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# Association between arsenic exposure from drinking water and hematuria: Results from the Health Effects of Arsenic Longitudinal Study

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ABSTRACT

Arsenic (As) exposure has been associated with both urologic malignancy and renal dysfunction; however, its association with hematuria is unknown. We evaluated the association between drinking water As exposure and hematuria in 7843 men enrolled in the Health Effects of Arsenic Longitudinal Study (HEALS). Cross-sectional analysis of baseline data was conducted with As exposure assessed in both well water and urinary As measurements, while hematuria was measured using urine dipstick. Prospective analyses with Cox proportional regression models were based on urinary As and dipstick measurements obtained biannually since baseline up to six years. At baseline, urinary As was significantly related to prevalence of hematuria ($P$-trend < 0.01), with increasing quintiles of exposure corresponding with respective prevalence odds ratios of 1.00 (reference), 1.29 (95% CI: 1.04–1.59), 1.41 (95% CI: 1.15–1.74), 1.46 (95% CI: 1.19–1.79), and 1.56 (95% CI: 1.27–1.91). Compared to those with relatively little absolute urinary As change during follow-up (−10.40 to 41.17 μg/l), hazard ratios for hematuria were 0.99 (95% CI: 0.80–1.22) and 0.80 (95% CI: 0.65–0.99) for those whose urinary As decreased by >47.49 μg/l and 10.87 to 47.49 μg/l since last visit, respectively, and 1.17 (95% CI: 0.94–1.45) and 1.36 (95% CI: 1.10–1.66) for those with between-visit increases of 10.40 to 41.17 μg/l and >41.17 μg/l, respectively. These data indicate a positive association of As exposure with both prevalence and incidence of dipstick hematuria. This exposure effect appears modifiable by relatively short-term changes in drinking water As.

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## Introduction

Hematuria is a prevalent clinical finding, experienced by as much as 18% of the United States population at least once during their lifetime (Grossfeld et al., 2001). As the most common symptom of urinary tract disease, it is associated with a wide array of pathological processes, including glomerular dysfunction, papillary necrosis, urolithiasis, infection, benign prostatic hyperplasia, and malignancy, among others (Cohen and Brown, 2003). As such, the American Urological Association (AUA) best practice policy recommendations for asymptomatic microscopic hematuria were modified in 2012 to advise that, in the absence of a clear etiology, any adult with three or more red blood cells per high powered field on a single urinary specimen should undergo a complete diagnostic evaluation, to include cystoscopy and upper urinary tract imaging (Davis et al., 2012). With hematuria representing an indeterminate clinical presentation for both benign and malignant pathology, more targeted recommendations would rely upon effective identification of risk factors for hematuria-related disease.

Exposure to arsenic (As), a natural element of the Earth's crust and common drinking water contaminant, could play an important role in

*Abbreviations:* As, arsenic; HEALS, Health Effects of Arsenic Longitudinal Study.

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hematuria prevalence. The presence of this toxic substance in drinking water profoundly impacts human health and is an issue of critical public health importance as more than 200 million persons worldwide may be chronically exposed (Naujokas et al., 2013). In the United States alone, nearly 5% of the country (13 million individuals) relies on a primary water source with As concentrations exceeding recommended levels (Bissen and Frimmel, 2003). Recent evidence has suggested that As exposure may impair renal function and promote development of renal disease and renal cell carcinoma (Ferreccio et al., 2013; Hopenhayn-Rich et al., 1998; Hsueh et al., 2009; Huang et al., 2011; Yuan et al., 2010). Furthermore, with environmental exposures representing the most important factor in development of urothelial carcinoma (Volanis et al., 2010), As exposure from drinking water has been strongly linked with development of bladder cancer — especially at high levels of exposure and among smokers (Bates et al., 1995; Chen et al., 1985, 1986; Kurttio et al., 1999; Marshall et al., 2007; Steinmaus et al., 2013). It is therefore plausible that As may raise incidence of hematuria either by inducing non-malignant epithelial inflammation and renal dysfunction or, alternatively, through premalignant and malignant processes. Investigating the association between As and hematuria – particularly at low-to-moderate exposure levels – could provide insight on the underlying mechanisms by which As may lead to renal and urothelial disease. To date, however, no studies have examined the relationship between long-term exposure to drinking water As and prevalence of hematuria.

The Health Effects of Arsenic Longitudinal Study (HEALS) provides a unique opportunity to explore the impact of As on hematuria. We established this study in 2000 with 11,746 individuals in Araihazar, Bangladesh, exposed to mean drinking water As of 99 μg/l for an average of 8 years (Ahsan et al., 2006b; Chen et al., 2011a). Subsequent As mitigation efforts reduced urinary As levels in some subjects (Chen et al., 2007), thereby providing the opportunity to assess hematuria in the context of longitudinal changes in exposure level. In the present study, we conducted cross-sectional and prospective analyses within male HEALS participants to evaluate the association of As exposure (measured through well and urinary concentrations) with prevalence of dipstick hematuria at baseline and incidence of hematuria during follow-up.

## Materials and methods

*Study population.* The HEALS is an ongoing population-based prospective cohort study in Araihazar, Bangladesh that has been previously described (Ahsan et al., 2006a). Between October 2000 and May 2002, we recruited individuals from a well-defined 25 $km^2$ rural geographical area east of the capital city of Dhaka, under the criteria that all were married (to reduce loss to follow-up), between 18–75 years old, and had resided in the study area for at least 5 years. A precohort survey yielded 65,876 individuals in the study area, from which we identified a sampling frame of 14,828 eligible residents. With 2778 members of this sample not home during any of 3 attempted recruiting visits, we ultimately enrolled 11,746 of the remaining 12,050 individuals (97.5% response rate). From 2006 to 2008, HEALS was expanded to include an additional 8287 participants ("expansion cohort") following the same methodologies. At each enrollment period, trained study physicians conducted in-home baseline clinical assessments and structured interviews. Active follow-up occurs through in-person assessments that are conducted biennially for each enrollee, following the same procedures used in the baseline interview. Verbal consent was obtained from study participants and the study procedures were approved by the Institutional Review Boards of both Columbia University and University of Chicago, as well as by the Ethical Committee of the Bangladesh Medical Research Council. The present study utilized data collected up to the third follow-up for original cohort members and through the first follow-up visit for the expansion cohort.

Because menstruation status was not recorded at the time of urine collection, the present analysis was limited to male study participants. Of the 8148 total men enrolled in the HEALS during both recruitment periods, 256 were excluded for missing baseline urinary As data and 49 were excluded for missing baseline urine dipstick interpretation. This left 7843 individuals for inclusion in the present study.

*Hematuria assessment.* At the time of baseline and each of the follow-up visits, dipstick urinalysis was performed by a trained physician on freshly evacuated spot urine samples collected from the participants using the Chemstrip Micral Test Strips (Roche Diagnostics, USA). The study physicians were blinded to urinary As and well As levels (Ahsan et al., 2006b). The results of the urine test were based on a color scale that quantified hematuria as negative, trace, 50 Ery/μl, or 250 Ery/μl. In the present study, hematuria was defined as any dipstick finding with trace, 50 Ery/μl, or 250 Ery/μl.

*Arsenic exposure assessment.* At baseline, water samples from all 10,971 tube wells in the study area were collected. The samples were acidified to 1% with high-purity Optima hydrochloric acid (Fisher Scientific, Pittsburgh, Pennsylvania) for at least 48 h before analysis. Total As concentration was analyzed by high-resolution inductively-coupled plasma mass spectrometry with a detection limit of $<0.2$ μg/l. Detailed information on duration and source of exposure was included elsewhere (Ahsan et al., 2006b). As one of the eligibility criteria for the study, all participants were primary user of one of the tested tube wells, designated as the "index" well for at least 3 years. Individuals' choice of well was largely based on geographical convenience, and well As concentration was not well known among the study population before recruitment (Ahsan et al., 2006a). Though previous analysis of a time-series utilizing a subset of 20 tube wells in the study area indicates that the As concentration in well water is relatively stable over time (Cheng et al., 2005), it should be noted that in the original cohort, As mitigation efforts following initiation of the HEALS resulted in over half of those enrollees whose water source was deemed unsafe (based on the national standard of 50 μg As/l) switching to other wells (Chen et al., 2007).

Urine samples were collected from each participant at baseline as well as during each biennial in-person assessment. All samples were kept in portable coolers immediately after collection. Within 2 to 8 h, urine samples were processed and transferred to −20 °C freezers in the study office located in Dhaka. Samples were kept frozen and shipped to Columbia University on dry ice within 1–2 months. Total urinary As concentration in urine samples collected at baseline and all the follow-up visits were measured by graphite furnace atomic absorption (GFAA) spectrometry, using a PerkinElmer Analyst 600 graphite furnace system, as previously described (Nixon et al., 1991). Urinary creatinine was analyzed using a method based on the Jaffe reaction for adjustment of urinary total As concentration (Slot, 1965).

*Statistical analysis.* All covariate data were derived from the baseline interview. Sociodemographic factors consisted of age (years), education (years), and smoking status (never, past, or current). Study physicians measured blood pressure with an automatic sphygmomanometer and measured height and weight three times to provide the basis for body mass index (BMI) calculations. For eligible individuals, there were very few missing data on the aforementioned covariates (>99% complete).

Initial descriptive analyses compared baseline characteristics in those with and without baseline dipstick hematuria, as well as in participants free of hematuria at baseline who developed incident hematuria during the study period and the subset who did not present with hematuria at any follow-up. We also stratified the study population by the interpretation of baseline dipstick urinalysis for hematuria to further describe the overall cohort in terms of variables that included baseline As exposure measurements (water and urinary As).

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