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ScienceDirect
Toxicology and Applied Pharmacology 222 (2007) 337–343
Toxicology and Applied Pharmacology
www.elsevier.com/locate/ytaap

Drinking water arsenic exposure and blood pressure in healthy women of reproductive age in Inner Mongolia, China

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Received 2 February 2007; revised 2 April 2007; accepted 9 April 2007
Available online 19 April 2007

Abstract

The extremely high exposure levels evaluated in prior investigations relating elevated levels of drinking water arsenic and hypertension prevalence make extrapolation to potential vascular effects at lower exposure levels very difficult. A cross-sectional study was conducted on 8790 women who had recently been pregnant in an area of Inner Mongolia, China known to have a gradient of drinking water arsenic exposure. This study observed increased systolic blood pressure levels with increasing drinking water arsenic, at lower exposure levels than previously reported in the literature. As compared to the referent category (below limit of detection to 20 μg of As/L), the overall population mean systolic blood pressure rose 1.29 mm Hg (95% CI 0.82, 1.75), 1.28 mm Hg (95% CI 0.49, 2.07), and 2.22 mm Hg (95% CI 1.46, 2.97) as drinking water arsenic concentration increased from 21 to 50, 51 to 100, and >100 μg of As/L, respectively. Controlling for age and body weight ($n=3260$), the population mean systolic blood pressure rose 1.88 mm Hg (95% CI 1.03, 2.73), 3.90 mm Hg (95% CI 2.52, 5.29), and 6.83 mm Hg (95% CI 5.39, 8.27) as drinking water arsenic concentration increased, respectively. For diastolic blood pressure effect, while statistically significant, was not as pronounced as systolic blood pressure. Mean diastolic blood pressure rose 0.78 mm Hg (95% CI 0.39, 1.16), 1.57 mm Hg (95% CI 0.91, 2.22) and 1.32 mm Hg (95% CI 0.70, 1.95), respectively, for the overall population and rose 2.11 mm Hg (95% CI 1.38, 2.84), 2.74 mm Hg (95% CI 1.55, 3.93), and 3.08 mm Hg (95% CI 1.84, 4.31), respectively, for the adjusted population ($n=3260$) at drinking water arsenic concentrations of 21 to 50, 51 to 100, and >100 μg of As/L. If our study results are confirmed in other populations, the potential burden of cardiovascular disease attributable to drinking water arsenic is significant.

Keywords: Arsenic; Drinking water; Blood pressure; Cardiovascular disease; Post-natal; Reproductive health; Women; Inner Mongolia, China

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doi:10.1016/j.taap.2007.04.003

Introduction

Arsenic is known for its acute toxicity at high doses, as well as chronic effects as an established human carcinogen (Chen et al., 1988; Smith et al., 1992; Morales et al., 2000; World Health Organization, 2001). High levels of drinking water arsenic are associated with atherosclerosis, diabetes mellitus and peripheral vascular disease (Tseng, 1977; Wu et al., 1989; Tseng et al., 2000). However, it is only recently that chronic exposure to drinking water arsenic and the subsequent development of hypertension has been the subject of epidemiological studies (Chen et al., 1995; Rahman et al., 1999). Elevated blood pressure is strongly associated with several forms of cardiovascular disease (Stegmayr et al., 1997; Heart Disease Collaborative Research Group, 1998; Rodgers et al., 2000; Borghi et al., 2002). Even slight elevations in the mean blood pressure of a population can have a significant impact on morbidity in populations (Manson et al., 1992).

While high levels of drinking water arsenic exposure have been associated with adverse health outcomes, there is scientific interest in potential health effects at lower levels of drinking water arsenic. Two prior studies examining the relationship between drinking water arsenic and blood pressure (hypertension) used exposure categories well above the current US maximum contaminant limit of 10 μg of As/L (Chen et al., 1995; Rahman et al., 1999). More sensitive indicators of effect, such as population levels of blood pressure levels, may be more likely to show adverse vascular effects at lower levels of drinking water arsenic.

This cross-sectional study focused on the 6-week post-partum blood pressure levels of women of reproductive age in an area known to have a gradient of exposure to drinking water arsenic. Post-partum blood pressures are commonly used as a referent level since the cardiovascular challenge of pregnancy has passed and blood pressure has returned to baseline levels (MacGillivray et al., 1969; Ueland and Metcalfe, 1975). Associations between drinking water arsenic and population levels of blood pressure may provide evidence of a cardiovascular effect at lower levels of arsenic exposure than what has been previously published and help to target arsenic remediation efforts (Kwok, 2007).

Materials and methods

Study population. All health data used for this study were collected from a database of routine prenatal and post-partum healthcare visits recorded prospectively on the examination chart for pregnant women in Lin He, Hanggin Houqi, and Wu Yuan counties in Ba Men, Inner Mongolia, China. All women had a pregnancy outcome between December 1, 1996 and December 31, 1999. Demographic information such as age and body weight was collected during the first prenatal visit, usually before 10–12 weeks of gestation. Post-partum information was collected 6 weeks after delivery.

Exposure assessment. The drinking water arsenic exposure of each individual was determined based on a total of 14,866 well-water measurements in 2270 subvillages, measured throughout the study area by officials from the Ba Men Anti-Epidemic station between 1991 and 1997. Well-water measures were systematically collected and analyzed for arsenic from five randomly selected families in each subvillage from areas thought to have high drinking water arsenic levels throughout the Ba Men region. If any of the samples from a subvillage measured greater than the Chinese national standard of 50 μg of As/L, all wells within that particular subvillage were measured. Otherwise, all wells within the subvillage were assumed to be equivalent to the ones sampled (low exposed). This effectively led to an over-sampling of well-water measurements from the higher arsenic drinking water areas and under-sampling of areas thought to have low concentrations of drinking water arsenic. Three different analytic detection methods were used to measure arsenic concentration – Spectrophotometric methods with DCC-Ag (detection limit, 0.5 μg of As/L); Spot method (detection limit, 10 μg of As/L); and air-assisted Colorimetry method (detection limit, 20 μg of As/L). Details about the exposure database can be found elsewhere (Ning et al., 2007).

Exposure was assessed retrospectively by matching subjects to the arsenic well-water database. Categories of drinking water arsenic concentration were created based on cut-points of 50 and 100 μg of As/L. The final exposure categories were as follows (all units in μg of As/L): below the limit of detection (BLD) to 20; 21 to 50; 51 to 100; and >100. Individuals were eliminated from the analysis if their subvillage was not included in the drinking water arsenic database (n=2213).

Individuals were assigned to exposure categories based on the average well-water arsenic measurements of their subvillage. On average, the categorical estimate of drinking water arsenic for each subvillage was based on 4.7 well-water measurements (range of 1 to 67 wells, median and mode=5) within each of the 2270 subvillages. All analyses involved comparing these arsenic exposure categories. Subvillages were eliminated from analyses if any well-water measurements were not within the designated drinking water arsenic categories (BLD to 20, 21 to 50, 51 to 100, >100 μg of As/L), since assignment of values to specific women in the subvillage would be subject to error.

Blood pressure measurements. All data for this study were obtained from abstraction of contemporaneous clinical assessments of health. Clinic staff using a World Health Organization (WHO) recommended protocol (Rose et al., 1982) for blood pressure collection obtained all health information during routine prenatal and postnatal health visits. As recommended by this protocol, blood pressure measurements were obtained with an appropriately sized cuff snugly applied at the level of the heart after subjects had rested in a sitting position for at least 5 min. The blood pressure cuff was rapidly inflated to a level 30 mm Hg above the radial palpatory pressure and the pressure released at a rate of fall equal to 2 mm Hg/s. The systolic pressure was determined by the first perception of Korotkoff sound and the diastolic fifth-phase (Korotkoff Phase V) by the disappearance of sound. Readings were tabulated to the nearest 2 mm Hg (Rose et al., 1982). The woman's 6-week post-partum blood pressure measurements were used as the main health measurement for this study.

Statistical analysis. A cross-sectional study was conducted to characterize associations between drinking water arsenic concentrations and elevated blood pressure levels in adult women of reproductive age. Univariate statistics were calculated for systolic and diastolic blood pressure and assessed for normality. Group mean differences in blood pressure measures across arsenic exposure categories were performed using conventional analysis of variance techniques. Analysis of covariance was used to assess blood pressure change (in mm Hg) from the referent category (BLD to 20 μg of As/L) and the other arsenic categories. A test for trend in the β-coefficients of these models across the arsenic categories was calculated.

In previous studies, both age and body weight have been important covariates in the analyses of blood pressure (Vasan et al., 2001; Lewington et al., 2002). However, only 37% of the 8790 women had age and body weight measures. We examined the influence of age and body weight and restricted the sample to 3260 women who had measurements. Univariate statistics as well as analysis of covariance were used to assess whether there were measurable differences across arsenic categories between the women with and without age and body weight measures.

Results

The health data set had 22,138 women eligible for this study (Fig. 1). Women were excluded if their subvillage was not measured for drinking water arsenic (n=12,213) or if no reliable

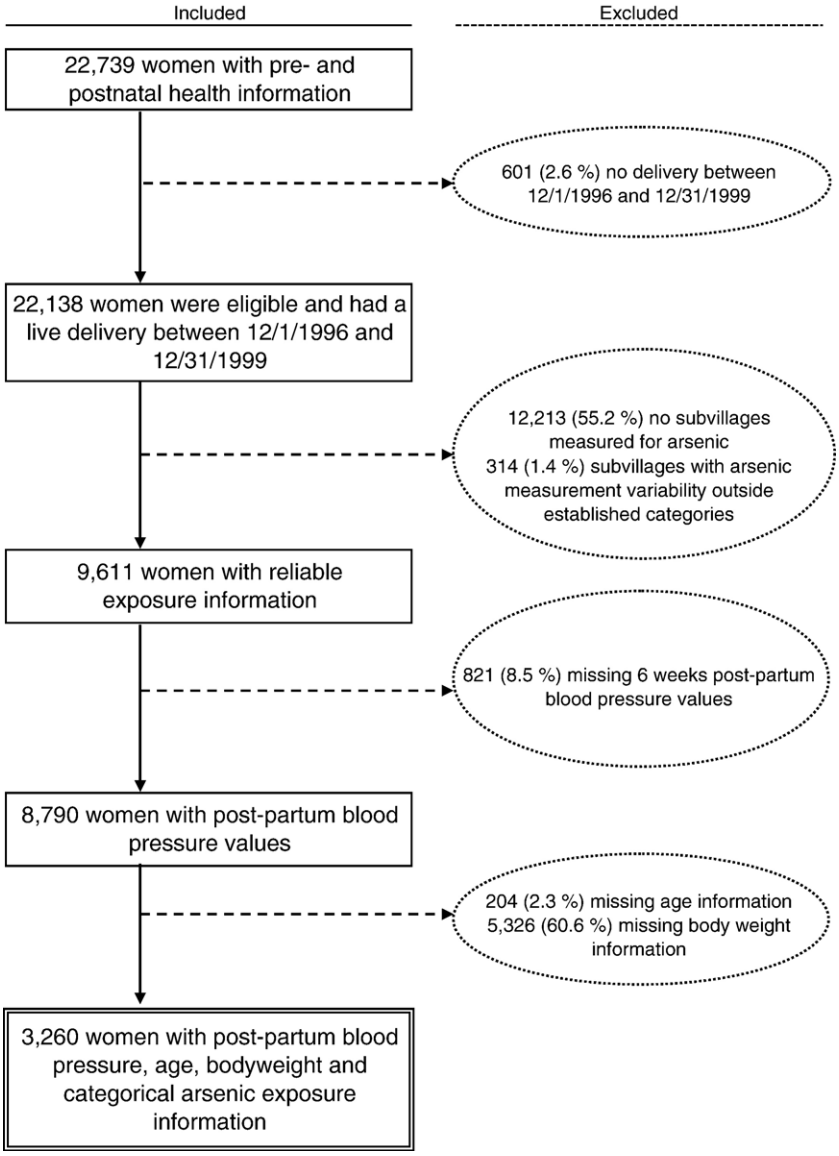

Fig. 1. Flowchart for selection of woman for arsenic exposure analysis.

exposure could be assigned due to variability of arsenic measures across exposure categories ($n=314$). Women were also excluded if no post-partum blood pressure values were recorded ($n=821$). In total, 8790 women had available health and exposure information.

Both mean systolic and mean diastolic blood pressures were higher at progressively higher levels of drinking water arsenic ($p<0.0001$) (Table 1). Women in this study ranged in age from 17 to 45 years. Neither mean age nor mean body weight differed across arsenic exposure categories ($p=0.73$ and $p=0.37$, respectively). However, as indicated in Fig. 1, a large number of women did not have bodyweight recorded on the ECPW ($n=5326$).

Table 2 presents the estimated effect of each arsenic category on the systolic and diastolic blood pressure overall ($n=8790$), the restricted crude and adjusted for age and body weight models ($n=3260$) including only those with age and body weight information. In the overall models for both systolic and diastolic blood pressure, a slight, but statistically significant increase in blood pressure was observed within each of the different arsenic categories compared to the referent.

The crude and adjusted models restricting to those women with body weight information show similar direction. Increasing arsenic exposure categories from 21 to 50, 51 to 100, and >100 μg of As/L lead to an increase in systolic blood pressure of 1.88 (95% CI=1.03, 2.73), 3.90 (95% CI=2.52, 5.29), and 6.84 mm Hg (95% CI=5.40, 8.28), respectively, compared to women in the referent exposure category (BLD to 20 μg of As/L). Controlling for age and body weight did not appreciably change these estimates with increases in systolic blood pressure of 1.88 (95% CI=1.03, 2.73), 3.90 (95% CI=2.52, 5.29), and 6.83 mm Hg (95% CI=5.39, 8.27), respectively.

Diastolic blood pressure exhibited similar tendencies as arsenic exposure categories increased from 21 to 50, 51 to 100, and >100 μg of As/L with a change of 2.10 (95% CI=1.37,

Table 1
Demographic characteristics of study population in Inner Mongolia[a], China by arsenic exposure categories

	n	Overall	Arsenic categories (μg/L)				ANOVA[b], *p*-value
			BLD[c] to 20, *n* (%)	21 to 50, *n* (%)	51 to 100, *n* (%)	>100, *n* (%)	
Number of individuals	8790		5982 (68.1)	1736 (19.7)	509 (5.8)	563 (6.4)	
Risk factor		Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	
Overall							
Systolic BP (mm Hg)	8790	106.0 (0.09)	105.6 (0.11)	106.8 (0.21)	106.8 (0.41)	107.8 (0.43)	<0.0001
Diastolic BP (mm Hg)	8790	71.1 (0.08)	70.7 (0.09)	71.5 (0.19)	72.3 (0.28)	72.0 (0.32)	<0.0001
Crude and adjusted							
Systolic BP (mm Hg)	3260	106.3 (0.16)	105.4 (0.19)	107.3 (0.42)	109.3 (0.64)	112.2 (0.63)	<0.0001
Diastolic BP (mm Hg)	3260	71.4 (0.14)	70.7 (0.16)	72.8 (0.41)	73.4 (0.43)	73.8 (0.56)	<0.0001
Age (years)	8586	25.5 (0.03)	25.6 (0.04)	25.5 (0.07)	25.6 (0.13)	25.5 (0.12)	0.73
Bodyweight (kg)	3307	56.3 (0.09)	56.3 (0.11)	56.3 (0.22)	56.4 (0.28)	55.6 (0.32)	0.37

[a] Lin He, Wu Yuan, and Hanggin Houqi counties.
[b] Analysis of variance between arsenic categories.
[c] Below limit of detection.

2.84), 2.72 (95% CI=1.53, 3.92), 3.17 mm Hg (95% CI=1.92, 4.41), respectively, compared to women in the referent exposure category (BLD to 20 μg of As/L). Likewise, controlling age and body weight did not dramatically change diastolic estimates with increases in diastolic blood pressure of 2.11 (95% CI=1.38, 2.84), 2.74 (95% CI=1.55, 3.93), 3.08 mm Hg (95% CI=1.84, 4.31), respectively. For both the systolic and diastolic blood pressures, there were statistically significant trends in these estimates across the arsenic categories ($p<0.0001$).

Table 3 presents the overall means for systolic blood pressure, diastolic blood pressure, age and body weight among those women excluded due to missing one or more of the covariate information. Systolic blood pressure was higher in the 21 to 50 μg of As/L group than compared to the referent group ($P<0.01$). However, the remaining covariates, diastolic blood pressure, age, and body weight did not exhibit any association across arsenic categories ($p=0.07$, 0.65, 0.29, respectively).

Discussion

The results of this study demonstrate a monotonic dose–response association between drinking water arsenic exposure and elevated levels of systolic and diastolic blood pressure in a population of healthy women of reproductive age. These women were recently pregnant and had a birth outcome in Ba Men, Inner Mongolia, China. The observed levels of systolic and diastolic blood pressure provide evidence of a relationship between drinking water arsenic exposure above 21 μg of As/L and blood pressure – a significantly lower exposure threshold than what has been previously reported in the literature (Chen et al., 1995; Rahman et al., 1999). This finding suggests that exposure to modest levels of drinking water arsenic (21 to 50 μg of As/L) may be associated with a slight but consequential elevation in the population blood pressure mean. Furthermore, a significant linear test for trend of the changes in systolic and diastolic blood pressure was observed across arsenic categories indicating a possible dose–response relationship.

Table 2
Analysis of covariance models – crude and adjusted differences in blood pressure by arsenic exposure

Model	Blood pressure	*n*	Arsenic category (μg/L)				Age (years)	Bodyweight (kg)
			BLD[a] to 20	21 to 50	51 to 100	>100		
Overall	Systolic	8790	Referent[b]	1.29**	1.28*	2.22**		
			(95% CI)	(0.82, 1.75)	(0.49, 2.07)	(1.46, 2.97)		
	Diastolic	8790	Referent[b]	0.78**	1.57**	1.32**		
			(95% CI)	(0.39, 1.16)	(0.91, 2.22)	(0.70, 1.95)		
Crude	Systolic	3260	Referent[b]	1.88**	3.90**	6.84**		
			(95% CI)	(1.03, 2.73)	(2.52, 5.29)	(5.40, 8.28)		
	Diastolic	3260	Referent[b]	2.10**	2.72**	3.17**		
			(95% CI)	(1.37, 2.84)	(1.53, 3.92)	(1.92, 4.41)		
Adjusted	Systolic	3260	Referent[b]	1.88**	3.90**	6.83**	0	−0.02
			(95% CI)	(1.03, 2.73)	(2.52, 5.29)	(5.39, 8.27)	(−0.11, 0.11)	(−0.08, 0.04)
	Diastolic	3260	Referent[b]	2.11**	2.74**	3.08**	0.03	−0.13**
			(95% CI)	(1.38, 2.84)	(1.55, 3.93)	(1.84, 4.31)	(−0.07, 0.12)	(−0.18, −0.08)

[a] Below limit of detection.
[b] Test for trend across arsenic categories, $p<0.0001$.
* $P<0.01$.
** $P<0.001$.

Table 3
Demographic characteristics of women excluded due to either missing blood pressure, age and/or body weight information by arsenic exposure categories[a]

	n	Overall	Arsenic categories (μg/L)				ANOVA[b], *p*-value
			BLD[c] to 20, *n* (%)	21 to 50, *n* (%)	51 to 100, *n* (%)	>100, *n* (%)	
Number of individuals	6351		4172 (65.7)	1365 (21.5)	370 (5.8)	444 (7.0)	
Risk factor	*n* (%)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	
Systolic BP (mm Hg)	5530 (87.1)	105.9 (0.11)	105.7 (0.14)	106.6 (0.23)	105.5 (0.51)	105.9 (0.52)	<0.01
Diastolic BP (mm Hg)	5530 (87.1)	70.9 (0.09)	70.8 (0.11)	70.9 (0.20)	71.7 (0.37)	71.3 (0.39)	0.07
Age (years)	5357 (84.3)	25.6 (0.04)	25.5 (0.04)	25.5 (0.08)	25.7 (0.16)	25.6 (0.14)	0.65
Bodyweight (kg)	384 (6.0)	56.4 (0.26)	56.6 (0.32)	56.1 (0.51)	56.5 (1.21)	52.7 (1.03)	0.29

[a] Lin He, Wu Yuan, and Hanggin Houqi counties.
[b] Analysis of variance between arsenic categories.
[c] Below limit of detection.

A shift in blood pressure of 2 mm Hg at the population level has serious implications for human health (Rose, 1981), since even slight changes in the population mean of blood pressure can lead to large shifts in risk for cardiovascular events. Prior studies have reported absolute and relative risks associated with blood pressure even at levels below what is considered hypertensive (Vasan et al., 2001; Lewington et al., 2002). These studies conclude that small differences in blood pressure levels influence risk, have a measurable impact on cardiovascular disease, and are continuous in nature. Thus, the risk association is proportionally the same per unit difference in blood pressure at *any* level of blood pressure. Importantly, there is no "threshold" to the benefit of a lower blood pressure, since these benefits apply to unit differences in blood pressure, small or large, and they are proportionally the same at any level of blood pressure (i.e. lowering of systolic blood pressure is beneficial all the way down to 70 mm Hg).

Regression estimates from the INTERSALT study estimated a change in prevalence of hypertension of 0.76% for each 1 mm Hg change in mean systolic blood pressure (Rose and Day, 1990). With over 13 million individuals in the United States exposed to drinking water arsenic levels above 10 μg of As/L (Arsenic Rule Benefits Review Panel, 2001), a population exposure such as drinking water arsenic that increases mean systolic blood pressure by only 2–3 mm Hg, might be expected to increase the size of the hypertensive population by one fifth in this age range (17–45 years). Furthermore, estimates based on the results of prospective observational studies (MacMahon et al., 1990) indicate that a 2–3 mm Hg increase in systolic blood pressure would translate into an increase in stroke incidence of 24 per 100,000 individuals and a stroke mortality increase of 10 per 100,000 individuals within this study population (He et al., 1995).

There are several features of a cross-sectional study design that limit extrapolation of the results of this study. Documentation does not exist indicating whether the women in the study lived in the area during or even before the well-water measurements were taken. However, this area has a very low migration rate with stable well-water arsenic concentrations over time (H. Ma, personal communication; Inner Mongolia Center for Endemic Disease Control and Research). Still, the drinking water consumption habits of these women were not known and the cumulative dosage of drinking water arsenic cannot be determined precisely unless individual level information is collected.

A considerable number of individuals with valid blood pressure measurements did not have body weight information. The differences in blood pressure were observed between the larger sample ($n=8790$) and the more restricted sample ($n=3260$) indicating that, while the direction of effect is consistent, some differences exist between those with and without body weight measurements that were not directly measured. Comparing the mean blood pressure levels of those included (Table 1) and those excluded (Table 3) from the study, there is not much difference in the low-arsenic exposed group. However, among the highly exposed group, there is more of a disparity that drives the stronger dose–response gradient seen in the models.

Among the women in this study living in subvillages with higher As concentrations, it is not known why the women with body weight measurements had a higher blood pressure than those who did not. Unmeasured confounders such as diet, smoking, and physical activity, which were not measured in this data set, could have influenced these differences. Nevertheless, we have no reason to believe that age, body weight or blood pressure was differentially recorded between the different areas of arsenic exposure. The possibility exists that these missing data were due to some random error that resulted in those who were more highly exposed to arsenic and had body weight measured had higher blood pressure than those who were more highly exposed and not measured for body weight. Since age and body weight are important covariates for blood pressure levels (Jenei et al., 2002; Lopez-Garcia et al., 2003), it was decided that all analyses include this information and be interpreted cautiously given the possibility that selection bias may be present in the adjusted models due to these unexplained differences in blood pressure and the presence of body weight measurements.

We performed a test for trend to determine whether a linear trend exists for each measure (systolic and diastolic blood pressure, age, and body weight) across the arsenic exposure categories. Comparing these results between the overall, crude and adjusted populations, the only instance where those included into the final crude and adjusted models differed

from those excluded was for the systolic blood pressure. Those excluded did not exhibit a linear trend whereas the systolic blood pressure for those included into the analysis did. As such, we have presented the overall results (which include those missing age and body weight information), as well as the crude and adjusted measures (only those with age and body weight information available) so that the readers can make an informed decision about the data. Since the findings from the overall models support the direction of the crude and adjusted models, it is likely that these are meaningful findings and not just an artifact due to the large sample sizes.

Use of age and body weight information during the prenatal period can also be a potential source of bias in this study since these measures were not taken at the same time as the blood pressure recordings. However, it has been shown that the majority of weight gain occurs late in pregnancy (Clark et al., 1997). Thus, body weight early in pregnancy can be used as an approximation of baseline levels.

Similarly, researchers have commonly used 6-week post-partum blood pressures as a referent level for studying hypertension since the cardiovascular challenge of pregnancy has passed and blood pressure has returned to baseline levels (MacGillivray et al., 1969; Ueland and Metcalfe, 1975). Even cases of preeclampsia, a life-threatening multi-system disorder characterized by hypertension and proteinuria, resolve by the sixth week, post-partum (Zeeman, 2006). Thus, there seems to be minimal bias from using a 6-week post-partum versus a pre-partum blood pressure measurement.

The findings from this study are consistent with previous studies on drinking water arsenic and prevalence of hypertension (Chen et al., 1995; Rahman et al., 1999). Moreover, the effects here are seen at lower arsenic exposure levels and in a younger, presumably healthier population. Recent studies have suggested associations between arsenic and carotid atherosclerosis (Wang et al., 2002; Chen et al., 2006; Wu et al., 2006) which may be on the same causal pathway as elevated blood pressure levels (Lonati et al., 1993; Escudero et al., 1996; Kimura et al., 1999). Excess cardiovascular disease may develop in this study population with continued exposure to drinking water arsenic. The potential burden of cardiovascular disease attributable to drinking water arsenic, if our study results are confirmed, may be significant. Furthermore, these cardiovascular effects could be related to reproductive health outcomes that have been linked to drinking water arsenic exposure (Ahmad et al., 2001; Hopenhayn et al., 2003; Milton et al., 2005; Hopenhayn et al., 2006; Kwok et al., 2006).

Carefully designed prospective studies with better measures of blood pressure and drinking water arsenic dosage – consisting of drinking water consumption habits and measures of individual well-water arsenic concentrations – are needed to further evaluate the association between arsenic exposure and increases in blood pressure. Future studies should properly collect, analyze and store biological specimens (e.g., urine, hair, toenails and blood) to better quantify internal dosage and potentially clarify the specific mechanisms by which arsenic induces any observed cardiovascular changes. Given the millions of individuals exposed to low levels of drinking water arsenic worldwide, the potential health risks associated with exposure to low levels of drinking water arsenic make this a topic worth further, more detailed study.

Acknowledgments

This research was conducted under U.S. Environmental Protection Agency Cooperative Agreement (R-82808401) between the National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency and the Inner Mongolia Center for Endemic Disease Control and Research in Inner Mongolia, China. The data analysis was supported in part by a professional development grant from RTI International (R. Kwok). Thanks to Rebecca Calderon (US EPA) for her overall support and guidance during this process. Thanks also to Obioha C. Ukoumunne (Murdoch Children's Research Institute, Melbourne, Australia) for his assistance with some of the statistical calculations.

References

Ahmad, S.A., Sayed, M.H., Barua, S., Kahn, M.H., Faruquee, M.H., Jalil, A., Hadi, S.A., Talukder, H.K., 2001. Arsenic in drinking water and pregnancy outcomes. Environ. Health Perspect. 109, 629–631.

Arsenic Rule Benefits Review Panel, 2001. Arsenic rule benefits analysis: An SAB review. A Review by the Arsenic Rule Benefits Review Panel (ARBRO) of the US EPA Science Advisory Board (SAB). US EPA, Washington, DC.

Borghi, C., Dormi, A., Ambrosioni, E., Gaddi, A., 2002. Relative role of systolic, diastolic and pulse pressure as risk factors for cardiovascular events in the Brisighella Heart Study. J. Hypertens. 20, 1737–1742.

Chen, C.J., Hsueh, Y.M., Lai, M.S., Shyu, M.P., Chen, S.Y., Wu, M.M., Kuo, T.L., Tai, T.Y., 1995. Increased prevalence of hypertension and long-term arsenic exposure. Hypertension 25, 53–60.

Chen, C.J., Wu, M.M., Lee, S.S., Wang, J.D., Cheng, S.H., Wu, H.Y., 1988. Atherogenicity and carcinogenicity of high-arsenic artesian well water: multiple risk factors and related malignant neoplasms of blackfoot disease. Arteriosclerosis 8, 452–460.

Chen, Y., Hakim, M.E., Parvez, F., Islam, T., Rahman, A.M., Ahsan, H., 2006. Arsenic exposure from drinking-water and carotid artery intima-medial thickness in healthy young adults in Bangladesh. J. Health Popul. Nutr. 24, 253–257.

Clark, S.L., Cotton, D.B., Hankins, G.D.V., Phelan, J.P. (Eds.), 1997. Critical Care Obstetrics. Blackwell Science, Malden.

Escudero, E., De Lena, S., Graff-Iversen, S., Almiron, M., Cingolani, H.E., 1996. Left ventricular diastolic function in young men with high normal blood pressure. Can. J. Cardiol. 12, 959–964.

He, J., Klag, M., Wu, Z., Whelton, P., 1995. Stroke in the People's Republic of China: I. Geographic variations in incidence and risk factors. Stroke 26, 2222–2227.

Heart Disease Collaborative Research Group, 1998. Blood pressure, cholesterol, and stroke in eastern Asia. Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Lancet 352, 1801–1807.

Hopenhayn, C., Bush, H.M., Bingcang, A., Hertz-Picciotto, I., 2006. Association between arsenic exposure from drinking water and anemia during pregnancy. J. Occup. Environ. Med./Am. Coll. Occup. Environ. Med. 48, 635–643.

Hopenhayn, C., Ferreccio, C., Browning, S.R., Huang, B., Peralta, C., Gibb, H., Hertz-Picciotto, I., 2003. Arsenic exposure from drinking water and birth weight. Epidemiology 14, 593–602.

Jenei, Z., Pall, D., Katona, E., Kakuk, G., Polgar, P., 2002. The epidemiology of hypertension and its associated risk factors in the city of Debrecen, Hungary. Public Health 116, 138–144.

Kimura, Y., Tomiyama, H., Nishikawa, E., Watanabe, G., Shiojima, K.,

Nakayama, T., Yoshida, H., Kuwata, S., Kinouchi, T., Doba, N., 1999. Characteristics of cardiovascular morphology and function in the high-normal subset of hypertension defined by JNC-VI recommendations. Hypertens Res. 22, 291–295.

Kwok, R.K., 2007. A review and rationale for studying the cardiovascular effects of drinking water arsenic in women of reproductive age. Toxicol. Appl. Pharmacol. 222, 344–350.

Kwok, R.K., Kaufmann, R.B., Jakariya, M., 2006. Arsenic in drinking-water and reproductive health outcomes: a study of participants in the Bangladesh Integrated Nutrition Programme. J. Health Popul. Nutr. 24, 190–205.

Lewington, S., Clarke, R., Qizilbash, N., Peto, R., Collins, R., 2002. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 360, 1903–1913.

Lonati, L., Cuspidi, C., Sampieri, L., Boselli, L., Bocciolone, M., Leonetti, G., Zanchetti, A., 1993. Ultrasonographic evaluation of cardiac and vascular changes in young borderline hypertensives. Cardiology 83, 298–303.

Lopez-Garcia, E., Banegas Banegas, J.R., Gutierrez-Fisac, J.L., Perez-Regadera, A.G., Ganan, L.D., Rodriguez-Artalejo, F., 2003. Relation between body weight and health-related quality of life among the elderly in Spain. Int. J. Obes. Relat. Metab. Disord. 27, 701–709.

MacGillivray, I., Rose, G., Rowe, B., 1969. Blood pressure survey in pregnancy. Clin. Sci. 37, 395–407.

MacMahon, S., Peto, R., Cutler, J., Collins, R., Sorlie, P., Neaton, J., Abbott, R., Godwin, J., Dyer, A., Stamler, J., 1990. Blood pressure, stroke, and coronary heart disease: Part 1. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 335, 765–774.

Manson, J.E., Tosteson, H., Ridker, P.M., Satterfield, S., Hebert, P., O'Connor, G.T., Buring, J.E., Hennekens, C.H., 1992. The primary prevention of myocardial infarction. N. Engl. J. Med. 326, 1406–1416.

Milton, A.H., Smith, W., Rahman, B., Hasan, Z., Kulsum, U., Dear, K., Rakibuddin, M., Ali, A., 2005. Chronic arsenic exposure and adverse pregnancy outcomes in Bangladesh. Epidemiology 16, 82–86.

Morales, K.H., Ryan, L., Kuo, T.L., Wu, M.M., Chen, C.J., 2000. Risk of internal cancers from arsenic in drinking water. Environ. Health Perspect. 108, 655–661.

Ning, Z., Lobdell, D.T., Kwok, R.K., Liu, Z., Zhang, S., Ma, C., Riediker, M., Mumford, J.L., 2007. Residential exposure to drinking water arsenic in Inner Mongolia, China. Toxicol. Appl. Pharmacol. 222, 351–356.

Rahman, M., Tondel, M., Ahmad, S., Chowdhury, I., Faruquee, M., Axelson, O., 1999. Hypertension and arsenic exposure in Bangladesh. Hypertension 33, 74–78.

Rodgers, A., Lawes, C., MacMahon, S., 2000. Reducing the global burden of blood pressure-related cardiovascular disease. J. Hypertens. (Suppl. 18), S3–S6.

Rose, G., 1981. Strategy of prevention: lessons from cardiovascular disease. Br. Med. J. (Clin. Res. Ed.) 282, 1847–1851.

Rose, G., Day, S., 1990. The population mean predicts the number of deviant individuals. BMJ 301, 1031–1034.

Rose, G.A., Blackburn, H., Gillum, R.F., Prineas, R.J., 1982. Physical examination: blood pressure. Cardiovascular Survey Methods. World Health Organization, Geneva, Switzerland, pp. 82–85.

Smith, A., Hopenhayn-Rich, C., Bates, M., Goeden, H., Hertz-Picciotto, I., Duggan, H., Wood, R., Kosnett, M., Smith, M., 1992. Cancer risks from arsenic in drinking water. Environ. Health Perspect. 97, 259–267.

Stegmayr, B., Asplund, K., Kuulasmaa, K., Rajakangas, A.M., Thorvaldsen, P., Tuomilehto, J., 1997. Stroke incidence and mortality correlated to stroke risk factors in the WHO MONICA Project. An ecological study of 18 populations. Stroke 28, 1367–1374.

Tseng, C.H., Tai, T.Y., Chong, C.K., Tseng, C.P., Lai, M.S., Lin, B.J., Chiou, H.Y., Hsueh, Y.M., Hsu, K.H., Chen, C.J., 2000. Long-term arsenic exposure and incidence of non-insulin-dependent diabetes mellitus: a cohort study in arseniasis–hyperendemic villages in Taiwan. Environ. Health Perspect. 108, 847–851.

Tseng, W., 1977. Effect and dose–response relationships of skin cancer and blackfoot disease with arsenic. Environ. Health Perspect. 19, 109–119.

Ueland, K., Metcalfe, J., 1975. Circulatory changes in pregnancy. Clin. Obstet. Gynecol. 18, 41–50.

Vasan, R.S., Larson, M.G., Leip, E.P., Evans, J.C., O'Donnell, C.J., Kannel, W.B., Levy, D., 2001. Impact of high-normal blood pressure on the risk of cardiovascular disease. N. Engl. J. Med. 345, 1291–1297.

Wang, C.H., Jeng, J.S., Yip, P.K., Chen, C.L., Hsu, L.I., Hsueh, Y.M., Chiou, H.Y., Wu, M.M., Chen, C.J., 2002. Biological gradient between long-term arsenic exposure and carotid atherosclerosis. Circulation 105, 1804–1809.

World Health Organization, 2001. Arsenic and Arsenic Compounds. World Health Organization, Geneva.

Wu, M.M., Chiou, H.Y., Hsueh, Y.M., Hong, C.T., Su, C.L., Chang, S.F., Huang, W.L., Wang, H.T., Wang, Y.H., Hsieh, Y.C., Chen, C.J., 2006. Effect of plasma homocysteine level and urinary monomethylarsonic acid on the risk of arsenic-associated carotid atherosclerosis. Toxicol Appl. Pharmacol. 216, 168–175.

Wu, M.M., Kuo, T.L., Hwang, Y.H., Chen, C.J., 1989. Dose–response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. Am. J. Epidemiol. 130, 1123–1132.

Zeeman, G.G., 2006. Obstetric critical care: a blueprint for improved outcomes. Crit. Care Med. 34, S208–S214.