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A cross-sectional study of general cognitive abilities among Uruguayan school children with low-level arsenic exposure, potential effect modification by methylation capacity and dietary folate

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ABSTRACT

Background: Few studies have evaluated the association between low-level arsenic (As) exposure and cognitive performance among children.
Objectives: In this cross-sectional study, we assessed the association between low-level As exposure and cognitive performance among 5–8 year-old children in Montevideo, and tested effect modification by As methylation capacity and children's dietary folate intake.
Methods: We measured total urinary As (UAs) concentrations and the proportion of monomethylarsonic acid (MMA) in the urine of 328 children. Seven subtests of the standardized Woodcock-Muñoz cognitive battery were used to assess cognitive performance, from which, the general intellectual abilities (GIA) score was derived. Total folate intake was estimated from two 24-h dietary recalls. Linear regression analyses were performed. Effect modification was assessed by stratifying at the median %MMA value and tertiles of total folate intake calculated as micrograms (μg) of dietary folate equivalents (dfe).
Results: The median UAs was 11.9 μg/l (range = 1.4–93.9), mean folate intake was 337.4 (SD = 123.3) μg dfe, and median %MMA was 9.42 (range = 2.6–24.8). There was no association between UAs and cognitive abilities, and no consistent effect modification by %MMA. UAs was associated inversely with concept formation, and positively with cognitive efficiency and numbers reversed subtest in the lowest folate intake tertile; UAs was also positively associated with sound integration in the second tertile and concept formation in the highest tertile of folate intake. There was no consistent pattern of effect modification by %MMA or folate intake.
Conclusion: There was no association between low-level As exposure and general cognitive abilities.

1. Introduction

Arsenic (As) is a metalloid that occurs naturally in the earth's crust, and is released into air, water, and soil through natural as well as anthropogenic activities (IARC, 2012). Human exposure to As and its compounds occurs primarily through ingestion of As-contaminated food and water (IARC, 2012). About 200 million people worldwide are exposed to As levels in water exceeding the World Health Organization (WHO)-recommended limit of 10 μg/L (George et al., 2014). Exposure to As is related to adverse health outcomes, including skin lesions, cardiovascular diseases, as well as cancer (Chen et al., 1996; Hopenhayn-Rich et al., 1998; Tondel et al., 1999; Tseng et al., 2003; Tsuda et al., 1995; Yoshida et al., 2004; IARC, 1987).

Among children, exposure to As is associated with deficits in intelligence quotient (IQ), cognitive development, and neurobehavioral function, although the evidence has been inconsistent (Calderon et al., 2001; Nahar et al., 2014; Rosado et al., 2007; Tsai et al., 2003; Wang et al., 2007; Hamadani et al., 2011; Wasserman et al., 2007, 2004, 2011). For instance, a cross-sectional component of the Health Effects of Arsenic Longitudinal Study (HEALS) in Bangladesh showed that among 201 children aged 9.5–10.5 years with mean urinary As levels of 116.6 μg/L (SD = 148.8), higher urinary As was inversely associated

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with performance and full-scale IQ, but not verbal IQ (Wasserman et al., 2004). Another cross-sectional analysis, also of HEALS data, showed that exposure to As from water (mean water As levels = 120.1 µg/L, SD = 134.4, mean urinary As levels = 110.7 µg/L, SD = 132.8) was inversely associated with raw scores of performance IQ as well as processing speed among 301 6-year old children (Wasserman et al., 2007). There was no association between water As concentrations and verbal IQ (Wasserman et al., 2007). In contrast, urinary As with mean levels of 78.09 µg/L (SD = 72.16) was inversely associated with verbal IQ in a third cross-sectional HEALS study, conducted among 299 8–11 year old children, even after adjusting for blood manganese levels (Wasserman et al., 2011).

Among 1700 young children, a longitudinal study estimated in utero exposure to As by measuring maternal, and later, the child's postnatal urinary As concentrations (Hamadani et al., 2011). This study found that urinary As, measured as the sum of inorganic arsenic (iAs) and its methylated metabolites - monomethylarsonic acid (MMA), and dimethylarsinic acid (DMA), was weakly inversely associated with both verbal IQ and full-scale IQ in 5-year old girls (effect size calculations showed that 100 µg/l U-As was associated with a decrement of 1–3 points in both verbal IQ and full scale IQ), whereas no such association was observed among boys (Hamadani et al., 2011). The median UAs was 80 µg/L (10–90 percentiles: 25–400 µg/L) among pregnant women, and 51 µg/L (20–238 µg/L) among children (Hamadani et al., 2011). A systematic review concluded that there is an inconsistent association, and a weak dose-response relationship between exposure to relatively low levels of As, most commonly found to be below 100 µg/L in the drinking water, and neurological outcomes in children (Tsuji et al., 2015). These inconsistencies can be attributed to the differences in study designs, sample sizes, and tests used to measure cognitive performance. It is important to note that very few studies have examined the association between low-level As and cognitive performance. In one study, U.S. children aged 8–10 y who had well water As concentrations ≥ 5 µg/L scored 5 points lower on full scale IQ score than children with water As < 5 µg/L (Wasserman et al., 2014).

Inorganic arsenic in the human body is metabolized to form MMA, followed by DMA (Tsuji et al., 2015). Rapid formation and excretion of DMA in the urine is an indicator of the metabolism, and hence, internal exposure (Vahter, 2001). High %MMA in urine indicates poor methylation capacity of individuals, and higher internal exposure. The major factors that hamper the efficiency of methylation of iAs to DMA are age, smoking, sex, nutritional status, and reduced liver function (Lindberg et al., 2008, 2010; Schmucker, 2005; Löveborn et al., 2016). Assessing potential effect modification by %MMA values in urine is indicative of the role of methylation capacity in relation to cognitive outcomes, and hence the use of %MMA as a susceptibility factor.

Very few studies on As exposure and cognitive performance have incorporated detailed measures of children's nutritional status. Calderon et al. conducted a study in Mexico that focused on the association between exposure to lead, As, undernutrition and neuropsychological development in children (Calderon et al., 2001). Height for age, a measure of growth, was positively associated with full-scale as well as performance IQ ($p < 0.01$) (Calderon et al., 2001). Previous studies have shown that folate intake plays an important role in the metabolism of As in the body, thereby influencing the levels of As metabolites excreted in urine (Argos et al., 2010; Peters et al., 2015). As stated above, the methylation cycles that occur once inorganic As enters the human body result in the sequential production of MMA and DMA (Challenger, 1945). In these reactions, S-adenosylmethionine is a methyl donor, and its regeneration from S-adenosylhomocysteine requires methyl groups, donated by dietary folate or other dietary sources (Vahter, 2001; Peters et al., 2015). Thus, folate plays an important role in both the methylation reactions of As. Results from randomized trials among adults show that folate may reduce blood As levels (Peters et al., 2015; Gamble et al., 2007). Several studies have also indicated that folate is independently associated with cognitive functioning in adults (Ravaglia et al., 2005; Kado et al., 2005; Ramos et al., 2005). The role of folate in one-carbon metabolism, which is required in the methylation reactions in the central nervous system and associated with neurocognitive performance, is hypothesized to underlie the folate-cognition association (Bottiglieri, 1996; Bryan et al., 2004). Although the interaction between folate status and lead has been studied in relation to cognition among children (Solon et al., 2008), few studies have assessed the role of folate in the association between children's As exposure and cognitive performance. Understanding the role of folate intake is essential as it could be used in mitigating the cognitive deficits due to As exposure.

We address these gaps by examining the cross-sectional association between low level As exposure, as measured by total urinary As (UAs), and cognitive performance among first-grade children in Montevideo, Uruguay. Additionally, we assessed potential effect modification of these associations by dietary folate intake and urinary %MMA (a purported indicator of methylation capacity).

2. Materials and methods

2.1. Study setting

We conducted this study in Montevideo, the capital of Uruguay. Montevideo has several industries, including an oil refinery and has an interweave of several heavily travelled motorways. The residents of Montevideo have been exposed to several metals (Kordas et al., 2010; Mañay et al., 2008; Queirolo et al., 2010), previous studies showed a median As concentration in drinking water of 0.45 µg/L (5–95% range: 0.16–0.93). The specific sources of As exposure are not well studied, but foods such as rice are an important contributor (Kordas et al., 2010, 2016). Groundwater is not a source of drinking water for most Montevideo residents, and the municipal water authority carefully monitors water contaminant levels. We carried out this study between July 2009 and August 2013 in private elementary schools in several neighborhoods of Montevideo considered at risk of pediatric metal exposure.

2.2. Participant recruitment

We contacted schools in the focal neighborhoods, and upon receiving the school director's affirmative response, scheduled meetings with the children's parents. After explaining the study rationale and procedures, we obtained parental consent. All first-grade children who regularly attended the participating schools were eligible. The sole exclusion criterion was a previous diagnosis of lead poisoning (defined as blood lead levels > 45 µg/dL). None of the children were excluded based on this criterion. Of the 673 eligible children from 11 private elementary schools that agreed to participate, 357 children aged 5–8 years and their mothers enrolled into the study. The research protocol was approved by the Institutional Review Boards at the Catholic University of Uruguay, Pennsylvania State University, and the State University of New York at Buffalo.

2.3. Measurements

2.3.1. Anthropometry

Trained pediatric nurses or nutritionists measured children's height in triplicate to the nearest 0.1 cm using a portable stadiometer (Seca 214, Shorr Productions, Colombia, MD), and weight in triplicate to the nearest 0.1 kg using a digital scale (Seca 872, Shorr Productions, Colombia, MD).

2.3.2. Parental questionnaires

Caregivers filled out questionnaires about socio-demographic characteristics of the family, child's medical history, and home environment. Questions regarding the monthly income, daily expenditures on food and clothes, home ownership, crowding at home, as well as family possessions of household items were included to assess household