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Abstract

Background: Cross-sectional studies have shown associations between arsenic exposure and prevalence of high BP; however, studies examining the relationship of arsenic exposure with longitudinal changes in blood pressure are lacking.

Method: We evaluated associations of arsenic exposure in relation to longitudinal change in blood pressure in 10,853 participants in the Health Effects of Arsenic Longitudinal Study (HEALS). Arsenic was measured in well water and in urine samples at baseline and in urine samples every two years after baseline. Mixed effect models were used to estimate the association of baseline well and urinary creatinine-adjusted arsenic with blood pressure annual change during follow-up (median, 6.7 years).

Result: In the HEALS population, the median water arsenic concentration at baseline was 62 $\mu\text{g/L}$. Individuals in the highest quartile of baseline water arsenic or urinary creatinine-adjusted arsenic had a greater annual increase in SBP compared with those in the reference group ($\beta=0.48$ mmHg/year; 95% CI: 0.35-0.61, and $\beta=0.43$ mmHg/year; 95% CI: 0.29-0.56) for water arsenic and urinary creatinine-adjusted arsenic, respectively) in fully adjusted models. Likewise, individuals in the highest quartile of baseline arsenic exposure had a greater annual increase in DBP ($\beta=0.39$ mmHg/year; 95% CI: 0.30, 0.49, and $\beta=0.45$ mmHg/year; 95% CI: 0.36, 0.55) for water arsenic and urinary creatinine-adjusted arsenic, respectively) compared with those in the lowest quartile.

Conclusion: Our findings suggest that long-term arsenic exposure may accelerate age-related increases in blood pressure. These findings may help explain associations between arsenic exposure and cardiovascular disease.

Introduction

There is a strong and direct relationship between high blood pressure (BP) and cardiovascular disease (CVD) mortality (Lewington et al. 2002). High BP remains prevalent in the US and internationally among adults over the age of 35 (Chobanian et al. 2003; Frohlich 1997). Rapid increases in the prevalence of high BP in low-income countries (Gupta and Gupta 2009; Ibrahim and Damasceno 2012; Lawes et al. 2003; Redon et al. 2011) has likely contributed to the rising epidemic of CVD in these populations (Ibrahim and Damasceno 2012). In recent decades, there has been growing awareness of the potential importance of environmental factors such as mercury (Houston 2011), lead (Navas-Acien et al. 2007), cadmium (Eum et al. 2008), and arsenic (Abhyankar et al. 2012) in the development of high BP. The identification and mitigation of environmental exposures associated with high BP may help reduce CVD risk (Abhyankar et al. 2012).

Previous studies have indicated associations between exposure to inorganic arsenic and the development of vascular diseases, including high BP, peripheral vascular diseases and ischemic heart disease (Abhyankar et al. 2012; Chen et al. 1996; Chen et al. 2007a; Tseng et al. 1996). A systematic review examining 11 cross-sectional studies on arsenic exposure and the prevalence of high blood pressure (Abhyankar et al. 2012) found that 10 of the 11 studies reported a positive association, while only one study indicated no association. The review included 8 studies with arsenic levels of moderate to high (average ≥ 50 $\mu\text{g/L}$) and 3 studies of relatively low arsenic levels (average < 50 $\mu\text{g/L}$). However, prospective cohort studies that can better characterize the association between arsenic and high BP are lacking. Longitudinal studies with repeated measurements of BP, which provide a powerful tool to evaluate health outcomes that change over time, are needed to assess whether arsenic is associated with increasing BP over time.

It is estimated that millions of Americans are exposed to drinking water with arsenic concentrations exceeding the WHO standard (10 µg/L) (Schulman 2000) . In Bangladesh, where the majority of the population relies on groundwater and arsenic contamination of wells is widespread, more than 50 million people have been chronically exposed (British Geological Survey 2007). In 2000, we established the Health Effects of Arsenic Longitudinal Study (HEALS), a large prospective cohort study of 11,746 individuals in Araihaazar, Bangladesh, to assess the health effects of arsenic exposure. In cross-sectional analyses using participants' baseline data, we previously reported a positive association between baseline arsenic exposure, measured either in urine or drinking water samples, and BP (Chen et al. 2007a). In order to characterize the rate of BP changes related to arsenic exposure, we assessed the association of baseline arsenic exposure (measured both in water and urine) with longitudinal changes in BP among 10,853 participants in Bangladesh, at well water arsenic concentrations ranging from 0.1 to 864 µg/L (median=62 µg/L).

Materials and methods

Study population

HEALS is an ongoing prospective cohort study in Araihaazar, Bangladesh. The principle aim of HEALS is to investigate the health effects of arsenic in drinking water. A detailed description of the cohort has been presented elsewhere (Ahsan et al. 2006). Briefly, before recruitment, water samples were collected for a set of 5,966 continuous wells in a well-defined geographic area of 25 km² in Araihaazar. Between October 2000 and May 2002, 11,746 men and women 18-75 years of age were recruited who met the following criteria: (1) married male or female (to reduce loss to follow-up), (2) resident of the study area for at least 5 years, and (3) primarily drinking water from one of the 5,966 study wells for at least 3 years (Ahsan et al. 2006), leading to a response

rate of 97.5% (original cohort). HEALS was expanded to include an additional 8,287 participants in 2007-2008 (expansion cohort) following the same methodologies (Wu et al. 2011). The present study focused on the original cohort because these individuals were followed for a longer period of time (median 6.7 years, range 0.9-8.3 years). Baseline interviews were conducted to gather information regarding history of well water use, demographics, and lifestyle characteristics. The cohort is being actively followed, with follow-up assessments conducted roughly every two years. The current analysis included data from the first (September 2002 to May 2004), second (September 2004 to May 2006), and third (June 2007 to March 2009) follow-ups, at which time a physical examination, collection of urine samples, and a structured interview were conducted using the same procedures as those used in the baseline interview. Informed consent was obtained from study participants, and study procedures were approved by the ethics committee of the Bangladesh Medical Research Council and the institutional review boards of Columbia University and the University of Chicago.

For the present study, we excluded individuals who died before the first follow-up (n=107), those taking hypertension treatment at baseline (n=126), those without systolic blood pressure (SBP) or diastolic blood pressure (DBP) measurements at baseline (n=380), and individuals for whom no measurements of SBP or DBP were recorded during the follow-up (n=406). The final study population was 10,853. The distributions of demographic and lifestyle factors between the overall and the study populations were very similar (Supplemental Material, Table S1).

Measurements of arsenic exposure

In rural Bangladesh, the majority of the population uses a single hand-pumped tube well for their primary source of drinking water. There is no municipal water treatment. Water samples from

5,966 tube wells were collected in 50mL acid-washed bottles after pumping each well for 5 min. Samples were immediately acidified to 1% HCL until December 2003, after which samples were acidified at Columbia University, normally several months after collection, as delayed acidification does not affect measurement results (van Geen et al. 2007). Total arsenic concentration was first determined by graphite furnace atomic absorption spectrometry (GFAA), with a detection limit of 5 µg/L. If water samples were found to have arsenic concentrations at or below the detection limit of GFAA, they were then analyzed by high-resolution inductively-coupled plasma mass spectrometry (HR ICPMS), with a detection limit of < 0.1 µg/L (Chen et al. 2007b). The long-term reproducibility determined from consistency standards included with each run is relatively stable over time (Cheng et al. 2004; Cheng et al. 2005; Van Geen et al. 2005).

Spot urine samples were collected in 50 mL acid washed tubes from 95.6, 94.5, 91.6 and 89.9% of the cohort participants at baseline, and at the first, second, and third follow-up visits, respectively. Total arsenic concentration was measured by GFAA spectrometry, using a PerkinElmer (Waltham, MA) AAnalyst 600 graphite furnace system with a detection limit of 2 µg/L, as previously described (Nixon et al. 1991). Urinary creatinine was analyzed by using a method based on the Jaffe reaction for adjustment of urinary total arsenic concentration (Slot 1965). The median of creatinine concentration at baseline was 52.3 mg/dL with range of 2.8 to 376.0 for men and 41.5 mg/dL with range of 1.3 to 303.1 for women.

Given that drinking water was the main source of arsenic exposure in the population (see Supplemental Material, Details on Arsenic Exposure) and urinary creatinine-adjusted arsenic can reflect internal dose of exposure (Marchiset-Ferlay et al. 2012), we used both as indicators for

arsenic exposure. At baseline, in order to help improve the health of the community and reduce their risks from arsenic exposure, an arsenic mitigation program was implemented to promote switching to wells with relatively lower water arsenic concentration ($< 50\mu\text{g/L}$) (Chen et al. 2007b). At the first follow-up, a total of 58% of the 6,512 participants who consumed well water with arsenic concentrations $\geq 50\mu\text{g/L}$ at baseline had switched to nearby wells. However, among those individuals that switched wells, only 27% participants had switched to wells with lower arsenic concentrations (i.e. below $50\mu\text{g/L}$) (Chen et al. 2007b). We used urinary creatinine-adjusted arsenic assessed at follow-up visits to track the change in exposure during follow-ups (Marchiset-Ferlay et al. 2012). Because arsenic level remained similar in the majority of the participants (see details in Supplemental Materials), the impact of visit-to-visit change of urinary creatinine-adjusted arsenic on BP change was considered short-term compared to urinary creatinine-adjusted arsenic at baseline, which reflected exposure from the baseline wells that participants had used for an average of 8.6 (median=7, range 3-50) years prior to baseline (Chen et al. 2010; Chen et al. 2011; Chen et al. 2013a; Chen et al. 2013b), and thus visit-to-visit change of urinary creatinine-adjusted arsenic was not considered as the main exposure of interest.

Blood pressure measurements

Blood pressure was measured at baseline and at each follow-up by trained clinicians using an automatic sphygmomanometer (HEM 712-C; Omron Healthcare GmbH, Hamburg, Germany), which has been validated to have 85 percent of readings falling within 10 mmHg (O'Brien et al. 2001). Measurements were taken with participants in a seated position after 5 minutes of rest, with the cuff around the upper left arm, in accordance with recommended guidelines (Pickering et al. 2005). Two BP measurements were taken at follow-ups and we used the arithmetic mean of

two for the analyses. The reliability of the blood pressure measurement was high, with all intraclass correlation coefficients between 0.92 and 0.94 at a given visit (Chen et al. 2007a).

The participation rate for the first, second and third follow-up was 96.9, 93.6, and 92.2% of the cohort participants at the baseline, respectively. Information on medication use was collected at baseline and during follow-ups. Study participants were asked about all medicines they were taking regularly, and were asked to show the medications or prescriptions to the interviewers. After standardizing to generic names, the medications were sorted into one of 44 medication categories (Scannell et al. 2013). Participants who reported taking anti-hypertensive medication were identified for the present study.

Lifestyle characteristics

Lifestyle characteristics were measured at baseline and follow-ups or only at baseline. Past or current use of cigarette smoking was ascertained in the questionnaire at each follow-up. Diabetes status was identified by asking participants if they were diagnosed with diabetes by a physician. Previously reported comparisons between self-reported diabetes status in our study and test results for glycosylated haemoglobin and glucosuria showed that only 1% of the individuals without self-reported diabetes tested positive on urinary glucose, whereas 61% of the individuals with self-reported diabetes tested positive ($p < 0.01$) which indicated good questionnaire validity (Chen et al. 2010; Chen et al. 2011). Body mass index (BMI) was calculated based on measured height and weight at each follow-up (kilograms per meter squared). Educational status was obtained at baseline.

Statistical analysis

We first conducted descriptive analyses to compare the distribution of demographic, life style characteristics and blood pressure measurements over time by baseline water arsenic categorized into quartiles in the overall study population.

We used longitudinal mixed effect models with a random slope and an intercept for each subject, to assess the association between baseline arsenic, using either water or urinary creatinine-adjusted arsenic, and annual change in blood pressure over time. The constructed mixed-effects model is a two-level model, in which the first level describes how BP changes in the population (fixed effect), while the second level of the model depicts how individual blood pressure changes over time (random effect). The mixed effect model also accounts for within-subject correlation between baseline and follow-up blood pressure measurements.

We first used the mixed effect model to assess the association of baseline demographic and lifestyle variables with annual BP change. The variables included baseline age (treated as continuous or tertile variables), sex (male, female), smoking status (never, past, current), history of diabetes (yes, no), baseline educational attainment in years (continuous or tertile variables), and BMI (kg/m²).

In order to investigate whether there was a dose-response relationship between long-term exposure to arsenic (either baseline water arsenic or baseline urinary creatinine-adjusted arsenic) and longitudinal BP change, arsenic concentrations were categorized into quartiles and the mixed effect model was also conducted as follows:

$$BP_{ij} = [\beta_0 + \beta_1 (TIME)_{ij} + \beta_2 AS_{0j2} + \beta_3 AS_{0j3} + \beta_4 AS_{0j4} + \beta_{12} AS_{0j2} (TIME)_{ij} + \beta_{13} AS_{0j3} (TIME)_{ij} + \beta_{14} AS_{0j4} (TIME)_{ij} + \alpha^T Z_{0j}] + [\mu_{0j} + \mu_{1j} (TIME)_{ij}] + r_{ij} \quad [1]$$

where baseline arsenic exposure (either water arsenic or urinary creatinine-adjusted arsenic) was categorized into quartiles and treated with dummy variable (AS_{0j2} , AS_{0j3} , AS_{0j4}). TIME is years since baseline at the time of BP measurement; β_k , $k=2,3,4$, is the difference in mean baseline BP for baseline arsenic in the k -th quartile compared with that in the first quartile (reference); β_{1k} , $k=2,3,4$ is the difference in annual BP change over time for baseline arsenic in the k -th quartile compared with the reference (i.e. the estimated effect of baseline arsenic levels on annual BP change); α^T is a row vector of regression coefficient estimates for covariates at baseline (T denotes vector transpose); and Z_{0j} is a vector of potential confounders. The terms in the first and second brackets are the fixed and random parts of the model, respectively. An unstructured variance structure was specified which assumes that there was no specific pattern in the covariance matrix. BP was normally distributed at baseline and follow-ups and therefore no transformation. To assess the association between baseline water arsenic and annual BP change, we first adjusted for sex and age (years) (model 1). We then additionally adjusted for BMI (time dependent), smoking status (time-dependent, categorized into current or not current), history of diabetes (time-dependent) and educational attainment (model 2) since these variables were considered as important risk factors for high BP in our population (Chen et al. 2007a). Because arsenic exposures may have changed from baseline levels in some participants, we further adjusted in the final model (model 3) for change in urinary creatinine-adjusted arsenic since baseline for each visit, calculated as the arsenic concentration at each follow-up minus arsenic concentration in the baseline. Similar models were constructed using baseline urinary creatinine-adjusted arsenic as the exposure variable. We also examined differences in rate of BP change associated with visit-to-visit changes in urinary creatinine-adjusted arsenic.

In all analyses, BP measurements were treated as missing for the visit when the use of anti-hypertension treatment was reported and thereafter. There were 126 participants being treated with anti-hypertension medication at baseline, 285 at the first follow-up, 412 at the second follow-up and 658 at the third follow-up, respectively. We also conducted the same analyses using different categories of arsenic exposure (tertiles or quintiles). We conducted sensitivity analyses excluding all subjects who were ever under treatment at baseline or at any follow-up visits. We used the same equipment and protocol to measure BP at baseline and at every follow-up visit. However, since BP measurements in the second follow-up appeared to be elevated compared with BP measurements at other time points, we did a sensitivity analysis to exclude BP measurements in that follow-up.

Lastly, we examined whether subjects with higher baseline arsenic exposure (water arsenic or urinary creatinine-adjusted arsenic) had higher BP at the end of follow-up. Linear regression models were used, with the arsenic exposure variables treated as categorical variables, adjusting for the same covariates. Adjusted mean levels of BP by quartiles of arsenic exposure variables were estimated using LSMEANS statement in SAS. All statistical analyses were conducted using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA). All tests conducted were two-sided, and $p < 0.05$ was considered significant.

Results

The final study population included 10,853 participants, with median follow-up time 6.7 years, ranging from 0.86 to 8.26 years. The median concentration was 62 $\mu\text{g/L}$ for water arsenic and 88 $\mu\text{g/L}$ for urinary arsenic, ranging from 0.1 to 864 $\mu\text{g/L}$ and 1 to 2273 $\mu\text{g/L}$, respectively. Of the study population, 9,070 had all four SBP measurements and 9,062 had all four DBP

measurements; 1,150 had three SBP measurements and 1,159 had three DBP measurements; and 633 had two measurements of SBP while 632 had two measurements of DBP in total. There were 10,853 subjects with available water arsenic concentrations and 10,549 subjects with available baseline urinary creatinine-adjusted arsenic concentrations for analysis.

Individuals with lower baseline arsenic exposure were slightly more likely to be those with higher educational attainment or baseline BMI (Table 1). There was no significant difference in SBP or DBP by water arsenic tertile groups at baseline, first follow-up or second follow-up. However, there were global differences of SBP and DBP measured at the third visit in relation to baseline water arsenic levels. Baseline water arsenic levels were positively associated with urinary creatinine-adjusted arsenic levels at baseline, first follow-up, second follow-up and third follow-up.

The rate of annual SBP increase tended to be greater with increasing baseline age (Table 2). Age was inversely associated with the rate of longitudinal DBP increase. There was a monotonic decrease with increasing age, comparing older age groups (30-40, >40 years of age) with younger age group (≤ 30 years of age), and the difference between the rate of DBP decrease among those >40 years at baseline was close to being significantly lower than the rate among those ≤ 30 years at baseline. The data are consistent with previous literature that documented a decreasing DBP with increasing age (Wright et al. 2011). The annual increase in SBP was greater in women compared with men, in those with higher educational attainment than subjects with a lower educational attainment level, and in those with a baseline BMI >20.45 kg/m² compared with 18.09-20.45 kg/m².

Tables 3 and 4 show the associations of arsenic exposure categorized into quartiles and annual change in SBP or DBP. For SBP, we observe a positive association without a dose-response relationship throughout three models; individuals in higher three quartiles of baseline water arsenic or urinary creatinine-adjusted arsenic had a greater annual increase in SBP compared with those in the reference group ($\beta=0.43-0.54$ mmHg/year and $\beta=0.39-0.44$ mmHg/year for water arsenic and urinary creatinine-adjusted arsenic in fully-adjusted models, respectively) (Table 3). Likewise, for DBP, a positive relationship was also observed; individuals in the higher three quartiles of baseline arsenic exposure had a greater annual increase in DBP ($\beta=0.39-0.41$ mmHg/year, and $\beta=0.37-0.45$ mmHg/year for water arsenic and urinary creatinine-adjusted arsenic in fully-adjusted models, respectively) compared with those in the lowest quartile (Table 4). For DBP there was a monotonic increase in the rate with increasing urinary creatinine-adjusted arsenic (Table 4). Analyses using different categories of arsenic exposure (tertiles or quintiles) showed similar results (Tables S2 and S3, Supplemental Materials). Sensitivity analyses were conducted by excluding all subjects who were under treatment for hypertension at baseline or follow-up (N=545) without change in the overall results (data not shown). In an analysis of associations with changes in creatinine-adjusted urinary arsenic over time, with the least amount of change between visits (creatinine-adjusted urinary arsenic at later visit minus creatinine-adjusted urinary arsenic at earlier visit) as the reference group (ranging from a decrease of 9 to an increase of 39 $\mu\text{g/g}$ creatinine), the greatest increase (> 39 $\mu\text{g/g}$ creatinine) had a positive but non-significant association with the mean annual increase in SBP ($\beta = 0.40$; 95% CI: $-0.04, 0.83$) and DBP ($\beta = 0.28$; 95% CI: $-0.03, 0.59$), while there was no association with a decrease of > 9 $\mu\text{g/g}$ creatinine over follow-up (data not shown). Because mean SBP and DBP both were highest at the second follow-up visit (suggesting a possible

systematic error in measurement), we repeated analyses excluding follow-up 2 data, but found similar results to analyses including data from all visits (data not shown).

Lastly, we assessed the association between baseline arsenic exposure and the absolute levels of BP at the third follow-up (Figure S1). In fully-adjusted models, individuals with highest level of baseline water arsenic had 3.95 mmHg (95% CI: 3.15, 4.76) greater SBP or 2.65 (95% CI: 2.21, 3.31) mmHg greater DBP compared with those in the reference group. Similarly, for urinary creatinine-adjusted arsenic, individuals with higher concentration had 3.47 mmHg (95% CI: 2.61, 4.33) increase in SBP or 2.62 mmHg (95% CI: 1.95, 3.03) increase in DBP compared with those in the lowest quartile. However, associations were similar across quartiles 2, 3, and 4, without evidence of a monotonic trend (Figure S1).

Discussion

To our knowledge, the present study is the first large epidemiologic study to examine the relationship between arsenic exposure from drinking water and longitudinal change in BP. We found positive associations of arsenic exposure, measured either in well water or urine samples, with annual change in SBP and DBP, over an average of 6.7 years of follow-up.

The association of arsenic exposure with BP has been indicated in several cross-sectional studies. A systematic review including 11 cross-sectional studies reported a pooled OR of 1.27 (95% CI: 1.09, 1.47; p-value for heterogeneity = 0.001) for high BP comparing the highest and lowest arsenic exposure categories (Abhyankar et al. 2012). However, cross-sectional assessments of the association between arsenic exposure and BP are limited by: 1) possible selection bias in capturing only individuals who have lived long enough; and 2) limited detection of the latent effects of arsenic exposure on BP. In contrast, longitudinal analyses mitigate some of these

problems and may be a superior method for examining arsenic exposure on BP change over time. Longitudinal analyses have previously revealed the effects of lead exposure on BP change (Glenn et al. 2003; Glenn et al. 2006). Our findings demonstrating an association between arsenic exposure and annual BP change contributes to the growing body of evidence indicating that environmental exposures may play a role in longitudinal BP change.

We did not find a monotonic relationship between arsenic exposure and the slope of BP change over time. In our previous cross-sectional study, the positive association between arsenic exposure from drinking water and baseline BP also was not stronger with increasing quartiles of arsenic exposure (Chen et al. 2007a). Mechanistic studies have indicated that the vascular effect of arsenic may be non-linear (Soucy et al. 2003) and may reach threshold when arsenic exposure exceeds a certain level. Alternatively, the baseline BP may have been affected by arsenic exposure already leading to a limited increase on the rate of BP change that can be further observed. In addition, the increased rate of blood pressure change may be limited in this relatively young cohort.

In the current study, exposure to water with arsenic concentration higher than 12 μ g/L was associated with increases of 0.43-0.54 mmHg/year and 0.39-0.41 mmHg/year for SBP and DBP, respectively. Evidence suggests that the risk of CVD rises continuously as both SBP and DBP increase from 115 mmHg and 75 mmHg, respectively (Lewington et al. 2002). Based on estimates from 61 prospective observational studies, even a 2 mmHg lower usual SBP would involve about 10% lower stroke mortality and about 7% lower mortality from ischemic heart disease or other vascular causes in middle age (Lewington et al. 2002). Although the estimate may not be the same in our study population, given the strong association between BP and CVD

risk, the differences in the rate of BP change associated with arsenic exposure, although small in magnitude annually, may have a cumulative effect on the risk of clinical events. Therefore, the differences in the rate of BP change associated with arsenic exposure, although small in magnitude annually, may have a cumulative effect on the risk of clinical events.

The potential association between arsenic exposure and high BP is supported by experimental studies. *In vitro* work has shown that arsenic promotes inflammatory activity, oxidative stress, and endothelial dysfunction through several mechanisms including the activation of stress response transcription factors such as activator protein-1 and nuclear factor- κ B (Abhyankar et al. 2012). In animal models, chronic exposure of rats and rabbits to arsenite has been shown to cause a considerable increase in peripheral vascular resistance (Abir et al. 2012). In rats, lifelong arsenic exposure increased BP only after 80 days, elevations that persisted through 200 days (Yang et al. 2007). Furthermore, arsenic exposure may also be related to renal dysfunction, leading to BP changes in individuals (Chen JW et al. 2011; Hsueh et al. 2009).

Our study, which is among the first to prospectively investigate the role of arsenic exposure in longitudinal blood pressure change, has several strengths. First, we have multiple research-quality BP measurements over 7 years of follow-up, which enables us to depict BP longitudinal change over time. Second, the low percentage of the population using anti-hypertensive medications (around 1% at baseline) and the absence of alcohol consumption due to religious beliefs allowed us to investigate BP change without the influence of medical therapy or alcohol. Finally, we have a rich set of covariates that allow us to adjust for confounders.

The study also has limitations. Although we used the same methodology for measuring BP since baseline and follow-ups, measurement errors for BP measurements could have occurred. We could not estimate the extent of the potential measurement errors. However, the relationships between conventional risk factors and longitudinal change in BP were consistent with those of the literature, supporting the validity of the BP measurement in this study. Also, sensitivity analysis excluding follow-up 2 that was conducted out of concern for error at follow-up 2 generated similar results. The self-reported well water use might also produce misclassifications of exposure. However, the correlation of well water arsenic concentration and urinary creatinine-adjusted arsenic at baseline was high ($\rho=0.70$), supporting the validity of self-reported data on well use and population-wide arsenic exposure in the population. The analyses were restricted to individuals with available data on repeated BP measurements. Since arsenic exposure has been related to CVD mortality in the cohort and high BP is a CVD risk factor, the exclusion of individuals without repeated BP measurements may have preferentially removed individuals with high BP that is associated with arsenic, leading to a potential bias towards the null on average. However, missing BP was not extensive (9,069 subjects have complete BP measurements) and the demographic distributions of our study population and the overall population were very similar (Table S1). In the analyses, we controlled for visit-to-visit changes in urinary creatinine-adjusted arsenic. However, given that arsenic exposure was similar in the majority of the participants, we may not have power to assess the effects of changes in urinary creatinine-adjusted arsenic. We did not assess the role of specific nutrients or nutritional intake in the present study. Future studies are needed to investigate whether the association of arsenic exposure and the rate of BP change differs by nutritional status.

Conclusion

We found positive associations between long-term arsenic exposure and BP increase over time, which might be one mechanism by which arsenic may lead to CVD. Further studies are needed to investigate other pre-clinical indicators or biomarkers of CVD with multiple measurements.

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Table 1. Baseline and follow-up characteristics of HEALS participants (N= 10,853).

Characteristics	Q1 ≤12 µg/L		Q2 12-62 µg/L		Q3 62-148 µg/L		Q4 >148 µg/L		P value ^a
	No.	Mean ± SD or %	No.	Mean ± SD or %	No.	Mean ± SD or %	No.	Mean ± SD or %	
Age, years	2752	36.9 ± 10.0	2711	36.6 ± 10.0	2688	36.6 ± 9.9	2702	37.0 ± 10.0	0.234
Male, %	1170	42.5	1143	42.2	1124	41.8	1151	42.6	0.935
Current smoker, %	813	29.6	792	29.2	747	27.8	751	27.8	0.334
Diabetes history, %	55	2.0	59	2.2	46	1.7	43	1.6	0.370
Education, years	2750	3.6 ± 3.9	2710	3.2 ± 3.7	2687	3.5 ± 3.9	2700	3.3 ± 3.7	0.002
BMI baseline, kg/m²	2730	19.9 ± 3.3	2701	19.7 ± 3.1	2670	19.7 ± 3.0	2690	19.4 ± 3.0	<0.001
Systolic Blood Pressure, mmHg									
Baseline	2752	113.6 ± 16.6	2711	114.7 ± 17.2	2688	113.6 ± 16.5	2702	113.5 ± 16.6	0.391
Follow up 1	2676	113.9 ± 16.8	2639	113.7 ± 17.0	2623	113.5 ± 17.1	2639	114.2 ± 17.4	0.442
Follow up 2	2557	118.4 ± 15.6	2475	117.8 ± 15.3	2492	117.8 ± 15.5	2489	117.4 ± 15.2	0.175
Follow up 3	2432	108.5 ± 14.9	2399	112.6 ± 14.8	2366	112.6 ± 15.7	2356	112.0 ± 15.6	<0.001
Diastolic Blood Pressure, mmHg									
Baseline	2750	73.8 ± 11.5	2711	73.6 ± 11.3	2685	73.4 ± 11.1	2700	73.1 ± 11.5	0.132
Follow up 1	2677	73.0 ± 10.2	2638	72.8 ± 10.3	2623	72.6 ± 10.2	2639	72.9 ± 10.3	0.557
Follow up 2	2557	76.3 ± 10.3	2475	76.2 ± 10.0	2492	76.1 ± 10.0	2489	76.0 ± 10.1	0.683
Follow up 3	2432	71.1 ± 9.9	2399	73.9 ± 10.0	2366	73.8 ± 10.2	2356	73.4 ± 10.1	<0.001
Urinary arsenic, µg/L									
Baseline	2711	51.0 ± 47.7	2662	99.2 ± 79.3	2576	150.9 ± 120.4	2600	258.2 ± 233.8	<0.001
Follow up 1	2671	54.3 ± 57.7	2633	106.9 ± 87.5	2625	145.3 ± 133.8	2629	185.7 ± 199.1	<0.001
Follow up 2	2621	54.7 ± 55.6	2534	105.7 ± 85.5	2547	139.1 ± 125.6	2542	178.5 ± 191.4	<0.001
Follow up 3	2564	51.6 ± 57.5	2510	92.8 ± 77.7	2499	118.6 ± 108.8	2484	149.2 ± 169.5	<0.001
Urinary creatinine-adjusted arsenic, µg/g creatinine									
Baseline	2711	99.8 ± 83.5	2662	209.1 ± 151.7	2576	316.8 ± 200.5	2600	525.8 ± 488.1	<0.001
Follow up 1	2671	96.7 ± 74.4	2633	193.1 ± 121.8	2625	264.2 ± 213.6	2629	344.9 ± 326.7	<0.001
Follow up 2	2621	98.5 ± 79.4	2534	198.0 ± 120.6	2547	259.2 ± 201.1	2542	333.1 ± 323.1	<0.001
Follow up 3	2564	99.0 ± 89.5	2510	190.2 ± 153.6	2499	247.8 ± 191.2	2484	305.1 ± 309.7	<0.001

Abbreviations: Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.

Q1: median=2.3, SD=3.3, range=11.9; Q2: median=34.0, SD=14.4, range=49.7; Q3: median=101.0, SD=25.2, range=86.0; Q4: median=239.0, SD=107.4, range=714.0.

^aP value represented global difference and was based on χ^2 test for categorical variables and ANOVA test for continuous variables.

Table 2. Relation of baseline characteristics and adjusted annual changes in blood pressure within 7 years of follow-up^a.

Baseline characteristics	SBP change/year (mmHg) β (95% CI)	P value	DBP change/year (mmHg) β (95% CI)	P value
Age (years)^b				
≤30	Ref.		Ref.	
30-40	0.14 (0.02, 0.27)	0.020	-0.05 (-0.14, 0.03)	0.201
>40	0.36 (0.23, 0.49)	<.001	-0.09 (-0.18, 0.01)	0.064
Sex (women compared to men)	0.34 (0.20, 0.48)	<.001	0.01 (-0.10, 0.10)	0.950
Smoking Status				
Never	Ref.		Ref.	
Past	-0.01 (-0.23, 0.22)	0.939	-0.05 (-0.21, 0.10)	0.529
Current	0.11 (-0.05, 0.26)	0.179	0.08 (-0.03, 0.19)	0.168
Diabetes history	-0.19 (-0.53, 0.14)	0.257	-0.22 (-0.46, 0.01)	0.060
Education length (years)				
0	Ref.		Ref.	
0-5	0.18 (0.06, 0.29)	0.003	0.06 (-0.02, 0.14)	0.135
>5	0.28 (0.16, 0.41)	<.001	0.02 (-0.07, 0.10)	0.669
BMI baseline (kg/m²)				
≤18.09	-0.03 (-0.15, 0.10)	0.660	0.07 (-0.01, 0.16)	0.089
18.09-20.45	Ref.		Ref.	
>20.45	0.19 (0.06, 0.31)	0.003	-0.07 (-0.16, 0.01)	0.09

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

^aWhen one variable was put in the model, all other variables were adjusted in the same model.

^bCategorized by tertiles

Table 3. Relation of baseline water arsenic, baseline urinary creatinine-adjusted arsenic and adjusted annual changes in systolic blood pressure (SBP) within 7 years.

Baseline Exposure	Range	Model 1 Change/year (mmHg)	Model 2 Change/year (mmHg)	Model 3 Change/year (mmHg)
Water arsenic (µg/L) N=10,853				
Q1	<12	Ref.	Ref.	Ref.
Q2	12-62	0.45 (0.32, 0.58)	0.42 (0.29, 0.56)	0.43 (0.29, 0.56)
Q3	62-148	0.60 (0.46, 0.73)	0.55 (0.42, 0.68)	0.54 (0.40, 0.67)
Q4	>148	0.51 (0.38, 0.65)	0.48 (0.34, 0.61)	0.48 (0.35, 0.61)
Urinary creatinine-adjusted arsenic (µg/g creatinine) N=10,549				
Q1	<106	Ref.	Ref.	Ref.
Q2	106-199	0.40 (0.26, 0.53)	0.38 (0.25, 0.52)	0.39 (0.25, 0.52)
Q3	199-352	0.45 (0.32, 0.59)	0.43 (0.30, 0.57)	0.44 (0.30, 0.58)
Q4	>352	0.45 (0.31, 0.58)	0.41 (0.27, 0.54)	0.43 (0.29, 0.56)

Abbreviations: Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4

Model 1: Controlled for baseline age and sex. Model 2: Controlled for model 1 covariates plus BMI, smoking status, educational status and history of diabetes. Model 3: Controlled for model 2 covariates plus change of urinary creatinine-adjusted arsenic since baseline.

Table 4. Relation of baseline water arsenic, baseline urinary creatinine-adjusted arsenic and adjusted annual changes in diastolic blood pressure (DBP) within 7 years.

Baseline Exposure	Range	Model 1 Change/year (mmHg)	Model 2 Change/year (mmHg)	Model 3 Change/year (mmHg)
Water arsenic ($\mu\text{g/L}$) N=10,846				
Q1	<12	Ref	Ref	Ref
Q2	12-62	0.44 (0.35, 0.53)	0.42 (0.33, 0.52)	0.41 (0.31, 0.50)
Q3	62-148	0.47 (0.38, 0.56)	0.42 (0.33, 0.52)	0.41 (0.32, 0.51)
Q4	>148	0.43 (0.34, 0.52)	0.40 (0.31, 0.49)	0.39 (0.30, 0.49)
Urinary creatinine-adjusted arsenic ($\mu\text{g/g creatinine}$) N=10,549				
Q1	<106	Ref.	Ref.	Ref.
Q2	106-199	0.38 (0.29, 0.48)	0.37 (0.27, 0.46)	0.37 (0.27, 0.46)
Q3	199-352	0.40 (0.30, 0.49)	0.37 (0.27, 0.46)	0.38 (0.28, 0.47)
Q4	>352	0.49 (0.40, 0.58)	0.45 (0.35, 0.54)	0.45 (0.36, 0.55)

Abbreviations: Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.

Model 1: Controlled for baseline age and sex. Model 2: Controlled for model 1 covariates plus BMI, smoking status, educational status and history of diabetes. Model 3: Controlled for model 2 covariates plus change of urinary creatinine-adjusted arsenic since baseline.