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Executive Functions in School Children from Montevideo, Uruguay and their Associations with Concurrent Low-level Arsenic Exposure

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Abstract

Objective: Arsenic is a known childhood neurotoxicant, but its neurotoxicity at low exposure levels is still not well established. The aim of our cross-sectional study was to test the association between low-level arsenic exposure and executive functions (EF) among children in Montevideo. We also assessed effect modification by arsenic methylation capacity, a susceptibility factor for the health effects of arsenic, and by B-vitamin intake, which impacts arsenic methylation.

Methods: Arsenic exposure was assessed as the specific gravity-adjusted sum of urinary arsenic metabolites (U-As) among 255 ~7 year-old children, and methylation capacity as the proportion of urinary monomethylarsonic acid (%MMA). Arsenic concentrations from kitchen water samples at participants' homes were assessed. B-vitamin intake was calculated from the average of two 24-hour dietary recalls. EF was measured using three tests from the Cambridge Neuropsychological Test Automated Battery – Stockings of Cambridge (SOC), Intra-dimensional/extra-dimensional shift task (IED), and Spatial Span (SSP). Generalized linear models assessed the association between U-As and EF measures; models were adjusted for age, sex, maternal education, possessions score, Home Observation for Measurement of the Environment Inventory score, season, and school clusters. Additional analyses were conducted to address issues of residual confounding and sample size. A "B-vitamin index" was calculated using principal

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component analysis. Effect modification by the index and urinary %MMA was assessed in strata split at the respective medians of these variables.

Results: The median (range) U-As and water arsenic levels were 9.9 μg/L (2.2, 47.7) and 0.45 μg/L (0.1, 18.9) respectively, indicating that exposure originated mainly from other sources. U-As was inversely associated with the number of stages completed (β = −0.02; 95% CI: −0.03, −0.002) and pre-executive shift errors (β = −0.08; 95% CI: −0.14, −0.02) of the IED task, and span length of the SSP task (β = −0.01; 95% CI: −0.02, −0.004). There was no clear pattern of effect modification by B-vitamin intake or urinary %MMA.

Conclusion: Low-level arsenic exposure may adversely affect executive function among children but additional, including longitudinal, studies are necessary to confirm these findings.

Keywords

Low-level arsenic; executive function; B-vitamins; children

1. Introduction

Because arsenic is ubiquitous in the environment, human exposure to this metalloid cannot be avoided altogether. Food and water are the most common sources of exposure globally, with >200 million people exposed to high levels of arsenic (>50 μg/L) from drinking water (George et al. 2014), and millions worldwide exposed to low-levels (Focazio et al. 2000; Naujokas et al. 2013). Children's exposure to arsenic has been associated with deficits in verbal intelligence quotient (IQ) (Calderon et al. 2001; Hamadani et al. 2011; Wasserman et al. 2011) as well as processing speed (Wasserman et al. 2007). The neurotoxicity of arsenic at low-level exposure is, however, not well established (Desai et al. 2018; Signes-Pastor et al. 2019; Wasserman et al. 2014).

Executive functions (EF) is an umbrella term for several inter-related cognitive domains such as working memory, planning, cognitive flexibility (Diamond 2013), which develop from early childhood well into adolescence (Juric et al. 2013). While IQ is used commonly in research studies and is well understood, it does not specifically measure important domains of EF, such as inhibitory control and cognitive shifting (Friedman et al. 2006). These domains are critical in daily and school functioning because they relate to life activities such as thinking before acting, facing unanticipated challenges, focusing, and resisting temptations (Diamond 2013), and to school readiness (Blair and Raver 2015; Blankenship et al. 2019; Welsh et al. 2010) and academic success (Bartels et al. 2002; Jensen 1998; Neisser et al. 1996; Sternberg et al. 2001). Inhibitory control of attention represents the ability to selectively focus on tasks at hand, while ignoring other stimuli (Diamond 2013), whereas cognitive shifting is the ability to switch between mental processes to generate appropriate behavioral responses (Dajani and Uddin 2015). EF deficits have been linked to attention deficit hyperactivity disorder (Barkley 1997). While the effects of other metals, like lead, on EF have been relatively well studied (Bellinger et al. 1994; Canfield et al. 2003b; Chiodo et al. 2004; Froehlich et al. 2007; Lanphear et al. 2000; Surkan et al. 2007), the associations between arsenic exposure and EF remain largely unexplored (Forns et al. 2014; Wasserman et al. 2014; Wasserman et al. 2011).

Susceptibility to arsenic-induced health outcomes may be influenced by arsenic methylation capacity (Del Razo et al. 1997; Pu et al. 2007; Steinmaus et al. 2006; Vahter 2001; Wu et al. 2006), which in turn is affected by B-vitamin intake and status (Gamble et al. 2006; Gamble et al. 2005; Gamble et al. 2007; Hall et al. 2009a; Hall et al. 2009b; Howe et al. 2017; Steinmaus et al. 2005). In the body, arsenic metabolizes via the one-carbon metabolism cycle, wherein inorganic arsenic is converted to monomethylarsonic acid (MMA), and then to dimethylarsinic acid (DMA) (Challenger 1945). Both MMA and DMA are excreted in urine; higher %MMA and lower %DMA in urine indicate lower methylation efficiency. Folate acts as a methyl donor, whereas vitamins B-2, B-6, B-12 act as cofactors in the reactions leading to methylation of inorganic arsenic (Hall and Gamble 2012; Mason 2003; Peters et al. 2015; Vahter 2007). Importantly, it is unclear to what extent arsenic methylation capacity or B-vitamins moderate the effect of arsenic on neurodevelopmental outcomes in children (Desai et al. 2018; Hamadani et al. 2011; Hsieh et al. 2014).

Our study aim was to assess the effect of low-level arsenic exposure on EF in school-age children. We hypothesized an inverse association between arsenic exposure and EF, and explored whether arsenic methylation capacity (urinary %MMA) and B-vitamin (B-1[thiamine], B-2 [riboflavin], B-3 [niacin], B-6, folate, and B-12) intake act as effect modifiers in this association.

2. Materials and Methods

2.1. Study Setting and Participant Recruitment

This study was conducted between July 2009 and August 2013 in private elementary schools in low- and middle-income neighborhoods of Montevideo, where metal exposure among children was previously demonstrated (Kordas et al. 2010; Mañay et al. 2008; Queirolo et al. 2010). The median concentration of arsenic in drinking water of the study children was 0.45 μg/L (range: 0.10, 18.9), but food also appeared to be a source of exposure (Kordas et al. 2016). In this study, 357 children ~7 years old attending first grade of elementary school, and their caregivers (typically mothers), were enrolled. The details of the recruitment can be found in a previous publication (Desai et al. 2018). Informed consent was obtained prior to beginning data collection. 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.

2.2. Urinary Arsenic

Total urinary arsenic concentration was measured as the sum of inorganic arsenic, MMA, and DMA, and arsenic methylation capacity as urinary %MMA. Urinary arsenic concentration was measured using HPLC-HG-ICP-MS (HG, hydride generation, selects inorganic arsenic and its methylated metabolites into the ICP-MS, Inductively Coupled Plasma Mass Spectrometry), as described previously (Desai et al. 2018; Kordas et al. 2016). The sum of urinary arsenic metabolites was adjusted for specific gravity; this measure is referred to as U-As hereafter.

2.3. Household Water Arsenic Assessment

The study staff visited the participants' homes and collected samples of water that was used for drinking or cooking; caregivers pointed out the water typically used for these purposes. Water was collected directly from the kitchen taps or from a water storage container in a 100 ml plastic cup. About 15 ml water was extracted from the cup using a syringe (Becton-Dickinson, Franklin Lake, NJ, USA) and passed through a 0.45 μm filter (VWR International, PA, USA) into a plastic bottle, previously rinsed with 10% HNO_3 and deionized water. The pH of the water was measured and adjusted to < 2. Water arsenic concentrations were measured at the Materials Characterization Laboratory of the Pennsylvania State University using Inductively Coupled Plasma Mass Spectrometry (ICP-MS) with Collision Cell Technology (Thermo Scientific XSERIES 2, Bremen, Germany). The limit of detection was 0.03 μg/L.

2.4. B-Vitamin Intake

Two non-consecutive 24- hour dietary recalls were conducted with the mother/caregiver, as described previously (Desai et al. 2018). The amount of each food consumed was calculated based on the average of the two recalls. The amounts of vitamins B-1, B-2, B-3, B-6, folate, and B-12 in the reported foods were calculated using the Uruguayan nutrient database or the United States Department of Agriculture (USDA) National Nutrient Database for Standard Reference, Release 28 (Version Current: September 2015) for foods not listed in the Uruguayan database (Instituto de Nutrición de Centro América y Panamá (INCAP) and Organización Panamericana de la salud (OPS) 2012; Instituto Nacional de Alimentación (INDA) 2010; Kordas et al. 2018; 2018). These details have been described in previous publications (Desai et al. 2018; Kordas et al. 2016). Each B-vitamin intake was adjusted for total energy intake and expressed per 1000 kcal/day.

2.5. Anthropometric measures

Trained nurses 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).

2.6. Parental questionnaires

Parents completed questionnaires about socio-demographic characteristics of the family. A household possessions score was derived based on a factor analysis that retained the ownership of five items – computer, car, refrigerator, laundry, and a landline telephone, as described previously (Kordas et al. 2018).

2.7. Home Observation for Measurement of the Environment (HOME) Inventory score

The Home Observation for Measurement of the Environment (HOME) Inventory (Bradley et al. 2003) was used to assess the quality of the children's home environments and the availability of developmental stimuli such as educational toys or books at home. The inventory consists of 59 items grouped into eight subscales—1) parental responsibility, 2) encouraging maturity, 3) emotional climate, 4) learning materials and opportunities,

5) active stimulation, 6) family participation, 7) parental involvement, and 8) physical environment. The total index score was used in statistical analyses.

The HOME Inventory was administered by a study staff during a visit to the child's home. The time of the visit was previously scheduled with the family during a phone call, which also consisted of explaining the purpose of the visit to the family. The family had the right to refuse the visit. The visit was generally scheduled between 9 am and 3 pm on a Saturday, with at least the mother and the child present at home. In case it was difficult for the mother to be present, the father or another caregiver was asked to participate. At the beginning of the visit, the study staff explained that some interview questions were directed toward the mother/other caregiver, whereas some questions were directed toward to study staff to make observations.

2.8. Hemoglobin measurement

A 25-gauge safety butterfly blood collection set (Vacutainer, Becton Dickinson, Franklin Lakes, NJ) was used by a phlebotomy nurse to collect fasting venous blood into a serum tube with clot activator and separator gel (Becton Dickinson, Franklin Lakes, NJ). A drop of venous blood was removed from the tube immediately after the blood draw and used to measure hemoglobin via a hemoglobinometer (HemoCue Inc, Lake Forest, CA). Quality control checks were performed daily with standard controls (low, medium, high) provided by the manufacturer.

2.9. Blood lead measurement

Using the blood collection system described above, a second blood sample was collected into heparin coated tubes (Vacutainer, Becton Dickinson, Franklin Lakes, NJ) for lead analysis. Blood lead concentrations were measured using Atomic Absorption Spectrometry (AAS, VARIAN SpectrAA-55B) at the Toxicology Laboratory "CEQUIMTOX" (Specialized Center for Chemical Toxicology), of the Faculty of Chemistry, University of the Republic of Uruguay, as detailed in a previous publication (Desai et al. 2018).

2.10. Hair manganese measurement

Hair samples were collected using previously disinfected blunt-tip, stainless steel scissors from the occipital region of the children's heads. One centimeter of hair from these samples was cut and kept in polyethylene vials. Hair samples were washed with 10 ml 1% Triton X-100 solution, rinsed vigorously, and then dried at 60°C for 24 hours in an oven. Subsequently, one ml of concentrated nitric acid was added and the hair samples were digested at 80°C for 11 hours. Digested samples were diluted by adding 20 ml of double distilled water and analyzed for manganese at the Materials Characterization Laboratory at Pennsylvania State University by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) with Collision Cell Technology (Thermo Scientific XSERIES 2, Bergen, Germany). The detection limit for manganese was 0.01 ng/ml.

2.11. Urinary cadmium measurement

Urinary cadmium was measured at the Karolinska Institutet, Sweden, as described previously (Kippler et al. 2007; Kippler et al. 2010). The samples were analyzed in two batches using an Agilent 7700× ICP-MS (Agilent Technologies, Tokyo, Japan). The limits of detection were 0.0005 μg/L for batch 1 and 0.001 μ/L for batch 2; there were no batch differences. Urinary cadmium concentrations were adjusted for urinary specific gravity to account for differences in the hydration status of participants.

2.12. Executive Function

The Cambridge Neuropsychological Test Automated Battery (CANTAB) was administered to participants to assess executive functions. First, the Big Circle Little Circle test, a motor function test, was administered to test their ability to follow directions and use the touch screen. Then, three CANTAB tests were administered in the following order: (i) Stockings of Cambridge (SOC), (ii) Intra-dimensional/extra-dimensional shift (IED), and (iii) Spatial Span (SSP).

The Stockings of Cambridge (SOC) is a spatial planning task, i.e., it measures the ability of an individual to plan and work accordingly. In this test, the participant sees two displays of colored balls enclosed in three “stockings.” One display is in the middle and one at the top of the screen. The participant is asked to reproduce the display that is present at the top of the screen by making changes to the display in the middle of the screen. These changes are to be made by clicking the ball the participant plans to move and then clicking the desired location. To make these changes, the balls in the display need to be moved one at a time and a ball at the bottom of the sock cannot be moved before the ball on top has been moved first. Trials increase in complexity and number of moves to be planned out. The outcome measure is the number of problems solved with minimum moves.

Intra-dimensional/extra-dimensional shift task (IED) measures visual attention. It includes the tasks of rule acquisition and reversal, and involves the use of color-filled shapes and white lines. The participant is asked to click on the correct color-filled shape on the screen by understanding and applying an implicit rule. The computer then shows the correct answer. After a few trials, the rule changes and once this new rule is learned, responding continues with additional trials. The criterion for learning each rule is 6 correct consecutive responses. If the child fails to achieve this criterion after 50 trials, the test terminates. A total of nine test stages exist - stages one and two include shapes only, stages three, four and five consist of a white line pattern overlaid on the shape. New shapes and white line patterns are introduced in stages six and seven, which is considered the intra-dimensional shift. The white line pattern then becomes the discriminating selection factor instead of the geometric shape in stages eight and nine, which is considered the extra-dimensional shift. The outcomes of interest are number of stages completed, total number of errors, pre-executive shift error, and post-executive shift error. For the total number of errors, the adjustment approach from the CANTAB Administration Guide was used; 25 errors were added for each failed stage based on the logic that 50 trials are given before failing a stage, and chance alone could explain half of the correct trials. This approach has been used in previous studies (Gau and Shang 2010; Potter et al. 2012). Five children failed the IED

task prior to stage four. In addition, two children received zero errors after they failed stage nine, when there are no more errors to accumulate. Data for these seven children were set to missing on the pre-executive shift error and the post-executive shift error.

The Spatial Span (SSP) task measures working memory. White squares are displayed on the screen, and the squares change color, one at a time. The participant is asked to touch the squares that changed color, remembering the sequence. The number of illuminated squares increases from 2 to 9. The outcome measures include span length and total number of errors. In our study, 17 children did not repeat the correct pattern during the two-square sequence after three attempts. These children were assigned a span length of one, the minimum possible value.

The reliability and validity of the CANTAB have been previously studied; for children, the test-retest intraclass correlation was 0.78–1.00 for the IED task, 0.72–1.00 for the SOC task, and 0.55 for the SSP task for an interval of 14–42 days (Gau and Shang 2010). The discriminant validity of the battery has also been shown through its use in assessing several outcomes such as epilepsy (Luciana and Nelson 2000), autism (Hughes et al. 1999; Hughes et al. 1994), as well as attention deficit hyperactivity disorder (Kempton et al. 1999).

2.13. Statistical analyses

All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive analyses included calculating the medians (range) and frequencies of sociodemographic, biochemical, and dietary characteristics of participants. The associations between U-As and EF measures were assessed using a separate generalized linear model for each endpoint, with the identity link function using generalized estimation equation to address data clustered by school. Models were adjusted for age, sex, maternal education (years), possessions score, HOME score, and season (to account for the season of diet recall, since season-based foods may affect both arsenic exposure and cognitive outcomes in general). These models are referred to as the base models, and had a sample size of 255 participants. Effect sizes were calculated by dividing the regression coefficients by the respective standard deviations observed in the study sample.

In additional analyses, models were adjusted for (i) known risk factor for the outcomes, blood lead levels and hemoglobin (Canfield et al. 2003a; Halterman et al. 2001; Health 2005; Jáuregui-Lobera 2014), n=244, and (ii) potential risk factors for the outcomes, urinary cadmium and hair manganese levels (Kippler et al. 2012; Rodríguez-Barranco et al. 2013), n=241. To overcome the reductions in sample size from exclusion of participants with missing covariate data, the models were re-analyzed among participants with complete exposure and outcome data, by replacing missing covariate values. The missing values for continuous covariates were replaced with the respective medians, whereas for categorical variables, a separate category for missing data was created (Kaiser 2014; Zhang 2016). This led to a sample size of 286 participants.

Urinary %MMA was stratified at the median; stratified analyses were conducted to assess effect modification by arsenic methylation capacity. These analyses were conducted among those with no seafood intake (n=228), because arsenolipids and arsenosugars found in

seafood metabolize to DMA (Raml et al. 2007; Schmeisser et al. 2006); increased %DMA from seafood intake may lead to reduced %MMA irrespective of methylation capacity. Principal component analysis was conducted with vitamins B-1, B-2, B-3, B-6, folate, and B-12, which led to the separation of two indices – (1) high loadings on all B-vitamins except folate, and (2) high loadings on folate alone. These separate indices were observed perhaps because flour in Uruguay is fortified with folate but not the other B-vitamins. A factor score was then calculated based on all B-vitamins except folate. The factor score was stratified at the median, and the strata used to assess effect modification by the overall B-vitamin intake. Similarly, stratified analyses by folate intake, split at the median, were conducted. Because effect modification by sex was observed in a recent Spanish study (Signes-Pastor et al. 2019), we also conducted analyses stratified by sex. Stratified analyses were adjusted for the same covariates as the base models. As exploratory analyses, we also conducted regressions stratified at the respective medians of blood lead, urinary cadmium, and hair manganese levels.

3. Results

Table 1 presents the sociodemographic, biochemical, and dietary characteristics of study participants. The median (range) age of participants was 7 (5, 9) years, and about 57% were boys. The median (range) U-As and urinary %MMA were 9.9 μg/L (2.2, 47.7) and 9.7% (2.6, 24.8) respectively. The correlation between water arsenic levels and U-As was 0.1 (p=0.2). Water arsenic as well as urinary %MMA levels were similar in boys and girls. The median (range) scores of the CANTAB subtests are shown in Supplemental Table 1, along with results obtained from participants of similar age groups from other studies for comparative purposes.

The associations between U-As and EF measures are shown in Table 2. U-As was inversely associated with the number of stages completed (β = −0.02; 95% CI: −0.03, −0.002), pre-executive shift errors (β = −0.08; 95% CI: −0.14, −0.02) on the IED task, and span length from the SSP task (β = −0.01; 95% CI: −0.02, −0.004) in the base models. Further adjustment for hemoglobin, blood lead, urinary cadmium, and hair manganese levels led to similar point estimates, also presented in Table 2. Results remained unchanged upon re-running models among 286 participants whose missing covariates were replaced (Supplemental Table 2). Effect size calculations for the statistically significant associations carried out to standardize results across outcomes revealed small effect sizes: each unit (μg/L) of U-As was associated with lower SOC stages completed, a measure of spatial planning, IED pre-executive shift errors, a measure of visual attention, and SSP span length, a measure of working memory, by 0.01–0.14 units, equivalent to 0.01–0.02 SD.

Table 3 shows the results of analyses stratified by urinary %MMA, the B-vitamin index, and folate intake. There was suggestive evidence of effect modification by folate intake; those with low folate intake had fewer pre-executive shift errors on the IED task compared to those with high folate intake. However, it is noteworthy that the 95% confidence intervals of the point estimates were largely overlapping between the strata in all the stratified analyses, indicating that there was either no effect modification, or that we did not have sufficient power to detect it. Similarly, we observed no effect modification by sex (Supplemental Table

3); the estimates were similar for boys and girls, with overlapping 95% confidence intervals. We observed some evidence of effect modification by lead, cadmium and manganese exposure for various CANTAB test outcomes, but with no clear pattern (Supplemental Table 4).

4. Discussion

Among ~7 year-old children from Montevideo exposed to low levels of arsenic, we found an inverse association between low-level arsenic exposure and executive functions of rule learning and reversal, visual attention, and working memory measured with the CANTAB, but the effect sizes were small. There was no clear pattern of effect modification by arsenic methylation capacity (urinary %MMA), or the B-vitamins (B-1, B-2, B-3, B-6, folate, B-12). Notably, we observed no association between arsenic exposure and general cognitive function among the same children in a previous study (Desai et al. 2018). Among participants of the INfancia y Medio Ambiente (INMA) birth cohort, detectable arsenic levels (compared to undetectable, 77.8% of the samples) from the placental tissue were associated with deficits in global and verbal executive function, endpoints derived from the McCarthy Scales of Children's Abilities, among 4–5 year-old children (Freire et al. 2018). Another study from the INMA cohort found inverse associations of children's urinary arsenic with motor function, but no association with executive function, similarly assessed based on the McCarthy Scales of Children's Abilities (Signes-Pastor et al. 2019). Both these studies were conducted among populations with drinking water containing low arsenic concentrations, indicating that arsenic from foods may be important. American children with water arsenic levels ≥ 5 μg/L (vs. < 5 μg/L, reference) had deficits in verbal comprehension, working memory, reasoning, and full scale IQ (Wasserman et al. 2014).

We assessed EF using three tasks from the CANTAB, a standardized battery that has been used to measure EF across different ages, including children as young as 4 years (De Luca et al. 2003; Luciana and Nelson 2002). Different domains of executive functions appear to have different developmental trajectories in children, for instance, cognitive flexibility, goal setting, and information processing have a critical developmental period that extends from 7 to 9 years of age (Anderson 2002). On the other hand, attentional control begins developing from infancy; children are able to inhibit impulse-based behaviors to an extent by 3 years of age, and this inhibition improves with age until about 11 years (Anderson 2002). Older children usually perform better on tests of EF compared to younger children (De Luca et al. 2003; Luciana 2003). Test performance of Montevideo first-graders was comparable to that observed among 6–11-year-old Brazilian children on SOC problems solved in minimum moves, SSP span length, and IED stages completed (Roque et al. 2011). Similarly, ~11 year-old children participating as controls in a study focused on attention deficit hyperactivity disorders had performance comparable to our participants with respect to minimum number of moves needed to solve the SOC and total errors on the IED (Fried et al. 2015). On the other hand, 6–17 year-old Canadian children participating as controls in a study of prenatal alcohol exposure, had slightly better performance than our participants, perhaps reflecting the age related maturation of several EF (Rasmussen et al. 2011).

Although the neural mechanisms underlying EFs are not fully understood, the prefrontal cortex of the brain plays a key role (Funahashi and Andreau 2013). Individuals with a damaged prefrontal cortex have normal IQs, long-term memory, as well as motor and language skills, however, they lack skills required to adapt to new rules or to select among several seemingly similar options and act accordingly (Funahashi and Andreau 2013). A deficit in these skills is attributed to poor planning, decision making, and working memory, all of which are important domains of EF (Funahashi and Andreau 2013). Animals with prefrontal cortex lesions exhibit similar deficits (Fuster 2015). Several mechanisms are thought to underlie the neurotoxicity of arsenic. For example, arsenic exposure is hypothesized to induce epigenetic modifications to the DNA, which can cause aberrant gene expression in the brain (Tyler and Allan 2014). Studies in animal models suggest the neurotoxicity of arsenic at high exposure levels. For example, arsenic exposure of 5 mg/kg of body weight for 2–3 months daily (Nagaraja and Desiraju 1994), as well as 0.1 g sodium arsenate per liter of drinking water for 11 days (Valkonen et al. 1983) were associated with decreased acetylcholinesterase activity in rat brain, indicating an impact on cholinergic signaling. Other studies in rats showed that arsenic affected monoaminergic signaling through reduced dopamine activity (Kannan et al. 2001; Rodriguez et al. 2003; Tripathi et al. 1997). Among humans, hampered dopaminergic activity in the prefrontal cortex and mesolimbic system is associated with deficits in visual working memory (SSP) and selective attention (intra-dimensional change), problems that increase notably in deep dopaminergic damage observed in pathologies like Parkinson's disease (Robbins 2000). Hippocampal dysfunction, and glutamatergic and glucocorticoid signaling, also associated with the hippocampus, are other proposed mechanisms of arsenic neurotoxicity (Tyler and Allan 2014). However, their role in EF impairments may be limited, given that EF are primarily associated with the prefrontal cortex. Oxidative stress is another hypothesized mechanism; arsenic exposure led to the production of reactive oxygen species and lipid peroxidation, and the reduction in the levels of the antioxidant glutathione and activity of the enzyme glutathione peroxidase in rat brains (Chaudhuri et al. 1999; Xi et al. 2010). Similarly, arsenic exposure affected glutathione enzymes and neuronal development in human brain cells *in vitro* (Chattopadhyay et al. 2002a; Chattopadhyay et al. 2002b).

We found an inverse association between U-As and pre-executive shift errors of the IED task, which was in the direction that we did not hypothesize. Interestingly, we observed no associations with post-executive errors of the same task. The IED is a complex task that necessitates understanding when the implicit rule of the test changes, i.e., when the "shift" in the definition of a correct response occurs. Following this shift, the task is relatively more difficult than prior to the shift, and responses may depend on the level of maturation of both the prefrontal cortex and the EF in question (De Luca et al. 2003). For example, the performance of 4–6 year-old children has been shown to be distinct from that of older children, suggesting that this task may be particularly sensitive to early brain development (Luciana 2003). Therefore, optimal responding is likely to develop first in tasks measuring pre-executive shift. In an attempt to disentangle the observed associations, we used pre-executive shift errors as a covariate in regressions modeling the association between arsenic exposure and post-executive shift errors. The results remained unchanged (results not shown). It is possible that, due to the age of the children in this study, the task

was similarly difficult to all children post-shift, regardless of any effect of environmental exposure on performance.

To address issues of residual confounding and unaccounted risk factors for the outcomes, we conducted a series of additional analyses. Previous studies suggest that even low levels of blood lead may been associated with EF deficits in children (Canfield et al. 2003b; Surkan et al. 2007), prompting us to adjust our models for blood lead levels. Although we found no association between low blood lead (mean = 4.2, SD = 2.1 μg/dL) and EF-related behaviors among our study participants (Barg et al. 2018), we had not assessed EF directly. We also adjusted our analyses for hemoglobin concentrations because iron deficiency has been inversely associated with cognitive performance (Halterman et al. 2001; Jáuregui-Lobera 2014). Finally, we adjusted for urinary cadmium and hair manganese because exposure to both metals is associated with neurodevelopmental deficits in children (Kippler et al. 2012; Rodríguez-Barranco et al. 2013). These adjustments did not change our results. Similarly, we found no clear patterns of effect modification by these metals in the relationship between arsenic exposure and EF endpoints. To compensate for reductions in sample size due to exclusion of participants with missing covariate data, we repeated the analysis in a larger sample obtained when we replaced missing covariate values with median values or when we created “missing” categories for categorical variables. The results remained unchanged.

Urinary %MMA is regarded as a susceptibility factor for arsenic-induced health outcomes (Vahter 2001). Higher urinary %DMA and lower %MMA and %inorganic arsenic indicate more efficient arsenic methylation. However, higher urinary %DMA could result from high intake of foods such as seafood, independent of methylation capacity (Navas-Acien et al. 2011). Since U-As was measured in this study as the sum of urinary inorganic arsenic, MMA, and DMA, a high DMA intake could lead to lower %MMA in urine. Hence, we assessed effect modification by urinary %MMA among participants with no seafood intake (n=228). Previous studies focusing on arsenic-induced neurodevelopmental outcomes have shown inconsistent results with respect to urinary %MMA. Taiwanese preschool children with developmental delays (n=63) had higher urinary %MMA levels compared to those without developmental delays (n=35) (Hsieh et al. 2014). However, among Bangladeshi children, there was no evidence of effect modification of the arsenic-IQ association by urinary %MMA (Hamadani et al. 2011). This study in Bangladesh had more than 1000 participants with median (10^{th}, 90^{th} percentile) U-As of 34 μg/L (12, 155) at 1.5 years of age and 51 μg/L (20, 238) at 5 years of age (Hamadani et al. 2011). Furthermore, there is suggestive evidence that children might have an overall efficient arsenic methylation capacity compared to adults (Löveborn et al. 2016). Consistent with the study in Bangladesh, we previously found no effect modification by urinary %MMA on general cognitive outcomes in Uruguayan children who were exposed to much lower levels of arsenic (Desai et al. 2018). Hence, it is unsurprising that we observed similar point estimates with overlapping confidence intervals analyses stratified by urinary %MMA (split at median).

Because of their role in the one-carbon metabolism cycle, which also methylates arsenic, B-vitamin intake and status have been associated with efficient arsenic methylation (Hall and Gamble 2012; Mason 2003; Peters et al. 2015; Vahter 2007). We hypothesized that a

high intake of B-vitamins would be associated with less detrimental effects of arsenic on measures of EF. The overlapping confidence intervals in the stratified analysis suggested no effect modification, or that our study was underpowered to detect it. Flour in Uruguay is fortified with folate, thereby leading to high folate intake levels in the population. Participants in our study appeared to have adequate B-vitamin intake levels, however, these data were obtained from two 24-hour dietary recalls, which may not reflect habitual intakes. Furthermore, the possibility of chance findings cannot be ruled out.

Our study has certain limitations. First, the participation rate was 53%, although it differed by school. Selection bias is possible if participation was associated with both the exposure and outcome. Families would have no knowledge of their arsenic exposure prior to the study so the possibility of them making a participation decision based on arsenic exposure is low. However, we have no way of knowing if families self-selected because of perceived learning or behavioral difficulties in their children. Given the range of participation by school (12 to 88.5%), we do not believe that self-selection based on measures related to the study's outcome were strongly at play. Based on anecdotal evidence, we believe that low rates of participation (~12%) in some schools had to do with a general misperception of research studies by school officials and parents. Second, we assessed arsenic concentrations in one spot urine sample, which is a measure of short-term exposure. Similarly, diet was assessed by averaging two 24-hour dietary recalls, which may not reflect habitual intakes. In addition, we used the USDA database as well as the Uruguayan database to assess B-vitamin intake. Measurement error is possible, even though we matched as closely as possible the foods consumed by participants to those listed in the databases.

On the other hand, the strengths of our study include the use of CANTAB to assess different aspects of EF, from short-term memory to set shifting and planning ability. Many tests in the CANTAB are standardized and use non-verbal cues, which means they can be administered in any geographical area irrespective of the language. Because it is computerized, the CANTAB scores are minimally affected by the differences among testers. Our findings remained unchanged even after a series of additional analyses, thereby increasing confidence in the observed inferences, although unmeasured confounding cannot be ruled out completely. Finally, EF continue to develop well into adolescence (Juric et al. 2013), and our study captures an important part of this trajectory.

5. Conclusion

Among ~7 year-old children in Montevideo exposed to low levels of arsenic, we observed a small adverse effect of arsenic on test performance in the intra-dimensional/extra-dimensional shift task and the spatial span task of the CANTAB used to measure executive functions. There was no clear pattern of effect modification of this relationship by exposure to other metals, arsenic methylation capacity or B-vitamin intake.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Anderson P. Assessment and development of executive function (EF) during childhood. Child Neuropsychology 2002;8:71–82 [PubMed: 12638061]

Barg G; Daleiro M; Queirolo E; Ravenscroft J; Mañay N; Peregalli F; Kordas K. Association of Low Lead Levels with Behavioral Problems and Executive Function Deficits in Schoolers from Montevideo, Uruguay. International journal of environmental research and public health 2018;15:2735 [PubMed: 30518085]

Barkley RA Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychological Bulletin 1997;121:65 [PubMed: 9000892]

Bartels M; Rietveld MJ; Van Baal GCM; Boomsma DI Heritability of educational achievement in 12-year-olds and the overlap with cognitive ability. Twin Research and Human Genetics 2002;5:544–553

Bellinger D; Hu H; Titlebaum L; Needleman HL Attentional correlates of dentin and bone lead levels in adolescents. Archives of Environmental Health: An International Journal 1994;49:98–105

Blair C; Raver CC School readiness and self-regulation: A developmental psychobiological approach. Annual Review of Psychology 2015;66:711–731

Blankenship TL; Slough MA; Calkins SD; Deater-Deckard K; Kim-Spoon J; Bell MA Attention and Executive Functioning in Infancy: Links to Childhood Executive Function and Reading Achievement. Developmental science 2019:e12824

Bradley RH; Caldwell BM; Corwyn RF The Child Care HOME Inventories: Assessing the quality of family child care homes. Early Childhood Research Quarterly 2003;18:294–309

Calderon J; Navarro M; Jimenez-Capdeville M; Santos-Diaz M; Golden A; Rodriguez-Leyva I; Borja-Aburto V; Dıaz-Barriga F. Exposure to arsenic and lead and neuropsychological development in Mexican children. Environmental research 2001;85:69–76 [PubMed: 11161656]

Canfield RL; Henderson CR Jr; Cory-Slechta DA; Cox C; Jusko TA; Lanphear BP Intellectual impairment in children with blood lead concentrations below 10 μg per deciliter. New England Journal of Medicine 2003a;348:1517–1526 [PubMed: 12700371]

Canfield RL; Kreher DA; Cornwell C; Henderson CR Low-level lead exposure, executive functioning, and learning in early childhood. Child Neuropsychology 2003b;9:35–53 [PubMed: 12815521]

Challenger F. Biological methylation. Chemical Reviews 1945;36:315–361

Chattopadhyay S; Bhaumik S; Chaudhury AN; Gupta SD Arsenic induced changes in growth development and apoptosis in neonatal and adult brain cells in vivo and in tissue culture. Toxicology letters 2002a;128:73–84 [PubMed: 11869819]

Chattopadhyay S; Bhaumik S; Purkayastha M; Basu S; Chaudhuri AN; Gupta SD Apoptosis and necrosis in developing brain cells due to arsenic toxicity and protection with antioxidants. Toxicology letters 2002b;136:65–76 [PubMed: 12368058]

Chaudhuri AN; Basu S; Chattopadhyay S; Gupta SD Effect of high arsenic content in drinking water on rat brain. 1999;

Chiodo LM; Jacobson SW; Jacobson JL Neurodevelopmental effects of postnatal lead exposure at very low levels. Neurotoxicology and teratology 2004;26:359–371 [PubMed: 15113598]

Dajani DR; Uddin LQ Demystifying cognitive flexibility: Implications for clinical and developmental neuroscience. Trends in Neurosciences 2015;38:571–578 [PubMed: 26343956]

De Luca CR; Wood SJ; Anderson V; Buchanan J-A; Proffitt TM; Mahony K; Pantelis C. Normative data from the CANTAB. I: development of executive function over the lifespan. Journal of clinical and experimental neuropsychology 2003;25:242–254 [PubMed: 12754681]

Del Razo LM; Garcia-Vargas GG; Albores A; Vargas H; Gonsebatt M; Montero R; Ostrosky-Wegman P; Kelsh M; Cebrian M. Altered profile of urinary arsenic metabolites in adults with chronic arsenicism A pilot study. Archives of toxicology 1997;71:211–217 [PubMed: 9101036]

Desai G; Barg G; Queirolo EI; Vahter M; Peregalli F; Mañay N; Kordas K. 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. Environmental research 2018;164:124–131 [PubMed: 29486343]

Diamond A. Executive functions. Annual Review of Psychology 2013;64:135–168

Focazio MJ; Welch AH; Watkins SA; Helsel DR; Horn MA A retrospective analysis on the occurrence of arsenic in ground-water resources of the United States and limitations in drinking-water-supply characterizations. Geological Survey (US); 2000

Forns J; Fort M; Casas M; Caceres A; Guxens M; Gascon M; Garcia-Esteban R; Julvez J; Grimalt JO; Sunyer J. Exposure to metals during pregnancy and neuropsychological development at the age of 4 years. Neurotoxicology 2014;40:16–22 [PubMed: 24211492]

Freire C; Amaya E; Gil F; Fernandez MF; Murcia M; Llop S; Andiarena A; Aurrekoetxea J; Bustamante M; Guxens M; Ezama E; Fernandez-Tardon G; Olea N. Prenatal co-exposure to neurotoxic metals and neurodevelopment in preschool children: The Environment and Childhood (INMA) Project. Science of the Total Environment 2018;621:340–351 [PubMed: 29190557]

Fried R; Hirshfeld-Becker D; Petty C; Batchelder H; Biederman J. How informative is the CANTAB to assess executive functioning in children with ADHD? A controlled study. Journal of Attention Disorders 2015;19:468–475 [PubMed: 22923781]

Friedman NP; Miyake A; Corley RP; Young SE; DeFries JC; Hewitt JK Not all executive functions are related to intelligence. Psychological Science 2006;17:172–179 [PubMed: 16466426]

Froehlich TE; Lanphear BP; Dietrich KN; Cory-Slechta DA; Wang N; Kahn RS Interactive effects of a DRD4 polymorphism, lead, and sex on executive functions in children. Biological Psychiatry 2007;62:243–249 [PubMed: 17239353]

Funahashi S; Andreau JM Prefrontal cortex and neural mechanisms of executive function. Journal of Physiology Paris 2013;107:471–482 [PubMed: 23684970]

Fuster J. The prefrontal cortex ed^eds: Academic Press; 2015

Gamble MV; Liu X; Ahsan H; Pilsner JR; Ilievski V; Slavkovich V; Parvez F; Chen Y; Levy D; Factor-Litvak P. Folate and arsenic metabolism: a double-blind, placebo-controlled folic acid–supplementation trial in Bangladesh. The American Journal of Clinical Nutrition 2006;84:1093–1101 [PubMed: 17093162]

Gamble MV; Liu X; Ahsan H; Pilsner R; Ilievski V; Slavkovich V; Parvez F; Levy D; Factor-Litvak P; Graziano JH Folate, homocysteine, and arsenic metabolism in arsenic-exposed individuals in Bangladesh. Environ Health Perspectives 2005;113:1683–1688

Gamble MV; Liu X; Slavkovich V; Pilsner JR; Ilievski V; Factor-Litvak P; Levy D; Alam S; Islam M; Parvez F. Folic acid supplementation lowers blood arsenic. The American Journal of Clinical Nutrition 2007;86:1202–1209 [PubMed: 17921403]

Gau SSF; Shang CY Executive functions as endophenotypes in ADHD: evidence from the Cambridge Neuropsychological Test Battery (CANTAB). Journal of Child Psychology and Psychiatry 2010;51:838–849 [PubMed: 20085608]

George CM; Sima L; Arias M; Mihalic J; Cabrera LZ; Danz D; Checkley W; Gilman RH Arsenic exposure in drinking water: an unrecognized health threat in Peru. Bulletin of the World Health Organization 2014;92:565–572 [PubMed: 25177071]

Hall MN; Gamble MV Nutritional manipulation of one-carbon metabolism: effects on arsenic methylation and toxicity. Journal of Toxicology 2012;2012

Hall MN; Liu X; Slavkovich V; Ilievski V; Mi Z; Alam S; Factor-Litvak P; Ahsan H; Graziano JH; Gamble MV Influence of cobalamin on arsenic metabolism in Bangladesh. Environmental Health Perspectives 2009a;117:1724 [PubMed: 20049124]

Hall MN; Liu X; Slavkovich V; Ilievski V; Pilsner JR; Alam S; Factor-Litvak P; Graziano JH; Gamble MV Folate, cobalamin, cysteine, homocysteine, and arsenic metabolism among children in Bangladesh. Environmental Health Perspectives 2009b;117:825 [PubMed: 19479028]

Halterman JS; Kaczorowski JM; Aligne CA; Auinger P; Szilagyi PG Iron deficiency and cognitive achievement among school-aged children and adolescents in the United States. Pediatrics-English Edition 2001;107:1381–1386

Hamadani J; Tofail F; Nermell B; Gardner R; Shiraji S; Bottai M; Arifeen S; Huda SN; Vahter M. Critical windows of exposure for arsenic-associated impairment of cognitive function in pre-school girls and boys: a population-based cohort study. International Journal of Epidemiology 2011;40:1593–1604 [PubMed: 22158669]

Health AAo.P.C.o.E. Lead exposure in children: prevention, detection, and management. Pediatrics 2005;116:1036 [PubMed: 16199720]

Howe CG; Li Z; Zens MS; Palys T; Chen Y; Channon JY; Karagas MR; Farzan SF Dietary B Vitamin Intake Is Associated with Lower Urinary Monomethyl Arsenic and Oxidative Stress Marker 15-F2t-Isoprostane among New Hampshire Adults. The Journal of nutrition 2017;147:2289–2296 [PubMed: 29070711]

Hsieh R-L; Huang Y-L; Shiue H-S; Huang S-R; Lin M-I; Mu S-C; Chung C-J; Hsueh Y-M Arsenic methylation capacity and developmental delay in preschool children in Taiwan. International journal of hygiene and environmental health 2014;217:678–686 [PubMed: 24698386]

Hughes C; Plumet M-H; Leboyer M. Towards a cognitive phenotype for autism: increased prevalence of executive dysfunction and superior spatial span amongst siblings of children with autism. The Journal of Child Psychology and Psychiatry and Allied Disciplines 1999;40:705–718 [PubMed: 10433405]

Hughes C; Russell J; Robbins TW Evidence for executive dysfunction in autism. Neuropsychologia 1994;32:477–492 [PubMed: 8047253]

Instituto de Nutrición de Centro América y Panamá (INCAP); Organización Panamericana de la salud (OPS). Tabla de Composición de Alimentos de Centroamérica. 2012

Instituto Nacional de Alimentación (INDA). Manual de alimentación para las familias uruguayas. 2010

Jáuregui-Lobera I. Iron deficiency and cognitive functions. Neuropsychiatric Disease and Treatment 2014;10:2087 [PubMed: 25419131]

Jensen AR The g factor: The science of mental ability ed^eds: Praeger Westport, CT; 1998

Juric LC; Richards MM; Introzzi I; Andrés ML; Urquijo S. Development patterns of executive functions in children. The Spanish Journal of Psychology 2013;16

Kaiser J. Dealing with missing values in data. Journal of Systems Integration 2014;5:42–51

Kannan GM; Tripathi N; Dube SN; Gupta M; Flora S; Flora SJ Toxic effects of arsenic (III) on some hematopoietic and central nervous system variables in rats and guinea pigs. Journal of Toxicology: Clinical Toxicology 2001;39:675–682 [PubMed: 11778665]

Kempton S; Vance A; Maruff P; Luk E; Costin J; Pantelis C. Executive function and attention deficit hyperactivity disorder: stimulant medication and better executive function performance in children. Psychological Medicine 1999;29:527–538 [PubMed: 10405075]

Kippler M; Ekström E-C; Lönnerdal B; Goessler W; Åkesson A; El Arifeen S; Persson L-Å; Vahter M. Influence of iron and zinc status on cadmium accumulation in Bangladeshi women. Toxicology and Applied Pharmacology 2007;222:221–226 [PubMed: 17543360]

Kippler M; Nermell B; Hamadani J; Tofail F; Moore S; Vahter M. Burden of cadmium in early childhood: longitudinal assessment of urinary cadmium in rural Bangladesh. Toxicology letters 2010;198:20–25 [PubMed: 20466048]

Kippler M; Tofail F; Hamadani JD; Gardner RM; Grantham-McGregor SM; Bottai M; Vahter M. Early-life cadmium exposure and child development in 5-year-old girls and boys: a cohort study in rural Bangladesh. Environmental health perspectives 2012;120:1462–1468 [PubMed: 22759600]

Kordas K; Burganowski R; Roy A; Peregalli F; Baccino V; Barcia E; Mangieri S; Ocampo V; Manay N; Martinez G; Vahter M; Queirolo EI Nutritional status and diet as predictors of children's lead concentrations in blood and urine. Environ Int 2018;111:43–51 [PubMed: 29172090]

Kordas K; Queirolo EI; Ettinger AS; Wright RO; Stoltzfus RJ Prevalence and predictors of exposure to multiple metals in preschool children from Montevideo, Uruguay. Science of the Total Environment 2010;408:4488–4494 [PubMed: 20619443]

Kordas K; Queirolo EI; Mañay N; Peregalli F; Hsiao PY; Lu Y; Vahter M. Low-level arsenic exposure: Nutritional and dietary predictors in first-grade Uruguayan children. Environmental research 2016;147:16–23 [PubMed: 26828624]

Lanphear BP; Dietrich K; Auinger P; Cox C. Cognitive deficits associated with blood lead concentrations< 10 microg/dL in US children and adolescents. Public Health Reports 2000;115:521 [PubMed: 11354334]

Löveborn HS; Kippler M; Lu Y; Ahmed S; Kuehnelt D; Raqib R; Vahter M. Arsenic metabolism in children differs from that in adults. Toxicological Sciences 2016:kfw060

Luciana M. Practitioner review: computerized assessment of neuropsychological function in children: clinical and research applications of the Cambridge Neuropsychological Testing Automated Battery (CANTAB). Journal of Child Psychology and Psychiatry 2003;44:649–663 [PubMed: 12831110]

Luciana M; Nelson C. Neurodevelopmental assessment of cognitive function using the Cambridge Neuropsychological Testing Automated Battery (CANTAB): validation and future goals. Functional Neuroimaging in Child Psychiatry Cambridge University Press, Cambridge 2000:379–397

Luciana M; Nelson CA Assessment of neuropsychological function through use of the Cambridge Neuropsychological Testing Automated Battery: performance in 4-to 12-year-old children. Developmental Neuropsychology 2002;22:595–624 [PubMed: 12661972]

Mañay N; Cousillas AZ; Alvarez C; Heller T. Lead contamination in Uruguay: the “La Teja” neighborhood case. Reviews of Environmental Contamination and Toxicology: Springer; 2008

Mason JB Biomarkers of nutrient exposure and status in one-carbon (methyl) metabolism. The Journal of nutrition 2003;133:941S–947S [PubMed: 12612180]

Nagaraja T; Desiraju T. Effects on operant learning and brain acetylcholine esterase activity in rats following chronic inorganic arsenic intake. Human & experimental toxicology 1994;13:353–356 [PubMed: 8043317]

Naujokas MF; Anderson B; Ahsan H; Aposhian HV; Graziano JH; Thompson C; Suk WA The broad scope of health effects from chronic arsenic exposure: update on a worldwide public health problem. Environmental Health Perspectives 2013;121:295 [PubMed: 23458756]

Navas-Acien A; Francesconi KA; Silbergeld EK; Guallar E. Seafood intake and urine concentrations of total arsenic, dimethylarsinate and arsenobetaine in the US population. Environmental research 2011;111:110–118 [PubMed: 21093857]

Neisser U; Boodoo G; Bouchard TJ Jr; Boykin AW; Brody N; Ceci SJ; Halpern DF; Loehlin JC; Perloff R; Sternberg RJ Intelligence: Knowns and unknowns. American Psychologist 1996;51:77

Peters BA; Hall MN; Liu X; Parvez F; Sanchez TR; van Geen A; Mey JL; Siddique AB; Shahriar H; Uddin MN Folic acid and creatine as therapeutic approaches to lower blood arsenic: a randomized controlled trial. Environmental Health Perspectives (Online) 2015;123:1294

Potter GG; McQuoid DR; Payne ME; Taylor WD; Steffens DC Association of attentional shift and reversal learning to functional deficits in geriatric depression. International Journal of Geriatric Psychiatry 2012;27:1172–1179 [PubMed: 22271429]

Pu Y-S; Yang S-M; Huang Y-K; Chung C-J; Huang SK; Chiu AW-H; Yang M-H; Chen C-J; Hsueh Y-M Urinary arsenic profile affects the risk of urothelial carcinoma even at low arsenic exposure. Toxicology and Applied Pharmacology 2007;218:99–106 [PubMed: 17196235]

Queirolo EI; Ettinger AS; Stoltzfus RJ; Kordas K. Association of anemia, child and family characteristics with elevated blood lead concentrations in preschool children from Montevideo, Uruguay. Archives of Environmental & Occupational Health 2010;65:94–100 [PubMed: 20439228]

Raml R; Rumpler A; Goessler W; Vahter M; Li L; Ochi T; Francesconi KA Thio-dimethylarsinate is a common metabolite in urine samples from arsenic-exposed women in Bangladesh. Toxicology and Applied Pharmacology 2007;222:374–380 [PubMed: 17276472]

Rasmussen C; Soleimani M; Pei J. Executive functioning and working memory deficits on the CANTAB® among children with prenatal alcohol exposure. Journal of Population Therapeutics and Clinical Pharmacology 2011;18

Robbins T. Chemical neuromodulation of frontal-executive functions in humans and other animals. Experimental Brain Research 2000;133:130–138 [PubMed: 10933217]

Rodríguez-Barranco M; Lacasaña M; Aguilar-Garduño C; Alguacil J; Gil F; González-Alzaga B; Rojas-García A. Association of arsenic, cadmium and manganese exposure with neurodevelopment and behavioural disorders in children: a systematic review and meta-analysis. Science of the Total Environment 2013;454:562–577 [PubMed: 23570911]

Rodriguez VM; Jimenez-Capdeville ME; Giordano M. The effects of arsenic exposure on the nervous system. Toxicology letters 2003;145:1–18 [PubMed: 12962969]

Roque DT; Teixeira RAA; Zachi EC; Ventura DF The use of the Cambridge Neuropsychological Test Automated Battery (CANTAB) in neuropsychological assessment: application in Brazilian research with control children and adults with neurological disorders. Psychology & Neuroscience 2011;4:255–265

Schmeisser E; Goessler W; Francesconi KA Human metabolism of arsenolipids present in cod liver. Analytical and bioanalytical chemistry 2006;385:367–376 [PubMed: 16568291]

Signes-Pastor A; Vioque J; Navarrete-Muñoz E; Carey M; García-Villarino M; Fernández-Somoano A; Tardón A; Santa-Marina L; Irizar A; Casas M. Inorganic arsenic exposure and neuropsychological development of children of 4–5 years of age living in Spain. Environmental research 2019;174:135–142 [PubMed: 31075694]

Steinmaus C; Bates MN; Yuan Y; Kalman D; Atallah R; Rey OA; Biggs ML; Hopenhayn C; Moore LE; Hoang BK Arsenic methylation and bladder cancer risk in case–control studies in Argentina and the United States. Journal of Occupational and Environmental Medicine 2006;48:478–488 [PubMed: 16688004]

Steinmaus C; Carrigan K; Kalman D; Atallah R; Yuan Y; Smith AH Dietary intake and arsenic methylation in a US population. Environmental Health Perspectives 2005;113:1153 [PubMed: 16140620]

Sternberg RJ; Grigorenko E; Bundy DA The predictive value of IQ. Merrill-Palmer Quarterly 2001;47:1–41

Surkan PJ; Zhang A; Trachtenberg F; Daniel DB; McKinlay S; Bellinger DC Neuropsychological function in children with blood lead levels< 10 μg/dL. Neurotoxicology 2007;28:1170–1177 [PubMed: 17868887]

Tripathi N; Kannan G; Pant B; Jaiswal D; Malhotra P; Flora S. Arsenic-induced changes in certain neurotransmitter levels and their recoveries following chelation in rat whole brain. Toxicology letters 1997;92:201–208 [PubMed: 9334831]

Tyler CR; Allan AM The effects of arsenic exposure on neurological and cognitive dysfunction in human and rodent studies: a review. Current Environmental Health Reports 2014;1:132–147 [PubMed: 24860722]

USDA. United States Department of Agriculture Food Composition Database. 2018

Vahter M. Mechanisms of arsenic biotransformation. Toxicology 2001;181:211–217

Vahter ME Interactions between arsenic-induced toxicity and nutrition in early life. The Journal of nutrition 2007;137:2798–2804 [PubMed: 18029502]

Valkonen S; Savolainen H; Järvisalo J. Arsenic distribution and neurochemical effects in peroral sodium arsenite exposure of rats. Bulletin of Environmental Contamination and Toxicology 1983;30:303–308 [PubMed: 6687817]

Wasserman GA; Liu X; Loiacono NJ; Kline J; Factor-Litvak P; van Geen A; Mey JL; Levy D; Abramson R; Schwartz A; Graziano JH A cross-sectional study of well water arsenic and child IQ in Maine schoolchildren. Environmental Health 2014;13:23 [PubMed: 24684736]

Wasserman GA; Liu X; Parvez F; Ahsan H; Factor-Litvak P; Kline J; Van Geen A; Slavkovich V; Lolacono NJ; Levy D. Water arsenic exposure and intellectual function in 6-year-old children in Araihazar, Bangladesh. Environmental Health Perspectives 2007:285–289 [PubMed: 17384779]

Wasserman GA; Liu X; Parvez F; Factor-Litvak P; Ahsan H; Levy D; Kline J; van Geen A; Mey J; Slavkovich V. Arsenic and manganese exposure and children's intellectual function. Neurotoxicology 2011;32:450–457 [PubMed: 21453724]

Welsh JA; Nix RL; Blair C; Bierman KL; Nelson KE The development of cognitive skills and gains in academic school readiness for children from low-income families. Journal of Educational Psychology 2010;102:43 [PubMed: 20411025]

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 Effect of plasma homocysteine level and urinary monomethylarsonic acid on the risk of arsenic-associated carotid atherosclerosis. Toxicology and Applied Pharmacology 2006;216:168–175 [PubMed: 16806340]

Xi S; Guo L; Qi R; Sun W; Jin Y; Sun G. Prenatal and early life arsenic exposure induced oxidative damage and altered activities and mRNA expressions of neurotransmitter metabolic enzymes in offspring rat brain. Journal of Biochemical and Molecular Toxicology 2010;24:368–378 [PubMed: 20376865]

Zhang Z. Missing data imputation: focusing on single imputation. Annals of Translational Medicine 2016;4

Table 1:

Sociodemographic, biochemical, and dietary characteristics of study participants

Variables	N	All participants
Age, months		
Median (range)	255	81 (57, 105)
Sex	255	
Girls, n (%)		111 (43.5)
Boys, n (%)		144 (56.5)
Maternal Education		
Years, median (range)	255	8 (4, 17)
HOME score[1]	255	
≤ 46, n (%)		133 (52.2)
> 46, n (%)		122 (47.8)
Household possessions score[2]	255	
≤ 3, n (%)		110 (43.1)
> 3, n (%)		145 (56.9)
Water arsenic, μg/L		
Median (range)	255	0.45 (0.1, 18.9)
Water arsenic, μg/L		
Median (range)	255	0.45 (0.1, 18.9)
Total urinary arsenic[3], μg/L		
Median (range)	255	9.89 (2.2, 47.7)
%MMA[4]		
Median (range)	255	9.68 (2.6, 24.8)
Vitamin B-1, mg/1000 kcal		
Median (range)	249	0.83 (0.2, 2.6)
Vitamin B-2, mg/1000 kcal		
Median (range)	249	1.00 (0.3, 2.2)
Vitamin B-3, mg/1000 kcal		
Median (range)	249	8.61 (3.7, 23.3)
Vitamin B-6, mg/1000 kcal		
Median (range)	249	0.68 (0.3, 1.7)
Folate, μg/1000 kcal		
Median (range)	249	214.1 (75.1, 466.5)
Vitamin B-12, μg/1000 kcal		
Median (range)	249	1.7 (0.3, 8.3)

[1]Home Observation for Measurement of the Environment Inventory score, split at median,

[2]Spit at median,

[3]Measured as sum of urinary inorganic arsenic, monomethylarsonous acid, and dimethylarsinic acid; adjusted for urinary specific gravity,

[4]Monomethylarsonous acid

Table 2:

Associations between arsenic exposure[a] and performance on three tasks of the CANTAB

Domain of Executive Function	CANTAB test	Outcome	Crude β (95% CI) N=255	Adjusted[1] β (95% CI) N=255	Adjusted[2] β (95% CI) N=241
Planning	Stockings of Cambridge	# Problems solved in minimum moves	−0.003 (−0.03, 0.03)	0.00043 (−0.02, 0.02)	−0.03 (−0.07, 0.01)
Rule Learning and Reversal, visual attention, shifting	Intra – Extra Dimensional Set Shift	# Stages completed	−0.01 (−0.03, 0.001)	**−0.02 (−0.03, −0.002)**	**−0.02 (−0.03, −0.002)**
		Total # errors	0.13 (−0.16, 0.43)	0.20 (−0.17, 0.57)	0.22 (−0.17, 0.61)
		# Pre- Executive Shift Error	−0.08 (−0.15, 0.004)	**−0.08 (−0.14, −0.02)**	**−0.07 (−0.13, −0.01)**
		# Post-Executive Shift Error	0.12 (−0.03, 0.27)	0.15 (−0.05, 0.35)	0.14 (−0.08, 0.35)
Working memory	Spatial Span	Span length	−0.01 (−0.03, 0.001)	**−0.01 (−0.02, −0.004)**	**−0.02 (−0.02, −0.01)**
		SS Total errors	−0.03 (−0.09, 0.03)	−0.01 (−0.06, 0.03)	−0.03 (−0.07, 0.01)

[a]Modeled as specific gravity-adjusted sum of urinary inorganic arsenic, monomethylarsonous acid, and dimethylarsinic acid;

[1]Adjusted for age, sex, maternal education, possessions score, Home Observation for Measurement of the Environment Inventory score, season, school clusters;

[2]further adjusted for blood lead, hemoglobin, urinary cadmium and hair manganese levels.

Table 3:

Associations between arsenic exposure[a] and performance on three tasks of the CANTAB, stratified by urinary %MMA and intake of B-vitamins

CANTAB test	Outcome	%MMA (n=228)		B-vitamin index (n=249)		Folate intake[b] (n=249)	
		Efficient methylators (n=115)	Inefficient methylators (n=113)	Low (n=124)	High (n=125)	Low (n=125)	High (n=124)
Stockings of Cambridge	# Problems solved in minimum moves	−0.03 (−0.07, 0.01)	0.01 (−0.01, 0.04)	−0.03 (−0.08, 0.02)	0.02 (−0.01, 0.04)	−0.01 (−0.05, 0.03)	0.004 (−0.02, 0.03)
Intra – Extra Dimensional Set Shift	# Stages completed	−0.02 (−0.03, 0.0001)	−0.002 (−0.02, 0.02)	−0.02 (−0.04, 0.01)	−0.01 (−0.02, 0.003)	−0.01 (−0.03, 0.01)	−0.02 (−0.04, −0.01)
	Total # errors	0.30 (−0.08, 0.69)	−0.13 (−0.53, 0.28)	0.26 (−0.29, 0.81)	0.03 (−0.18, 0.25)	0.05 (−0.42, 0.52)	0.46 (0.08, 0.84)
	# Pre- Executive Shift Error	−0.05 (−0.11, 0.02)	−0.12 (−0.24, 0.0001)	−0.07 (−0.12, −0.02)	−0.09 (−0.17, −0.01)	**−0.15 (−0.26, −0.05)**	**0.004 (−0.04, 0.05)**
	# Post-Executive Shift Error	0.18 (0.002, 0.26)	0.01 (−0.31, 0.33)	0.17 (−0.05, 0.40)	0.07 (−0.11, 0.25)	0.08 (−0.21, 0.37)	0.23 (0.04, 0.43)
Spatial Span	Span length	−0.02 (−0.03, −0.005)	0.002 (−0.01, 0.01)	−0.02 (−0.04, 0.002)	−0.004 (−0.01, 0.004)	−0.01 (−0.02, −0.01)	−0.01 (−0.03, 0.004)
	Spatial Span Total errors	−0.03 (−0.09, 0.02)	0.02 (−0.06, 0.11)	−0.04 (−0.13, 0.04)	0.02 (−0.02, 0.05)	0.02 (−0.04, 0.07)	−0.08 (−0.13, −0.02)

[a] Modeled as specific gravity-adjusted sum of urinary inorganic arsenic, monomethylarsonous acid, and dimethylarsinic acid,

[b] adjusted for total energy intake and expressed as grams/1000 kcal; Models adjusted for age, sex, maternal education, possessions score, Home Observation for Measurement of the Environment Inventory score, season, school clusters