAs) and blood biomarkers of cadmium (BCd), manganese (BMn), lead (BPb), and selenium (BSe) at the time of the BP measurements.

2. Methods

2.1. Overview

The parent study, the HEALS, is an ongoing prospective cohort study in Araihazar, Bangladesh. Details of the study have been presented elsewhere (Ahsan et al., 2006). Briefly, between October 2000 and May 2002, we recruited the original cohort, including 11,746 married men and women aged 18–75 years who were residents of the study area for at least 5 years and had been drinking from their household well for at least 3 years. At baseline, immediately after recruitment, an As mitigation program was implemented to promote well switching to safe wells, i.e., those that met the Bangladesh standard of $< 50\,\mu g/L$. The cohort is being followed up every 1–4 years with in-person visits, which include a physical examination and collection of urine samples. A field clinic was established exclusively for the cohort participants to receive medical diagnoses and treatments and facilitate the follow-up (Ahsan et al., 2006). Urinary As (UAs) is measured at baseline and every follow-up for over 95% of the participants.

Details of the adolescent study have been presented elsewhere (Wasserman et al., 2018). Briefly, we identified the first-born children of 927 HEALS female participants whose assessment of exposure to water As was complete from baseline through 2009. The children were born between 1996 and 2002. The recruitment for this cross-sectional study of adolescent participants took place between December 2012 and December 2016 (Wasserman et al., 2018), when targeted adolescents were anticipated to be 14–17 years old. Field teams visited families at home to obtain parental informed consent and child assent, to collect data on sociodemographic information, and to make appointments for a clinic visit. At the field clinic visits, BP was measured, and urine samples were collected. Of the 927 adolescents, 201 were excluded based on the following criteria: 12 adolescents were outside the anticipated age range; 12 had died; 29 had moved away; 111 refused participation and 37 were excluded for other reasons; ultimately, 726 were assessed. This study was approved by the Columbia University Medical Center and the Bangladesh Medical Research Council Institutional Review Board.

We collected sociodemographic characteristics during a structured interview with a parent during the home visit. During the clinic visits, child's height, weight, and BP were measured as previously described (Pierce et al., 2010). BP was measured only once by trained clinicians using an automatic sphygmomanometer (HEM 712-C; Omron Healthcare GmbH, Hamburg, Germany). We used an automated sphygmomanometer, which has been validated to have 85 percent of readings falling within 5–10 mmHg of the mercury standard (O'Brien et al., 2001). Measurements were taken with adolescents in a seated position after 5 min of rest, with the cuff around the upper left arm, in accordance with recommended guidelines. We used BP as a continuous variable in all analyses.

2.2. Urinary measurements

Spot urine samples were collected from the mothers at baseline and at all follow-up visits of the HEALS and from the adolescents when they were recruited for the present study. Total UAs concentrations were measured by graphite furnace atomic absorption, using a PerkinElmer AAnalyst 600 system (Waltham, MA) with a detection limit of $2\,\mu g/L$ (Nixon et al., 1991). UAs levels were adjusted for urinary creatinine (UCr) concentrations ($\mu g/g$ Cr), which were analyzed by a colorimetric method based on the Jaffé reaction (Slot, 1965).

Since women bring water into the home and typically all household members drink water from a single tube well, a mother's exposure over time offers an excellent proxy for her child's exposure over time. Among the HEALS children in our previous studies (Parvez et al., 2011; Wasserman et al., 2007, 2011), the correlation between children's UAs and mother's UAs (Spearman correlation coefficient $r = 0.75$) was the same as the correlation between the mother's own UAs and water As ($r = 0.75$), corroborating that both mother and child are largely consuming water from the same source. Therefore, in the present study, we used maternal UAs which was measured every 1–4 years during HEALS follow-up as proxy measures of early childhood and childhood As exposure for the adolescents. We defined early childhood exposure as the maternal UAs measured when the adolescents were one year prior to the birth (*in utero*) to < 5 years old (A1). Maternal UAs was measured two times during A1 for 325 adolescents and three times for 61 adolescents, and the average of the two and three measurements was used. Similarly, we also defined childhood exposure as the maternal UAs measured when the adolescents were 5–12 years of age (A2). During A2, maternal UAs was measured two times for 325 adolecents, three times for 308 adolecents, and four times for 26 adolecents. When there were multiple maternal UAs measured in A2, the average was estimated and used in the analyses. Among adolescents who had multiple maternal UAs within A1 or A2, the intraclass correlation coefficients (ICCs) of repeated maternal UAs ranged from 0.56 to 0.80, indicating that they are moderately to highly correlated with one another. We used average of the measures to improve reproducibility, which may be more accurately reflective of usual exposure level. Current UAs was definied as concentration tested in urine samples collected from the adolescents at the time of their recruitment (14–17 years of age, A3).

2.3. Blood measurements

Venous whole blood samples were collected from the adolescents and analyzed for As (BAs), BCd, BMn, BPb, and BSe concentrations by inductively-coupled plasma mass spectrometry (ICP-MS) using a PerkinElmer NexION 350 S equipped with an Elemental Scientific SC-4 DX autosampler (Omaha, NE) (Pruszkowski et al., 1998; Stroh, 1988). The intra-precision coefficients of variation for BAs, BCd, BMn, BPb, and BSe were 3.7%, 7.8%, 3.2%, 1.6%, 2.0%, respectively, and the interprecision coefficients were 7.3%, 16.0%, 5.9%, 3.9%, and 5.3%, respectively.

2.4. Statistical analyses

A total of 722 adolescents had complete data on BP. There were 719, 695, and 720 adolescents with complete data on current UAs at A3, maternal UAs at A1, and maternal UAs at A2, respectively, for respective analyses. We calculated descriptive statistics for socio-demographic and As exposure variables, mean and standard deviation for continuous variables and distribution (%) for categorical variables, by tertiles of current UAs at A3. We used Chi-square and Kruskal-Wallis tests to detect group differences in categorical and continuous variables, respectively. Spearman correlation coefficients were used to examine bivariate association between continuous variables on the original scale.

The adolescents' current UAs, BAs, BCd, BMn, BPb, and BSe at A3 (14–17 years of age), and maternal UAs composites that represent early childhood exposure and childhood exposure all had right skewed distributions. To reduce the impact of extreme values in regression analysis, we logarithmically transformed the variables. Use of log base 2 enabled us to present effect size for associations per doubling of the exposure. Linear regression analysis was conducted to assess As exposure in relation to SBP and DBP adjusted for covariates. The predictors of As exposure in the model took the following forms: (1) categorized at tertiles of adolescents' current UAs at A3, maternal UAs at A1, and maternal UAs at A2, using the lowest tertile as the reference; (2) continuous (log base 2 transformed) As exposure variables; (3) combination of two exposures for the joint effect of maternal UAs at A1 and adolescents' current UAs at A3. We adjusted for potential confounding variables including adolescents' sex, age (years), and BMI (kg/m^2) that were associated with SBP and/or DBP ($P < 0.05$). These factors were also related to As exposure in our study population (Chen et al., 2011, 2013a). Further adjustment for other potential confounders such as adolescents' education and mother's education generated similar results (data not shown).

Additionally, for significant associations between As exposure measures and BP in the overall study sample, we conducted stratified analyses to evaluate the extent to which the associations differ by levels of BMI at adolescence above or below sample median of 17.7 kg/m^2. Additional exploratory stratified analyses by sex and age (dichotomized at median of 14.4 years) were also conducted. The *P* value for the cross-product term between the dichotomized BMI and the exposures as continuous variables was used to judge the statistical significance of the additive interaction.

Sensitivity analyses were also conducted with additional adjustment for BCd, BMn, BPb, and BSe; using BAs as the biomarker of exposure instead; or using specific gravity (SG) to adjust UAs in place of UCr to account for dilution, with the following equation: $UAs_{sample} \times (SG_{mean} - 1) \div (SG_{sample} - 1)$ (Gamble and Liu, 2005; MacPherson et al., 2018; Steinmaus et al., 2009). All analyses were performed using SAS (version 9.4; SAS Institute Inc, Cary, NC).

As exposure measured at different life stages (current UAs at A3, maternal UAs at A1, and maternal UAs at A2) were positively correlated with one another (pairwise Spearman correlation coefficient r 0.46–0.75). We used Weighted Quantile Sum (WQS) regression method (Carrico et al., 2015) to evaluate the overall effect of the correlated exposures at different life stages on BP. It has been demonstrated that WQS regression can be used to address collinearity and high-dimensionality (Carrico et al., 2015). We used this method to estimate an index as weighted sum of the three exposure variables at different life stages scored as tertiles, and then evaluate the coefficient of the index for its association with BP in the regression models. The regression coefficient for the weighted index indicates change in SBP associated with a unit (tertile) increase in the weighted index; the *p*-value for the coefficient was used to evaluate the statistical significance of the association. Weights were calculated for exposure at each life stage using bootstrapping to determine the relative contribution to the total effect (Carrico et al., 2015). The weights are non-negative and constrained to sum to 1, thereby reducing dimensionality and addressing issues associated with collinearity. WQS regression analyses were conducted using the "gWQS" package in R (version 3.4.0; R Core Team, Vienna, Austria) (Renzetti et al., 2016).

We also employed Bayesian Kernel Machine Regression (BKMR) to investigate the joint effects of co-exposure to current UAs, BCd, BMn, BPb, and BSe. Briefly, BKMR identifies important mixture members and accounts for the correlated structure of mixture components, estimating complex and potentially non-linear exposure-response functions and evaluating potentially non-additive and non-linear interactions (Bobb et al., 2014; Coull et al., 2015). BKMR uses a flexible kernel function of the elements in the mixture to assess exposure to the mixture in a regression model without specifying *a priori* the shape of the exposure-response functions, while incorporating a component-wise variable selection process. BKMR analyses were conducted using the "BKMR" package in R. For both the WQS and BKMR analyses, all exposures were log_2-transformed in the models to preserve consistency with the main analysis, and the same covariates as in the main analysis were included in the models for confounding adjustment.

3. Results

Those in the higher tertiles of adolescents' current UAs at A3 were older, had lower BMI, or had fewer years of formal education (Table 1). Mothers of adolescents in the higher current UAs tertiles on average received fewer years of formal educational attainment. Among other concurrent exposures, BCd and BSe were significantly inversely related to current UAs tertiles.

In the overall study sample, SBP in adolescents with the highest tertile of current UAs at A3 (≥145.2 μg/g Cr) was 2.4-mmHg [95% confidence interval (CI): 0.5, 4.2] higher than SBP in those with the lowest tertile of current UAs at A3 (≤71.2 μg/g Cr) (Table 2). A doubling of current UAs at A3 was associated with a 0.7-mmHg (95% CI: 0.1, 1.3) increase in SBP. There was no significant association between current UAs at A3 and DBP (Table 2). The association between current UAs at A3 and SBP did not change with additional adjustment for BCd, BMn, BPb, and BSe (Table S1). We observed similar patterns of associations when we used adolescents' current BAs at A3 (Table S2) or SG-adjusted UAs (Table S3) as the exposure variables. For instance, a doubling of SG-adjusted UAs was associated with an increase of 0.9-mmHg (95% CI: 0.3, 1.4) in SBP (Table S3).

Compared with adolescents in the lowest tertile of maternal UAs at A1 (≤132.4 μg/g Cr), SBP was higher in those in the second (132.5–272.3 μg/g Cr) and third tertiles (≥272.4 μg/g Cr) by 2.2-mmHg (95% CI: 0.4, 4.1) and 1.9-mmHg (95% CI: 0.01, 3.8), respectively (Table 2). Every doubling of maternal UAs at A1 was associated with a 0.7-mmHg (95% CI: 0.05, 1.4) increase in SBP. On the other hand, maternal UAs at A2 was not significantly associated with SBP. There was no significant association between maternal UAs at A1 or A2 with DBP (Table 2).

The associations of As exposure measures with SBP did not differ by sex or age (Table S4 and Table S5). The positive associations of adolescents' current UAs at A3 and maternal UAs at A1 with SBP were stronger in adolescents with BMI above the median (*P* for

Table 1
Characteristics of the study sample overall and by tertile of adolescents' current urinary arsenic at A3 (14–17 years of age)[a].

	Overall (n = 719)	Tertile of adolescents' current urinary arsenic at A3[b]			P^c
		1 (n = 239)	2 (n = 240)	3 (n = 240)	
Adolescent variables					
Male, n (%)	333 (46.3)	116 (48.5)	105 (43.8)	112 (46.7)	0.68
Age, years	14.6 ± 0.7	14.6 ± 0.7	14.6 ± 0.6	14.7 ± 0.7	0.03
BMI, kg/m^2	18.3 ± 2.9	18.8 ± 3.2	18.1 ± 2.9	18.0 ± 2.3	0.01
Education, years	6.9 ± 2.2	7.2 ± 2.1	6.9 ± 2.1	6.5 ± 2.3	< 0.01
SBP, mmHg	99.0 ± 10.9	98.8 ± 11.2	98.0 ± 10.5	100.3 ± 11.1	0.10
DBP, mmHg	64.6 ± 9.3	64.8 ± 8.9	63.6 ± 9.2	65.3 ± 9.7	0.13
BCd, μg/L	0.61 ± 0.31	0.67 ± 0.36	0.62 ± 0.31	0.54 ± 0.24	< 0.01
BMn, μg/L	11.4 ± 3.7	11.6 ± 3.6	11.3 ± 3.7	11.4 ± 3.6	0.53
BPb, μg/L	98.1 ± 43.3	99.8 ± 44.7	101.1 ± 43.3	93.4 ± 41.6	0.12
BSe, μg/L	132.2 ± 18.1	133.8 ± 16.8	132.8 ± 19.2	130.1 ± 18.2	0.04
Family characteristics					
Maternal age at baseline, years	27.2 ± 5.4	27.0 ± 5.6	27.5 ± 5.5	27.2 ± 5.2	0.65
Maternal education, years	3.6 ± 3.6	4.1 ± 3.7	3.6 ± 3.5	3.2 ± 3.4	0.02
Arsenic exposure variables					
Adolescents' current UAs at A3, μg/g Cr	158.4 ± 207.1	45.8 ± 13.9	103.9 ± 21.2	324.9 ± 291.0	< 0.01
Adolescents' current BAs at A3, μg/L	4.9 ± 4.7	2.1 ± 1.2	3.7 ± 3.5	8.9 ± 6.1	< 0.01
Maternal UAs at A1[d], μg/g Cr	264.5 ± 247.5	184.8 ± 194.0	241.1 ± 202.5	370.9 ± 298.6	< 0.01
Maternal UAs at A2[e], μg/g Cr	235.6 ± 234.2	141.3 ± 124.6	204.1 ± 164.5	361.5 ± 311.1	< 0.01

Continuous variables are presented as mean ± SD and categorical variables are expressed as n (%).

[a] Data were missing on maternal education for 7 subjects, on adolescents' current blood arsenic, cadmium, lead, and selenium for 3 subjects, on maternal UAs at A1 for 27 subjects, and on maternal UAs at A2 for 2 subjects.

[b] Tertile 1: 15.8–71.2 μg/g Cr; tertile 2: 71.3–145.1 μg/g Cr; tertile 3: 145.2–2886.9 μg/g Cr.

[c] P values were computed with the Chi-square test or Kruskal-Wallis test.

[d] Average maternal UAs when the adolescents were *in utero* to 5 years old.

[e] Average maternal UAs when the adolescents were 5–12 years old.

Table 2
Mean difference in SBP and DBP in relation to adolescent' current urinary arsenic at A3 (14–17 years of age) and maternal urinary arsenic at A1 (< 5 years old) and A2 (5–12 years old).

As exposure	n	β[a] (95% CI)	
		SBP	DBP
Adolescents' current UAs at A3, μg/g Cr			
Tertile 1 (15.8–71.2)	239	Ref	Ref
Tertile 2 (71.3–145.1)	240	0.3 (−1.6, 2.1)	−0.7 (−2.3, 1.0)
Tertile 3 (145.2–2886.9)	240	2.4 (0.5, 4.2)	1.0 (−0.6, 2.6)
Continuous arsenic[b]	719	0.7 (0.1, 1.3)	0.4 (−0.2, 0.9)
Maternal UAs at A1[c], μg/g Cr			
Tertile 1 (20.0–132.4)	231	Ref	Ref
Tertile 2 (132.5–272.3)	232	2.2 (0.4, 4.1)	1.0 (−0.7, 2.6)
Tertile 3 (272.4–3073.8)	232	1.9 (0.01, 3.8)	0.6 (−1.1, 2.3)
Continuous arsenic[b]	695	0.7 (0.05, 1.4)	0.1 (−0.5, 0.7)
Maternal UAs at A2[d], μg/g Cr			
Tertile 1 (26.6–117.5)	240	Ref	Ref
Tertile 2 (117.6–239.6)	240	1.2 (−0.7, 3.0)	−0.3 (−1.9, 1.4)
Tertile 3 (239.7–3221.0)	240	1.2 (−0.7, 3.0)	0.2 (−1.5, 1.8)
Continuous arsenic[b]	720	0.6 (−0.2, 1.3)	0.2 (−0.4, 0.8)

[a] Adjusted for sex, age (years), and BMI.

[b] Per doubling of arsenic exposure (log base 2 transformed).

[c] Among adolescents with complete data.

[d] Among adolescents with complete data.

interaction = 0.03 and 0.03, respectively), compared with the associations in those with a lower BMI (Fig. 1). Similar patterns of associations were observed with additional adjustment for BCd, BMn, BPb, and BSe (Table S1), and using current BAs at A3 (Table S2) or SG-adjusted UAs (Table S3) as the exposure variable.

In the overall study sample, adolescents with a higher level of current UAs at A3 (> 102.6 μg/g Cr; median) and a higher level of maternal UAs at A1 (> 189.8 μg/g Cr; median) had a higher SBP by 2.5-mmHg (95% CI: 0.6, 4.4), compared with those with lower exposure in the two periods (Table 3). In adolescents with BMI above the median, the joint effect was stronger. Compared with adolescents with lower maternal UAs at A1 and lower current UAs at A3, those with higher maternal UAs at A1 and higher current UAs at A3 had a higher SBP by 6.4-mmHg (95% CI: 3.6, 9.3), greater than the difference associated with higher current UAs at A3 alone (2.9 mmHg; 95% CI: 0.4, 6.1) or the difference associated with higher maternal UAs at A1 alone (2.0 mmHg; 95% CI: 1.2, 5.2).

Results from WQS regression models, examining associations of the weighted index for adolescents' UAs at A3, maternal UAs at A1, and maternal UAs at A2 with SBP, are shown in Table 4. The weighted index was significantly associated with SBP in the study sample ($P = 0.02$), indicating a significant overall effect; each tertile increase in the weighted index was related to a difference of 1.5-mmHg (95% CI: 0.3, 2.6) in SBP. Adolescents' UAs at A3 had the greatest weight (53%), followed by maternal UAs at A1 (35%) and maternal UAs at A2 (12%). In adolescents with BMI above the median, the weighted index was significantly associated with SBP ($P < 0.01$); each tertile increase in the weighted index was related to a difference of 3.7-mmHg (95% CI: 1.9, 5.4) in SBP. Maternal UAs at A1 (45%) and adolescents' UAs at A3 (40%) contributed similarly to the overall effect, followed by maternal UAs at A2 (16%).

Analysis with BKMR largely confirms findings of the regression model (Table S1; Table S6) that included $\log_2$-transformed current BCd, BMn, BPb, and BSe in addition to UAs at A3 (Fig. 2). We observed significantly positive associations of current UAs and BMn with SBP, and marginally significant associations of BSe and BCd with SBP. All observed associations were monotonic, linear or near-linear. No interactions between the exposures were observed (results not shown). We observed an increasing overall effect on SBP with increasing levels of all exposures, albeit non-significant (Fig. S1). We observed statistically significant associations of UAs, BSe, BPb and BCd with DBP. For BPb and BCd we observed deviations from linearity. We found some evidence of interaction between BPb and the other exposures (Fig. S2). The significant positive association between BPb and DBP became steeper at higher levels of BCd, and the association between BPb and DBP became flatter at higher levels of BSe. We found statistically significantly increasing levels of DBP with increasing levels of mixture exposure (Fig. S1).

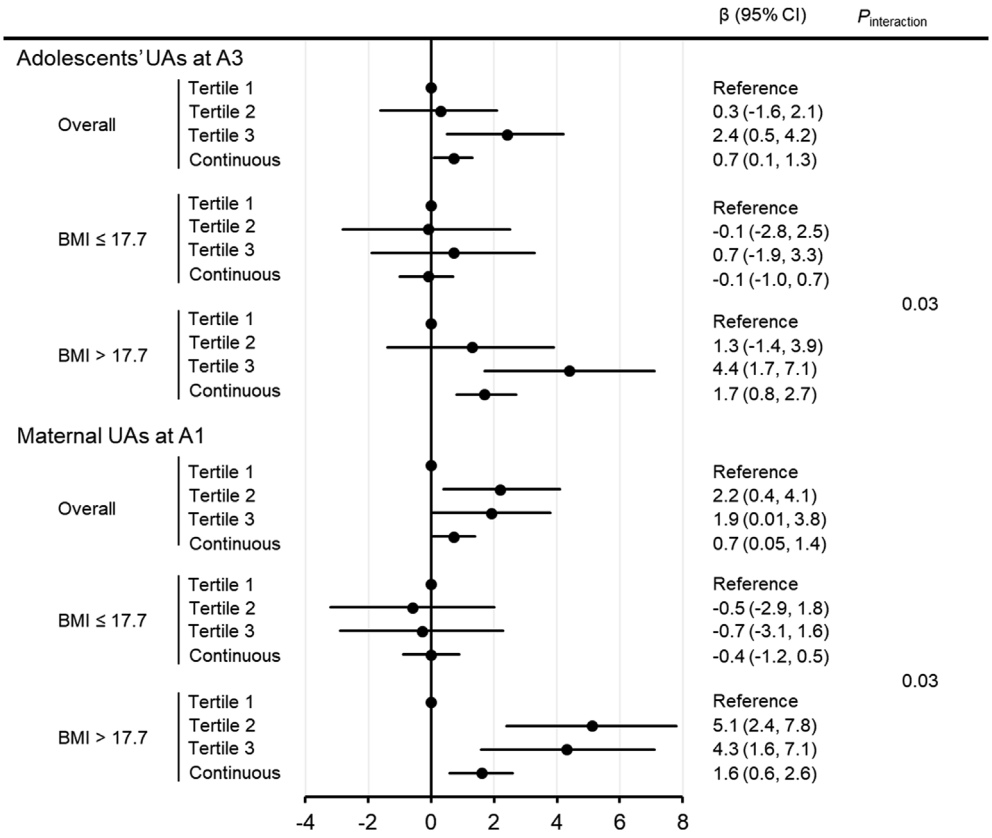

Fig. 1. Mean difference in SBP in relation to adolescents' current urinary arsenic at A3 (14–17 years of age) and maternal urinary arsenic at A1 (< 5 years old), overall and by BMI status. Models were adjusted for sex, age (years), and BMI.

4. Discussion

In this study of adolescents, we observed that higher adolescents' current As exposure at A3 (14–17 years of age), as well as early childhood exposure, measured using maternal UAs at A1 (*in utero* to < 5 years old), were positively associated with SBP in the overall study sample. These associations were stronger among adolescents with a higher BMI, compared with those with a lower BMI. The association of adolescents' current As exposure with SBP was evident controlling for other exposures including Cd, Mn, Pb, and Se in mixture analyses. We did not identify any interaction between As and any other elements. Our results suggest that As exposure may exert its effects on BP independently even with presence of other elements in our study population.

A systematic review of cross-sectional studies concluded that adults with higher levels of As exposure were 1.27 (95% CI: 1.09, 1.47) times more likely to have hypertension compared with those with As exposure at low levels (Abhyankar et al., 2012). More recently, in a longitudinal analysis in HEALS (Jiang et al., 2015), we found that BP in individuals with higher levels of As exposure raised more rapidly over time than that in individuals with lower levels. Our study in adolescents further suggests that the cardiovascular effects of As exposure found in adults such as the effect on raising BP are observable as early as adolescence.

Several epidemiologic studies have investigated the effects of early-life exposure to As on BP among children. In 1887 children in Bangladesh, maternal UAs during pregnancy (mean level: 80 μg/L) and childhood UAs at 18 months of age (mean level: 34 μg/L) were related to higher BP in children who were on average 4.5 years of age (Hawkesworth et al., 2013). In a cross-sectional study of 161 children aged 3–8 years in Central Mexico each 1-μg/L increase in urinary total As was positively associated with an increase of 0.021 and 0.013-mmHg in SBP and DBP (Osorio-Yanez et al., 2015), respectively. Our findings are consistent with the studies in young children, suggesting an effect of *in utero* or early-life exposure on BP. Our study in adolescents provides critical evidence of cardiovascular impacts of exposure to As at different life stages in childhood and adolescence. While the effects of adolescents' current As exposure on BP are likely apparent in adolescence

Table 3
Mean difference in SBP in relation to joint effect of adolescents' current urinary arsenic at A3 (14–17 years of age) and maternal urinary arsenic at A1 (< 5 years old), overall and by BMI status.

Maternal UAs[a] at A1, μg/g Cr	Adolescents' UAs[a] at A3, μg/g Cr	All		BMI ≤ 17.7		BMI > 17.7	
		n	β[b] (95% CI)	n	β[b] (95% CI)	n	β[b] (95% CI)
≤189.8	≤102.6	235	Ref	124	Ref	111	Ref
≤189.8	> 102.6	112	0.4 (−1.9, 2.8)	47	−1.2 (−4.6, 2.2)	65	2.9 (−0.4, 6.1)
> 189.8	≤102.6	115	0.4 (−1.9, 2.8)	46	−0.5 (−4.0, 2.9)	69	2.0 (−1.2, 5.2)
> 189.8	> 102.6	230	2.5 (0.6, 4.4)	130	−0.3 (−2.8, 2.2)	100	6.4 (3.6, 9.3)

[a] UAs values are dichotomized at the median.
[b] Adjusted for sex, age (years), and BMI.

Table 4
Mean difference in SBP in relation to weighted quantile sum regression index, overall and by BMI status.

	WQS		Weight		
	β[a] (95% CI)	*P*	Adolescents' UAs at A3	Maternal UAs at A1	Maternal UAs at A2
All	1.5 (0.3, 2.6)	0.01	0.53	0.35	0.12
BMI > 17.7	3.7 (1.9, 5.4)	< 0.01	0.40	0.45	0.16
BMI ≤ 17.7	−0.2 (−1.7, 1.3)	0.78	-[b]	-[b]	-[b]

[a] β was estimated mean change in SBP for a-unit increase in the WQS index, adjusted for sex, age (years), and BMI.
[b] Weights were not given because the association between the weighted index and SBP was not statistically significant.

during which the cardiovascular function develops and matures, the data suggest that effect of early childhood exposure remained.

Several animal studies evaluated the cardiovascular effects of early-life exposure to As. *In utero* exposure to As via pregnant dams' drinking water doubled the number of atherosclerotic plaques in offspring mice and also appeared to affect endothelial cell function and vascular tone (Srivastava et al., 2007). Mice exposed to As beginning at postnatal week 3 had up to 5-fold increases in atherosclerotic lesion formation in the aorta (Srivastava et al., 2009). Expression profiling of vascular lesions showed clear increases in markers of inflammation and oxidative stress. These experimental data support a role for *in utero* and early-life As exposure in atherogenesis, BP, and other CVD-related outcomes.

Interestingly, in our study, adolescents' current As exposure at 14–17 years of age and early childhood exposure (< 5 years old) were positively associated with SBP in those with higher BMI (> 17.7 kg/m^2), and the associations were stronger than those among adolescents with lower BMI. The WQS models also indicate that among adolescents with higher BMI, current As exposure and early childhood exposure contributed the most to the overall effect of As exposure at three life stages on SBP, suggesting an increased susceptibility to early and current As exposure due to a concurrent risk factor of higher SBP (higher BMI). Adiposity, which can be measured using BMI, plays an important role in the regulation of many homeostatic systems, including those controlling BP (doCarmo et al., 2016; Hall et al., 2010; Landsberg et al., 2013). In another study from HEALS that examined As exposure and plasma biomarkers of CVD, we also found stronger effects on some of the biomarkers among participants with higher BMI (Wu et al., 2012). These findings support *a priori* evidence that higher BMI may modify the cardiovascular effects of As exposure and, if confirmed by future studies, may help risk-stratify individuals and justify intervention or mitigation effects in pregnant women, infants, or individuals with varying history of As exposure.

Our findings in the main analyses on As exposure and BP in adolescents were mostly limited to SBP. Notably, in the Framingham Heart Study, SBP was a stronger predictor than DBP of CVD mortality in adults (Franklin et al., 2001); other work that measured SBP and DBP in young adults (15–29 years, mean 20.5 years) (McCarron et al., 2000) reported similar findings. Interestingly, numerous studies in children and adolescents found a positive association between BMI and SBP, but not DBP (Jiang et al., 1995; Paradis et al., 2004; Sorof and Daniels, 2002). Some studies suggest that the root cause of higher SBP in children, especially in those with a higher BMI, is primarily due to a combination of factors, including vascular dysfunction, that raise systemic vascular resistance (Torrance et al., 2007). Mounting evidence suggests a role of As in oxidative stress (Valko et al., 2005), inflammation (Wu et al., 2003), and endothelial dysfunction/nitric oxide

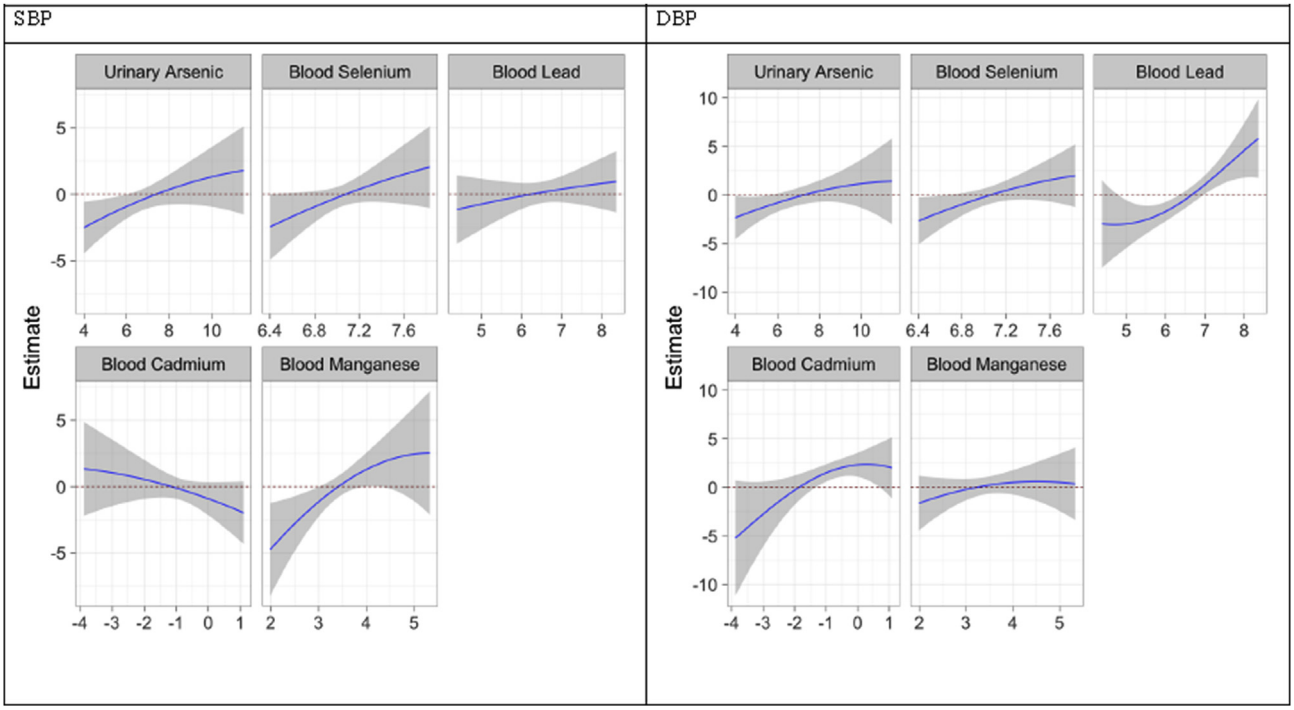

Fig. 2. Element-specific effect estimates of adolescents' blood levels of the mixture at A3 (14–17 years of age) on SBP and DBP of adolescents in Araihazar, Bangladesh, estimated by Bayesian Kernel Machine Regression (BKMR). Models were adjusted for sex, age (years), and BMI. Single predictor associations and 95% confidence bands for each element with other elements fixed at the median. Estimate represents the predicted standardized SBP and DBP. All element concentrations (UAs, BMn, BPb, BCd, BSe) were log base 2 transformed.

inhibition (Pi et al., 2000), and it may be possible that As exposure increases SBP through these pathways.

Using BKMR, we also confirmed a significant association between adolescents' current UAs at 14–17 years of age and BP, while considering exposures to BCd, BMn, BPb, and BSe and their interactions. In our data, in addition to a significant positive association of As with both SBP and DBP, we also found that BMn was positively related to SBP, and that BSe, BPb and BCd were positively related to DBP. Overall, the existing literature on the effect of Pb, Cd, Mn, and Se on BP in children is mixed. A longitudinal study reported a positive association between umbilical cord BPb and BP during childhood (Gump et al., 2005). Our earlier work in 282 children aged 5.5 years residing in Kosovo, in the former Yugoslavia, suggested a small association between BPb and BP (Factor-Litvak et al., 1996). Another study found that maternal tibia Pb was associated with higher BP in girls (Zhang et al., 2012). For Cd, studies assessing effects of BCd or maternal UCd during pregnancy in children of age 2, 5, 7, were null (Cao et al., 2009; Hawkesworth et al., 2013). Limited studies in adults have reported positive (Cowan et al., 2009; Lee and Kim, 2011), null (Olsen et al., 2012), and negative (Mordukhovich et al., 2012; Wu et al., 2017) associations between Mn exposure and BP; however, no studies have been conducted among children or adolescents. While a cross-sectional study of BSe and BP in children found no association (Taittonen et al., 1997), an early study that included a large number of adolescents suggest a positive association between serum Se and both SBP and DBP (Spagnolo et al., 1991). Findings from the BKMR indicate an interaction of BPb, BCd, and BSe in DBP. Experimental data have demonstrated complex interactions among toxic metals/metalloids and essential metals of interest. For instance, chronic exposure of rats to low-dose mixtures of Pb and Cd in drinking water demonstrated significant interactive effects on biomarkers of oxidative stress, nephrotoxicity, and heme biosynthesis (Wang and Fowler, 2008; Whittaker et al., 2011). However, epidemiologic data are limited. Future large studies on effects of metal mixtures on BP or related outcomes are needed.

The present study has several strengths. The range of As exposures is wide and extremely well characterized over time, from early childhood through adolescence. We have a large number of study participants consuming As across a range of interest that is equivalent to common exposure levels in the US and elsewhere. The stratified analyses by BMI suggest that the effect was stronger in individuals with higher BMI. The BKMR model confirmed no interactions between As and other metals. These data suggest that the association of As exposure with SBP is not confounded by malnutrition or concurrent exposure to other metals in the population. One potential limitation is that As exposure at different life stages were not measured directly. However, as mentioned, both mother and child largely consume water from the same source, and maternal urinary As can be considered as a good surrogate exposure measure. Urinary levels of other elements were not measured. Urinary levels of certain elements such as Cd may be a better marker of long-term exposure. Measurement errors in confounders (other elements) may lead to some residual confounding in comparing urinary As with blood markers of other elements. Total urinary As is considered a long-term biomarker for inorganic As exposure from drinking water in the cohort (Ahsan et al., 2006) because participants usually use the same wells for a long period of time and consumption of seafood contributed very little to total urinary As in our study population. Total urinary As was not related to urinary arsenobetaine (AsB) and arsenocholine (AsC) (0.13 and 0.06, respectively); AsB and AsC accounted for only 3% of total urinary As in our study population (Chen et al., 2010). We cannot differentiate *in utero* effects from early childhood effects, as the number of adolescents with only *in utero* (and not post-natal) exposure was limited. Finally, blood pressure was measured only once, which may be a potential source of error. However, the standardized measurement using validated instrument may have minimized the measurement error.

In conclusion, we observed that adolescents' current As exposure and early childhood exposure, were positively associated with SBP in adolescents. The associations were independent of other exposures, and were stronger in adolescents with higher BMI. Our findings suggest a role of As exposure at early childhood and adolescence in raising BP at adolescence.

Competing financial interests

The authors declare no competing financial interest.

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Appendix A. Supplementary data

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