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A cross-sectional study of water arsenic exposure and intellectual function in adolescence in Araihazar, Bangladesh☆,☆☆

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ABSTRACT

Background: Exposure to inorganic arsenic (As) from drinking water is associated with modest deficits in intellectual function in young children; it is unclear whether deficits occur during adolescence, when key brain functions are more fully developed.

Objectives: We sought to determine the degree to which As exposure is associated with adolescent intelligence, and the contributory roles of lead, cadmium, manganese and selenium.

Methods: We recruited a cross-section of 726 14–16 year olds (mean age = 14.8 years) whose mothers are participants in the Bangladesh Health Effects of Arsenic Longitudinal Study (HEALS), and whose household well water As levels, which varied widely, were well characterized. Using a culturally modified version of the WISC-IV, we examined raw Full Scale scores, and Verbal Comprehension, Perceptual Reasoning, Working Memory and Processing Speed Indices. Blood levels of As (BAs), Mn, Pb, Cd and Se were assessed at the time of the visit, as was creatinine-adjusted urinary As (UAs/Cr).

Results: Linear regression analyses revealed that BAs was significantly negatively associated with all WISC-IV scores except for Perceptual Reasoning. With UAs/Cr as the exposure variable, we observed significantly negative associations for all WISC-IV scores. Except for Se, blood levels of other metals, were also associated with lower WISC-IV scores. Controlling for covariates, doubling BAs, or UAs/Cr, was associated with a mean decrement (95% CI) of 3.3 (1.1, 5.5), or 3.0 (1.2, 4.5) points, respectively, in raw Full scale scores with a sample mean of 177.6 (SD = 36.8). Confirmatory analyses using Bayesian Kernel Machine Regression, which identifies important mixture members, supported these findings; the primary contributor of the mixture was BAs, followed by BCd.

Conclusions: Our data indicate that the adverse consequences of As exposure on neurodevelopment observed in other cross-sectional studies of younger children are also apparent during adolescence. They also implicate Cd as a neurotoxic element that deserves more attention.

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1. Introduction

The World Health Organization (WHO) has estimated that > 200 million people across 70 countries are chronically exposed to levels of inorganic arsenic (As) in drinking water (WAs) that exceed the WHO guideline and the U.S. Environmental Protection Agency (EPA) maximum contaminant level (MCL) of 10 μg/L (WHO, 2008). The National Research Council (NRC), in a recent review, created a hierarchy of the many adverse health outcomes resulting from this exposure. The top tier for concern, with strong evidence of a causal association, included lung, skin and bladder cancer, ischemic heart disease, and skin lesions. The second tier of concern (of three), with weaker support for causality, included six additional adverse health outcomes, including neurodevelopmental deficits (U.S. National Research Council, 2013), the topic of this investigation. Not surprisingly, the U.S. Agency for Toxic Substances and Disease Registry (ATSDR) gives As its highest ranking among chemicals that pose public health hazards (ATSDR, 2015).

Over the past two decades, As has shown consistent associations with neurodevelopmental deficits in children (reviewed in (Rodriguez-Barranco et al., 2013; Tolins et al., 2014; Tyler and Allan, 2014)), although different studies show associations with different developmental domains, reflecting in part the variety of assessment methods. Some studies highlight associations with verbal domains (Calderon et al., 2001), some with memory and attention (Rosado et al., 2007) and others utilize a range of subtests (von Ehrenstein et al., 2007). Most studies are based on populations outside the United States and have made use of a wide range of tests of intellectual function with varying cultural adaptations. In one US study (Wright et al., 2006), levels of As in hair were related primarily to verbal intelligence scores.

In Bangladesh, in 10-year old children drinking from wells with widely ranging WAs concentrations (0.1–790 μg/L), and using an earlier version of the WISC (WISC-III), we found negative associations between WAs and Performance scales (Wasserman et al., 2004). Adverse associations with Performance scores on the WPPSI-III were also observed, but of smaller size in a younger sample of Bangladeshi 6-year olds (Wasserman et al., 2007).

In the re-standardization that created the WISC-IV, certain WISC-III Performance subtests were reorganized into Working Memory, Processing Speed and Perceptual Reasoning domains (and other subtests revised, added or eliminated). The Digit Span subtest is common to both WISC-IV Working Memory and WISC-III Performance Scale. More recently, we reported negative associations between As measured in blood (BAs) and WISC-IV Working Memory in 8–11 year olds; with adjustment for blood manganese (BMn), and for other covariates, this association was of borderline statistical significance (Wasserman et al., 2011). In a follow-up study *of these same children*, two years after installation of deep wells with low WAs concentrations, 12 year old children's WISC-IV Working Memory scores showed significant improvement, but other test indices were unchanged (Wasserman et al., 2015). Finally, in a parallel US investigation among elementary school children in Maine (Wasserman et al., 2014), after adjusting for other sociodemographic covariates, exposure to well WAs > 5 μg/L was adversely associated with most WISC-IV Indices, most strongly with Working Memory and Verbal Comprehension. Average WISC-IV Full Scale IQ and Working Memory scores were roughly 5 points lower in children with WAs ≥ 5 μg/L compared to those with WAs < 5 μg/L.

Recent research has begun to focus on the impact of exposures to mixtures of metals on children's health. A recent systematic review reported on nine studies that evaluated the association of metal mixtures with child cognitive and motor development (Claus Henn et al., 2014), studies that collectively focused on exposures to Pb, Mn, Cd, As and Hg. In the current study, we assess the impact of the first four of these elements in a setting where dietary fish intake (i.e., Hg) is minimal. In addition, we explored potential beneficial effects of selenium (Se), an element known to lessen the overt toxicity of As by facilitating its elimination via bile (Levander, 1977). In the current study, we explore the contributions of these additional elements and utilize a relatively new statistical method to delineate their impacts in a mixture exposure scenario. In addition, we explore a developmental period - adolescence - not typically evaluated in studies of developmental neurotoxicology, but one that is important for our understanding of the long-term impact of As on neurodevelopment. Key structures and processing capacities that support certain domains of intellectual function do not emerge until later childhood or early adolescence. Assessments at younger ages may not readily discriminate the impact of exposure, especially for frontal and prefrontal functions that are not fully operational until adolescence (Sander et al., 2012). The current study adds to our understanding of the relation of As to neurodevelopment by extending observations to a sample of adolescents.

2. Materials and methods

2.1. Study overview and timeline

Between October 2000 and May 2002, 11,746 men and women 18–75 years of age were recruited into the Health Effects of Arsenic Longitudinal Study (HEALS) in Araihazar, Bangladesh (Ahsan et al., 2005). To be eligible for inclusion into HEALS, individuals – including the mothers of the current adolescent study participants – had to have been drinking from their household well for at least three years. The current adolescent study participants were born during that three year period. Thus, their maternal HEALS baseline urinary As concentration adjusted for creatinine (mUAscr) is an indicator of in utero As exposure.

Since women bring water into the household, mothers' WAs levels over time offer a useful proxy for their children's exposure. As evidence for this proxy relationship, we note that for 502 HEALS mother-child pairs in two of our earlier As studies (Wasserman et al., 2007; Wasserman et al., 2004), the correlation between children's urinary arsenic (UAs) and mother's UAs (measured most closely to the child's test date) was high ($r_{(500)} = 0.75$, $p < 0.0001$), corroborating that both the mother and the young child largely consume water from the same source.

In order to assure a range of levels of early WAs exposure, we recruited adolescent offspring of these HEALS female participants from four strata, based on maternal WAs history. We began with 927 households (in 51 villages) for whom mother's WAs history was complete from baseline through her fourth HEALS follow-up visit, and whose households included a child aged 14 years up to (but not including) 17 years, at the time of recruitment. Four strata of these 927 HEALS women included: (1) 264 with WAs < 10 μg/L at HEALS baseline (representing the child's prenatal exposure) and < 10 μg/L at follow-up visits corresponding to child ages 3, 6, and 9 years; (2) 304 with WAs between 10 and 50 μg/L at HEALS baseline and all relevant follow-up visits; (3) 252 with WAs > 50 μg/L at all visits; and (4) 107 with WAs > 50 μg/L at baseline and then < 50 μg/L on all subsequent assessments. The recruitment of adolescent participants took place between December 2012 and December 2016. This study was approved by the Columbia University Medical Center IRB and the Bangladesh Medical Research Council IRB.

2.2. Participants

Of the 927-targeted households, 12 home visits found no child in the anticipated age range, and in 12 additional homes, the child had died. Of the remaining 903 households with potentially eligible children, 29 were excluded because they had moved away (20 migrating to another region in Bangladesh, one residing in a foreign country, and eight who had married and moved away). Of the remaining 874 households, 25 were excluded for other reasons (14 with a child with a severe deficit noted at the home visit (e.g., autism), one with a pair of twins, and nine whose children aged out before they could be assessed). Of the 849