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Low-level arsenic exposure: nutritional and dietary predictors in first-grade Uruguayan children

Katarzyna Kordas[1,2], **Elena I Queirolo**[3], **Nelly Mañay**[4], **Fabiana Peregalli**[3], **Pao Ying Hsiao**[5], **Ying Lu**[6], and **Marie Vahter**[6]

[1]School of Social and Community Medicine, University of Bristol, Bristol, UK

[2]Department of Nutritional Sciences, Pennsylvania State University, University Park, PA, USA

[3]Center for Research, Catholic University of Uruguay, Montevideo, Uruguay

[4]Faculty of Chemistry, University of the Republic of Uruguay, Montevideo, Uruguay

[5]Department of Food and Nutrition, Indiana University of Pennsylvania, Indiana, PA, USA

[6]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Abstract

Arsenic exposure in children is a public health concern but is understudied in relation to the predictors, and effects of low-level exposure. We examined the extent and dietary predictors of exposure to inorganic arsenic in 5–8 year old children from Montevideo, Uruguay. Children were recruited at school; 357 were enrolled, 328 collected morning urine samples, and 317 had two 24-hour dietary recalls. Urinary arsenic metabolites, i.e. inorganic arsenic (iAs), methylarsonic acid (MMA), and dimethylarsinic acid (DMA), were measured using high-performance liquid chromatography with hydride generation and inductively coupled plasma mass spectrometry (HPLC-HG-ICP-MS), and the sum concentration (U-As) used for exposure assessment. Proportions of arsenic metabolites (%iAs, %MMA and %DMA) in urine were modelled in OLS regressions as functions of food groups, dietary patterns, nutrient intake, and nutritional status. Exposure to arsenic was low (median U-As: 9.9 μg/L) and household water (water As: median 0.45 μg/L) was not a major contributor to exposure. Children with higher consumption of rice had higher U-As but lower %iAs, %MMA, and higher %DMA. Children with higher meat consumption had lower %iAs and higher %DMA. Higher scores on ”nutrient dense” dietary pattern were related to lower %iAs and %MMA, and higher %DMA. Higher intake of dietary folate was associated with lower %MMA and higher %DMA. Overweight children had lower %MMA and higher %DMA than normal-weight children. In summary, rice was an important predictor of exposure to inorganic arsenic and DMA. Higher meat and folate consumption, diet rich in green leafy and red-orange vegetables and eggs, and higher BMI contributed to higher arsenic methylation capacity.

Corresponding author: Katarzyna Kordas, PhD, School of Social and Community Medicine, University of Bristol, Oakfield House, Oakfield Grove, Bristol BS8 2BN, United Kingdom, Kasia.kordas@bristol.ac.uk.

Keywords

Urinary arsenic; child; predictors; Uruguay

INTRODUCTION

The health effects of exposure to inorganic arsenic, a highly toxic and carcinogenic element, in adults are well documented (ATSDR 2007), whereas children's exposure is less well studied. Nevertheless, arsenic exposure in children is a public health concern because of its potential negative effects on growth and development (ATSDR 2007, Naujokas, Anderson et al. 2013), with both preschool (Hamadani, Tofail et al. 2011, Hsieh, Huang et al. 2014) and school (Wasserman, Liu et al. 2004, Rosado, Ronquillo et al. 2007) children experiencing cognitive deficits.

Arsenic exposure is common, from sources such as contaminated drinking water and industrial activities (Tolins, Ruchirawat et al. 2014), and an estimated 200 million people worldwide are affected from drinking water alone. Based on its abundance, toxicity and potential for exposure, arsenic poses significant threat to human health (ATSDR 2011). Certain food may also contribute to inorganic arsenic exposure. In Europe, processed grain products, rice, milk and dairy are the main contributors of inorganic arsenic in food (EFSA 2014), including baby foods (Meharg, Sun et al. 2008, Ljung, Palm et al. 2011, Rintala, Ekholm et al. 2014). Furthermore, higher consumption of fish, fruits, grains, legumes, meat and rice was associated with higher concentrations of urinary arsenic in the NHANES study (Rey deCastro, Caldwell et al. 2014). Among US children (6–17 years of age), urinary arsenic increased significantly with each cup of rice consumed (Davis, Mackenzie et al. 2012).

The role of nutrients in arsenic metabolism has also been studied, focusing on folate and other B-vitamins (Gamble, Liu et al. 2006, Gamble, Liu et al. 2007, Hall, Liu et al. 2009, Argos, Rathouz et al. 2010, Peters, Hall et al. 2015), but many of these studies were carried out in Bangladeshi adults with elevated arsenic exposure through drinking water and there is limited understanding of these relationships in children, especially with different exposure situations and dietary preferences.

The objectives of this study were to: 1) determine the extent of exposure to inorganic arsenic, 2) clarify whether drinking water is an important source of exposure, and 3) investigate the influence of nutritional status, nutrient intake, and diet on urinary arsenic concentrations in a group of 5–8 year old children in Montevideo, Uruguay.

METHODS

Study setting

The study was conducted in Montevideo, the capital of Uruguay. Children in Montevideo are exposed to multiple toxic metals including lead, arsenic, cadmium, and manganese (Mañay, Cousillas et al. 2008, Kordas, Queirolo et al. 2010). Still, the problem of metal exposure in children (perhaps with the exception of lead) has received limited attention. Arsenic is

emitted from municipal and hazardous waste incineration, metal smelting, glass manufacturing and mining, as well as agricultural chemical production and application (EPA. 2000). Although some of these industries are present in Montevideo, the specific sources of arsenic contamination are not well characterized. Water, an important source of exposure, is generally delivered to households via the state provider, and arsenic concentrations are closely monitored.

Participant Recruitment

The study was carried out in private elementary schools in several Montevideo neighbourhoods, between November 2009 and August 2013, with recruitment methodology described elsewhere (Roy, Queirolo et al. 2015). In addition to media advertising, private elementary schools in the selected neighbourhoods were contacted to gauge interest in participation, and when agreed, informational meetings were scheduled for parents. All first grade children regularly attending the participating schools were eligible. The sole exclusion criterion was a blood lead level >45 μg/dL, based on parental report of any previous assessments carried out by paediatricians or specialist clinics; none of the children were excluded.

Of the 673 eligible children from 11 participating schools, 357 children (53%), aged 6 – 9 years, and their mothers were enrolled upon providing written consent. Of those, 332 provided urine samples, and arsenic species could be determined in 328 samples.

The study was approved by the Ethics Committee for Research Involving Human Participants at the Catholic University of Uruguay and the Office of Research Protections at the Pennsylvania State University.

Assessments

Caregivers completed questionnaires about family socio-demographic characteristics, child's medical history and home environment, including questions on crowding at home and family possessions of household items like TV, video, telephone, refrigerator, etc.

Two 24-hour dietary recalls were conducted by trained nutritionists with the mother or another caregiver familiar with the child's diet. The child was present at the time and contributed to the recall. One recall took place at the school and the second over the phone without prior appointment, at least 2 weeks later, either on a weekday or a weekend. Neutral probing questions were asked and photographs and models of foods, plates and serving/eating utensils were presented to aid in the estimation of serving sizes. All foods were assigned a unique code and entered, along with amounts consumed into a database containing the nutrient composition of typical Uruguayan foods and preparations, and considering current mineral fortification laws in Uruguay.

Children's height was measured in triplicate to the nearest of 0.1 cm, using a portable stadiometer (Seca 214, Shorr Productions, Colombia, MD). They were weighed without shoes in light clothing, in triplicate to the nearest 0.1 kg using a digital scale (Seca 872, Shorr Productions, Colombia, MD). BMI for age z-scores (BAZ) were derived using the WHO AnthroPlus (http://www.who.int/growthref/tools/en/).

Approximately 3 ml of fasting blood was collected by a phlebotomy nurse at the school (8 – 11 am), using a 25-gauge safety butterfly blood collection set (Vacutainer, Becton Dickinson, Franklin Lakes, NJ) into a serum tube with clot activator and separator gel (Becton Dickinson, Franklin Lakes, NJ). Samples were left to stand for 45 min, centrifuged 10 min at 3000 rpm, and later stored at −20°C at the Research Center, Catholic University of Uruguay.

Hemoglobin (Hb) was measured at the time of the blood draw using a portable hemoglobinometer (HemoCue Inc, Lake Forest, CA). Serum ferritin (SF) concentrations were determined in duplicate using one of two methods, according to manufacturer instructions: 1) an immunoradiometric assay (Coat-A-Count Ferritin IRMA; SIEMENS Diagnostic Products, USA) and 2) an enzyme immunoassay (Spectro Ferritin, RAMCO Laboratories, Texas, USA). The ELISA assay was used when the laboratory no longer had the capability to handle radioactive materials. Intra- and inter-assay coefficients (CV) were 4.2% & 9.5% respectively for the IRMA method and 1.7% and 7.6% for the ELISA method. The use of different assays was addressed by deriving a correction factor, with the IRMA method serving as gold standard, and both values being log-transformed prior to the derivation step, and back-transformed for the main analysis.

Children provided first void urine samples on the morning of the clinic in screw-top cups previously rinsed with 10% HNO_3 and deionized water. The samples were transported on ice to the Center for Research, Catholic University of Uruguay, and stored at −20°C in 10 mL plastic tubes also rinsed as above.

Individual arsenic exposure was assessed based on the concentration of inorganic arsenic (iAs) and its methylated metabolites in urine (MMA and DMA). The sum of arsenic species (iAs, MMA and DMA), hereinafter referred to as U-As, reflects exposure to inorganic arsenic from all sources. The concentrations of arsenic species were 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). Briefly, the separation of the metabolites of inorganic arsenic (i.e. arsenite As(III) and arsenate As(V)), methylarsonic acid (MMA(V)) and dimethylarsinic acid (DMA(V)) was performed by Agilent 1100 series HPLC system (Agilent Technologies, Waldbronn, Germany), with an anion exchange column (Hamilton PRP X-100, 10 μm, 250 × 4.6 mm) and 10 μL injection volume. The LC separation was online with HG and ICP-MS (Agilent 7500ce, Agilent Technologies, Tokyo, Japan) and operated as described previously (Li, Ekstrom et al. 2008, Gardner, Hamadani et al. 2011). Standard solutions of the four arsenic species were prepared from sodium arsenite (Purum p.a., ≥99.0%; Fluka Chemika, Switzerland), sodium hydrogenarsenate hepahydrate (98+%, A.C.S. reagent, Aldrich Chemical Company, WI, USA), sodium dimethylarsinate trihydate (Merck, Schuchardt, Germany), and disodium methylarsenate hexahydrate (>97.5 %, Supelco, Bellefonte, PA, USA). The working standard solutions (one for each arsenic metabolite) were gravimetrically prepared fresh daily for 7-points calibration curves. The limit of detection (LOD) was 0.1 μg/L for inorganic As (III) and MMA, 0.2 μg/L for DMA, and 0.3–0.5 μg/L for inorganic As (V). The intra- and inter-assay CVs were ~4%. Seven of the urine samples (2.1%) were below LOD

for As(III) and 26(7.9%) were below LOD for AS(V). We used the measured values in statistical analyses.

For quality control, we analyzed NIES CRM (National Institute for Environmental Studies, Japan; Certified Reference Material) No. 18 human urine. The certified value for DMA was 36 ± 9 μg/L and our mean measured value was 45 ± 3 (n=20, measured in two days), which is in agreement with previous studies (Scheer, Findenig et al. 2012, Ahmed, Moore et al. 2014).

To compensate for the variation in dilution of the urine samples, U-As was adjusted the average specific gravity (SG, Mean [range]: 1.02 [1.00 – 1.04]), measured by a digital refractometer (RD 712 Clinical Refractometer, EUROMEX microscopes, Holland). Adjustment by SG is less affected by body size, socioeconomic status and arsenic exposure, than creatinine adjustment (Nermell, Lindberg et al. 2008).

Household water was collected directly from the kitchen taps or water storage containers (Carreón Valencia, López Carillo, Romieu 1995) and passed through a 0.45 μm filter (VWR International, PA, USA) into a plastic bottle, previously rinsed with 10% nitric acid and deionized water. The pH was measured adjusted to < 2 with nitric acid. The samples were analyzed for As and Fe by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) with Collision Cell Technology (Thermo Scientific XSERIES 2, Bremen, Germany). The detection limits were 0.03 μg/L for As and 0.7 μg/L for Fe.

Statistical analyses

Variable handling and construction—Anemia was defined as Hb <11.5 g/L, but due to low prevalence, further analyses were conducted with Hb split at the median. Iron deficiency (ID) was defined as SF <15 ng/mL. Mothers reported on whether they, their partners, or both had jobs potentially associated with metal exposure (foundry worker, mechanic, painter, print shop worker, plumber, car battery recycler, etc.). A variable representing any potential exposure was constructed. Mothers reported on family ownership of 15 household items and their responses were entered into a factor analysis. A single factor index of socioeconomic status was created, retaining 5 items with factor loadings >0.3: computer, car, refrigerator, washing machine and household phone. This measure (range 0–5) was at the median.

For the intake of iron, total folate, energy, and proportion of energy from fat, protein and carbohydrates, values from the two recalls were averaged. Where a single recall was collected, that single value was used. Because nutrient intake depends on total energy intake, iron and folate intake was represented on a per-1000 kcal basis. The distribution of intakes was not normal and was split at the median for analysis. Based on published literature (EFSA 2014, Rey deCastro, Caldwell et al. 2014) several food groups were created for analysis: meats (red and white meats), grain and wheat-based foods (flours, rice, oats, granola, cereal bars, polenta, grain-based dishes, pasta, breads, pizza, dinner pies), dairy (milk, cheese, yogurt), and fruit. The intake of rice was also analyzed separately. Fish and legumes were not considered due to low intakes. The distribution of intakes was skewed and included a large proportion of non-consumers; these variables were dichotomized at the median. Two food patterns were identified: 1) “processed foods”—higher consumption of

breads, processed meats, fats and oils, and sweetened beverages, but also of yogurt; reduced intake of milk, pastries and pizza dinners; 2) “nutrient dense”—higher consumption of dark leaf and red-orange vegetables, higher consumption of eggs, beans & peas, potatoes; reduced consumption of pasta and sauces/condiments. Factor scores were dichotomized at the median.

Predictors of urinary arsenic concentrations—The concentrations of U-As and inorganic arsenic metabolites were examined using descriptive statistics. Ordinary least squares (OLS) regressions were used to test the extent to which water, nutritional status, nutrient intake and diet (foods and dietary patterns) predicted urinary arsenic species by modeling urinary arsenic concentrations as dependent variables and water arsenic and nutritional variables as independent predictors. Few consistent sex differences were found in stratified analyses so results from the full sample are presented. Covariates included age, sex, BMI, crowding, household possessions, source of drinking water, and location of the school. All models for % metabolites were adjusted for U-As. Models including nutrient or dietary variables were adjusted for season of recall.

RESULTS

The sample consisted of roughly equal numbers of boys and girls with a mean age of 6.7 years (Table 1). Most of the mothers (~60%) reported some secondary education; 30% were unemployed/stay-at-home. The 328 children included in the study generally did not differ from those who were excluded. However, those who provided urine samples were more likely to have parents with potential occupational exposure to metals (27.8 vs. 6.4%, $p<0.01$).

Children’s exposure to arsenic from water was low, and only two individuals had water arsenic levels above the WHO guideline of 10 μg/L (Table 2). Potential daily ingestion of arsenic from water was estimated based on mean [95% CI] daily tap water intake (315 [264, 366] mL), and the median and mean water arsenic concentrations (0.61 and 0.45 μg/L, respectively) found in the present study. The potential intake of inorganic arsenic from tap water was low, 0.1–0.2 μg/day.

Most study children had detectable concentrations of arsenic metabolites in urine; the median U-As being 9.9 μg/L (Table 2; range of values: 1.5 – 48.7 μg/L). Inorganic arsenic (iAs) made up ~11% of the measured species, MMA ~10%, and DMA ~79%. The concentrations of iAs (rho=0.63, $p<0.01$), MMA (0.79, $p<0.01$) and DMA (0.99, $p<0.01$) were correlated with U-As. The %iAs and %MMA were lower (β [95% CI]: −0.28 [−0.36, − 0.21] and −0.10 [−0.15, −0.05], respectively, $p<0.01$), and %DMA was higher in children with higher U-As (β [95% CI]: 0.39 [0.29, 0.48], $p<0.01$). There were no differences between boys and girls. Arsenic concentrations in drinking water were not associated with urinary arsenic species (Supplemental Figure 1); children who consumed bottled water had slightly higher %iAs and lower %DMA than those drinking tap water (Supplemental Table 1).

The consumption of foods potentially affecting arsenic exposure was relatively low (median [5%, 95%]): rice (0 [0, 50] g/day), wheat and grain products (272 [100, 540] g/day), red and white meat (50 [0, 195] g/day), dairy (400 [120, 695] g/day), fruit (100 [0, 390] g/day). Girls and boys differed on the consumption of wheat and grain based products (girls: 240 [99, 476], boys: 300 [110, 573] g/day, $p<0.001$ median test).

Despite low consumption, higher rice intake was associated with higher U-As, but lower %iAs and %MMA, and higher %DMA in covariate-adjusted regressions (Table 3). Higher meat consumption was associated with lower %iAs and higher %DMA. Dairy was not associated with urinary arsenic (data not shown). Similarly, higher scores on the "nutrient dense" pattern were associated with lower %iAs and %MMA, and higher %DMA (Table 3).

Approximately 40% of the children were overweight, 18% were obese (Table 4), and only 7% were underweight (BAZ<-1 SD). Very few children (3.4%) had anemia, but 40% had ID. The mean energy intake exceeded 2100 kcal/day, and was higher in boys than girls (Table 4). There were no sex differences in the intake of fat (~30%), protein (~13%) and carbohydrates (~56%) as proportion of total energy or micronutrients.

In covariate-adjusted models, higher BMI was associated with lower %MMA and higher %DMA (Table 5). In particular, overweight children had lower %MMA (8.9 ± 3.3 vs.10.4 ± 3.6, $p<0.01$), and higher %DMA (80.1 ± 7.2 vs. 78.0 ± 7.3) than normal-weight children. Similarly, obese children had lower %MMA and higher %DMA than non-obese children (%MMA: 7.8 ± 3.1 vs. 10.2 ± 3.5 and %DMA: 81.9 ± 7.4 vs. 78.2 ± 7.1). ID was statistically associated with lower %iAs ($p<0.05$) and somewhat higher %DMA ($p<0.1$). Higher intake of total dietary folate was associated with lower %MMA and higher %DMA ($p<0.05$). Diets with higher %fat were associated with higher %DMA ($p<0.05$). Concentration of iron in drinking water, dietary iron, and kilocalorie intake were not associated with urinary arsenic species (data not shown).

DISCUSSION

Millions of children are exposed to low-level inorganic arsenic from water, food and other sources, but there is little understanding of what predictors are associated with exposure and how low-level arsenic affects child health and development. This study produced several key findings: 1) arsenic exposure in 5–8 year olds from Montevideo was low and water arsenic did not meaningfully contribute to this exposure; 2) exposure originated mostly from food; 3) rice consumption contributed to higher total urinary arsenic concentrations, and to lower %iAs and higher %DMA, indicating exposure to DMA from rice; 4) higher intake of dietary folate was associated with lower %MMA and higher %DMA; 5) higher consumption of meat and diets with higher proportion of energy from fat were also associated with higher %DMA; and 6) higher BMI was an important predictor of higher urinary %DMA, but not of arsenic exposure.

Low-level arsenic has been documented in Uruguayan preschool children and their mothers based on arsenic concentrations in hair (Kordas, Queirolo et al. 2010), but the extent, sources and predictors of exposure remain poorly characterized. Although there is some evidence

that arsenic concentrations in natural aquifers in Uruguay exceed international recommendations (Mañay, Goso et al. 2013), very little exposure or risk assessment has been done. In Montevideo, we found low arsenic exposure from household water: 95% of the water arsenic concentrations were below 1 μg/L, the median was 0.45 μg/L, and only two samples exceeded 10 μg/L, the WHO drinking water standard. Arsenic exposure has been studied more extensively in other South American regions, including Brazil and Argentina and there, arsenic exposure from drinking water appears higher (Momoyo Sakuma, Mello De Capitani et al. 2010, Buchhamer, Blanes et al. 2012, Concha, Nermell et al. 20016). On the other hand, South Asian children of similar age may drink water with several hundred μg/L (Wasserman, Liu et al. 2011, Nahar, Inaoka et al. 2014).

Despite the low exposure through drinking water, the concentrations of arsenic metabolites in children's urine varied up to 49 μg/L, suggesting contribution of inorganic arsenic from sources other than water. In fact, rice contributed to higher urinary arsenic concentrations. There is increasing concern that foods of plant origin are a source of arsenic exposure (EFSA 2014). For example, the content of inorganic arsenic in dry rice may range from 0.1 to 0.4 mg/kg (Hojsak, Braegger et al. 2015). In NHANES 2003–2008, each 0.25 cup increase in daily rice consumption was associated with higher concentrations of the sum of arsenic species in urine in children (6–17 years of age) (Davis, Mackenzie et al. 2012), which is consistent with our findings. The median urinary arsenic concentration in the US children was 8.9 μg/L, again, similar to the present study (9.9 μg/L). Another NHANES study showed a strong association between the consumption of rice or rice products and urinary concentrations of DMA (deCastro, Caldwell et al. 2014). We also found that higher rice consumption was associated with higher urinary concentration of DMA (data not shown) and %DMA, and correspondingly lower %iAs and %MMA. Rice contains mostly inorganic arsenic but varying concentrations of DMA are also found (Zhao, Zhu et al. 2013). Our findings likely reflect children's exposure to DMA from rice rather than higher methylation efficiency.

Rice consumption was a clear predictor of inorganic arsenic exposure among the study children, despite relatively low levels of intake. We conducted two 24-hour recalls and these should give a good approximation of recent diet and the general patterns of consumption. In this population, for whom rice is not a staple food, it is entirely plausible that rice consumption will be low. To note, the consumption of rice in our study was similar to that reported by other authors. For example, US children were classified as rice consumers if they ate at least 14 g dry weight of rice; these children had higher total urinary arsenic as well as DMA concentrations compared to non-consumers (Davis, Mackenzie et al. 2012). Thus, our study is consistent with others in this regard, and in line with the finding that when water arsenic concentrations are low, other sources, including food, have a more prominent contribution to the arsenic exposure (Meliker, Franzblau et al. 2006, Lindberg, Kumar et al. 2007). Thus, it appears that even modest rice consumption is associated with higher urinary arsenic concentrations (sum of arsenic species and %DMA) in a population with generally low arsenic exposure.

Another interesting finding was that children with higher scores on the "nutrient dense" pattern had lower %iAs and higher %DMA. Vegetables, strongly represented by dark green

leafy and orange-flesh vegetables in this pattern, and eggs, are good sources of folate. We specifically found that higher total dietary folate intake was associated with lower %MMA and higher %DMA. The role of folate in arsenic metabolism and detoxification has received considerable attention, with two RCTs reporting a clear benefit of folic acid supplementation in lowering blood arsenic concentrations in both folate deficient and sufficient adults (Gamble, Liu et al. 2007, Peters, Hall et al. 2015). Arsenic is methylated in the body by methyltransferases, including As methyltransferase (AS3MT), with SAM as main methyl donor (Marafante 1984). Folate plays an important role in one-carbon metabolism by recruiting methyl groups and is associated with individual variation in arsenic methylation capacity (Howe, Niedzwiecki et al. 2014). Although we did not measure folate status, low dietary folate intake (<300 and 200 μg/d) was observed in 15% and 4% of the study children, respectively, suggesting that deficiency is not prevalent. Regardless of folate status, higher folate consumption appears to contribute to more efficient arsenic methylation, and consequently, detoxification. Higher vegetable consumption could be an important strategy to increase arsenic methylation, through the provision of folate, although the exposure may not be reduced.

Meat consumption was also associated with higher %DMA and lower %iAs, but not with higher arsenic exposure. This may reflect an increase in the methylation capacity of arsenic because meats are good sources of protein, choline and methionine, main precursors of the methyl group donor S-adenosylmethionine, and shown to influence arsenic methylation in experimental studies (Vahter and Marafante 1987). Although not significant, higher protein intake in our study was associated with lower %MMA and higher %DMA. In NHANES, higher meat intake was marginally associated with higher urinary DMA concentrations in children, but that corresponded to just a few μg of arsenic per kilogram of meat, and thus probably less than 0.5 μg/L in urine per serving of meat (deCastro, Caldwell et al. 2014). Finally, in a study of US adults, those in the lowest quartile of protein intake excreted higher %MMA and lower %DMA than those with highest protein intake (Steinmaus, Carrigan et al. 2005).

A higher BMI, as well as overweight and obesity were associated with lower %MMA and higher %DMA. Very few children were underweight (7%) and there was no association between underweight and any of the arsenic species (data not shown). There is some support for these findings. In adult women from Northern Mexico/Southern US, higher BMI was associated with lower %MMA (Gomez-Rubio, Roberge et al. 2011). BMI was also associated with lower %MMA and higher %DMA in Central European men (Lindberg, Kumar et al. 2007). In the Strong Heart Study (SHS), BMI, % body fat, as well as fat free mass, were all associated with lower %MMA and higher %DMA in a population of adults (Gribble, Crainiceanu et al. 2013). In contrast, obese Taiwanese children had lower total urinary arsenic concentrations, but did not differ on methylated arsenic species from normal-weight children. However, many had elevated insulin levels, which were associated with poorer methylation capacity (Su, Lin et al. 2012). It is unclear how BMI and the urinary arsenic metabolites are related, as BMI reflects both adipose tissue and fat free mass. It is possible that the associations in our study were due to a higher capacity to methylate inorganic arsenic, but we cannot exclude more ingested DMA. Children with the highest BMI (BMI-for-age Z, BAZ scores > 2 SD) consumed more rice than non-obese children

(17.3 ± 17.9 vs. 12.3 ± 18.0 g, p=0.011 in Wilcoxon rank sum test), although there were no differences between children with BAZ > 1 and normal-weight children. Additionally, a higher BMI may reflect higher intake and availability of protein and methyl groups, which play a role in arsenic methylation (Vahter 2007). Children with obesity also consumed higher amounts of meats than non-obese children but this was not statistically significant (74.2 ± 68.5 vs. 66.0 ± 68.9 g).

A somewhat unexpected result was that children consuming higher proportion of energy from fat had higher %DMA, but not increase in U-As. There is no demonstrated relationship between fat and arsenic metabolism. In our study, %fat was modestly correlated with meat consumption (Spearman rho=0.18, p<0.001); adjustment for meat intake somewhat attenuated the association between fat intake and %DMA (1.6 [−2.6, 0.9]). Thus, fat consumption may be a proxy for additional dietary components or it may reflect confounding by unmeasured factors. However, it is important to point out that our study is cross-sectional, and therefore, we cannot make any claims about the causality of the observed associations between higher fat consumption or higher BMI and higher %DMA. In light of the adverse health effects of overweight and obesity, our findings should be interpreted with caution.

Our findings should be interpreted in light of certain limitations. First, we may have limited generalizability because ~50% of eligible families chose to participate in the study. We had ethical approval to collect information only on participating families, thus, we cannot speak to differences between participants and non-participants. Nevertheless, the overall response of the study families to our requests for urine samples was very high and almost 90% of children provided samples, showing excellent protocol adherence. Second, dietary intake was based on parental recall over two days, which may not reflect typical intakes. We tried to limit error from recall by providing aids to estimate serving sizes, ask about snacking, and asking the child to help recall school meals. The consistency of our findings with previously published literature further suggests use of sound methodology. Arsenic exposure was measured in water and urine using well accepted methods, a definite strength.

In conclusion, most research on the links between dietary factors and biomarkers of arsenic has come from areas where arsenic exposure is high. Thus, our study is of direct relevance for children in Europe and USA. We found that arsenic exposure was low in Uruguayan children, but higher consumption of rice was associated with higher arsenic exposure, partly as DMA. Higher BMI, higher intake of meat and total dietary folate, and dietary pattern consisting of high proportion of vegetables contributed to children’s ability to methylate inorganic arsenic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Worldwide, millions of children are exposed to low-level inorganic arsenic from water, food and other sources.
- There is little understanding of what predictors are associated with exposure and how low-level arsenic affects child health and development.
- This study found that in this setting with low-level arsenic concentrations in children's urine, exposure originated mostly from food, specifically rice
- Higher intake of dietary folate was associated with lower %MMA and higher %DMA;
- Higher consumption of meat and higher BMI was an important predictor of higher urinary %DMA.

Table 1

Household and demographic characteristics of the study participants.

Characteristic	N	% with missing values	Mean ± SD or %	Range
Child gender	328	0		
Girls			44.8%	
Age (months)	327	0.3	81.0 ± 6.6	57 – 105
Maternal education	320	2.4		
Any primary			19.4%	
Secondary or higher			80.6%	
Mother unemployed/stay-at-home	309	5.8	30.7%	
Parents with potential occupational metal exposure	327	0.3	27.8%	
Household crowded[1]	297	9.5	22.2%	
Household possessions	299	8.8	3.5 ± 1.1	0 – 5
Source of drinking water	294	10.4		
Unfiltered tap/tank			31.6%	
Filtered tap			19.0%	
Bottled/other			49.3%	

[1] Household crowded=more than 2 persons per bedroom living in house.

Table 2

Arsenic concentrations in water and urine samples of the study children.

Arsenic species	Overall	Girls	Boys
Household water As, μg/L	0.45 [0.16, 0.93][1]	0.47 [0.15, 0.87]	0.44 [0.17, 1.0]
	Urinary Arsenic		
U-As[2], μg/L	9.9 [4.1, 27.3]	9.9 [4.1, 26.1]	9.9 [4.3, 27.3]
iAs[3], μg/L	1.01 [0.40, 2.7]	1.04 [0.47, 2.8]	0.98 [0.40, 2.6]
MMA[4], μg/L	0.95 [0.32, 2.5]	1.00 [0.31, 2.2]	0.91 [0.34, 2.6]
DMA[5], μg/L	1.9 [3.0, 23.0]	7.9 [2.9, 23.0]	7.8 [3.1, 22.8]
% iAs	11.4 ± 5.8[6]	11.6 ± 5.6	11.2 ± 6.0
%MMA	9.7 ± 3.5	9.6 ± 3.6	9.9 ± 3.5
% DMA	78.9 ± 7.3	78.8 ± 7.4	79.0 ± 7.2

[1]Value given as median [5%, 95%];

[2]U-As=Sum of inorganic arsenic metabolites, adjusted for mean specific gravity (1.020);

[3]iAs=inorganic arsenic, adjusted for mean specific gravity (1.020);

[4]MMA=methylarsonic acid, adjusted for mean specific gravity (1.020);

[5]DMA=dimethylarsinic acid, adjusted for mean specific gravity (1.020);

[6]Value given as M±SD.

Table 3

Associations of average daily intake of foods and dietary patterns with the sum of urinary arsenic species, and percent methylated arsenic metabolites.

Predictor	U-As[1]		%iAs		%MMA		%DMA	
	Unadjusted mean value	β [95% CI][2]	Unadjusted mean value	β [95% CI][2,3]	Unadjusted mean value	β [95% CI][2,3]	Unadjusted mean value	β [95% CI][2,3]
Rice (g/day)								
< 5	11.0 ± 7.2	Ref.	12.5 ± 6.1	Ref.	10.4 ± 3.6	Ref.	77.0 ± 7.2	Ref.
≥ 5	13.5 ± 8.4***	2.6 [0.9, 4.4]***	10.2 ± 5.3***	−1.9 [−3.2, −0.6]***	9.0 ± 3.3***	−0.9 [−1.7, −0.1]**	80.9 ± 7.0***	2.8 [1.3, 4.4]***
Wheat and grain products (g/day)								
< 273	11.4 ± 6.9	Ref.	11.0 ± 5.6	Ref.	9.7 ± 3.4	Ref.	79.3 ± 7.0	Ref.
≥ 273	13.0 ± 8.7*	1.4 [−0.4, 3.3]	11.7 ± 6.1*	1.0 [−0.3, 2.4]	9.8 ± 3.7	0.2 [−0.7, 1.0]	78.6 ± 7.7*	−1.1 [−2.7, 0.5]
Meats (g/day)								
< 55	12.9 ± 8.5	Ref.	11.0 ± 5.9	Ref.	10.1 ± 3.5	Ref.	78.1 ± 7.3	Ref.
≥ 55	11.5 ± 7.0	−1.4 [−3.2, 0.3]	10.8 ± 5.7**	−1.3 [−2.5, −0.01]**	9.3 ± 3.5**	−0.7 [−1.5, 0.04]*	79.9 ± 7.3**	1.9 [0.4, 3.4]**
Fruit (g/day)								
<102	12.4 ± 7.6	Ref.	11.7 ± 5.7	Ref.	9.3 ± 3.4	Ref	79.0 ± 7.2	Ref.
≥ 102	12.1 ± 8.2	−0.2 [−2.0, 1.6]	11.0 ± 6.0	−0.5 [−1.8, 0.8]	10.2 ± 3.6**	0.7 [−0.1, 1.5]*	78.9 ± 7.6	−0.3 [−1.8, 1.2]
Processed foods pattern score[4]								
< −0.16	12.2 ± 7.7	Ref.	11.3 ± 6.2	Ref.	9.4 ± 3.7	Ref.	79.3 ± 7.9	Ref.
≥ −0.16	12.3 ± 8.1	−0.4 [−2.2, 1.4]	11.4 ± 5.5	0.02 [−1.3, 1.3]	10.0 ± 3.3	0.7 [−0.1, 1.6]*	78.7 ± 6.7	−0.7 [−2.4, 1.3]
Nutrient dense pattern score[5]								
< −0.23	12.5 ± 8.4	Ref.	12.3 ± 6.1	Ref.	10.0 ± 3.8	Ref.	77.8 ± 7.4	Ref.
≥ −0.23	12.0 ± 7.3	−0.7 [−2.5, 1.2]	10.4 ± 5.4	−1.8 [−3.1, −0.5]***	9.4 ± 3.2	−0.9 [−1.8, −0.1]**	80.1 ± 7.1	2.6 [1.0, 4.2]***

[1] U-As=Sum of inorganic arsenic metabolites, adjusted for mean specific gravity (1.020);

[2] Models adjusted for age (categorized at the median), sex, BMI (continuous variable), household crowding, household possessions (categorized at the median), source of drinking water, location of the school, and season of recall;

[3] Models additionally adjusted for U-As;

[4] The “processed foods” pattern included higher consumption of breads, processed meats, fats and oils, and sweetened beverages (but also of yogurt); reduced intake of milk, pastries and pizza dinners.

[5]The "nutrient dense" pattern included higher consumption of dark leaf and red-orange vegetables, higher consumption of eggs, beans & peas, potatoes; reduced consumption of pasta and sauces/condiments.

Table 4

Nutritional status and nutrient intake among study children.

Nutritional indicator	Overall	Girls	Boys
Serum ferritin, ng/mL	18.1 [3.0, 48.3]	20.4 [3.1, 48.5][1]	17.2 [2.9, 48.0]
< 15.0	38.7%	35.6%[2]	41.1%
Hemoglobin, g/dL	13.2 ± 1.1	13.1 ± 1.1[3]	13.2 ± 1.1
<11.5	3.8%	4.3%	3.4%
BMI, kg/m^2	16.9 ± 2.6	17.2 ± 3.0	16.7 ± 2.6
Overweight[4]	39.8%	43.0%	37.3%
Obese[5]	17.9%	17.6%	18.1%
Energy intake, kcal	2193 ± 565	2107 ± 548	2262 ± 570**
%Protein[6]	13.6 ± 5.7	13.3 ± 2.7	13.9 ± 7.3
%Fat[6]	29.9 ± 6.1	29.4 ± 6.4	30.3 ± 5.9
%Carbohydrate[6]	56.4 ± 9.2	57.3 ± 7.5	55.8 ± 10.3
Dietary iron, mg/1000 kcal/day	4.4 [2.8, 8.3]	4.4 [2.8, 8.7]	4.3 [2.8, 8.0]
Total dietary folate, µg/1000 kcal/day	222 ± 66	214 ± 66	228 ± 64*

[1] Value given as Median [5%, 95%];

[2] value given as percent;

[3] value given as Mean ± SD;

[4] Overweight=BMI-for-age Z score > 1 SD;

[5] Obese=BMI-for-age Z score > 2 SD;

** boys differ from girls at p<0.05;

[6] Proportion of total energy;

* boys differ from girls at p<0.1.

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Table 5

Associations of nutritional status and calculated average daily intake of select nutrients with urinary arsenic concentrations, and percent methylated arsenic metabolites.

Predictor	U-As[1]		%iAs		%MMA		%DMA	
	Unadjusted mean value	β [95% CI][2]	Unadjusted mean value	β [95% CI][2,3]	Unadjusted mean value	β [95% CI][2,3]	Unadjusted mean value	β [95% CI][2,3]
Nutritional status								
BMI, kg/m^2								
< 16.5	12.0 ± 7.5	Ref.	11.9 ± 6.1	Ref.	10.5 ± 3.6	Ref.	77.6 ± 7.4	Ref.
≥ 16.5	12.4 ± 8.2	0.1 [−1.7, 1.8]	11.0 ± 5.5	−1.0 [−2.3, 0.3]	9.0 ± 3.3	−1.5 [−2.3, 0.3]***	80.0 ± 7.1	2.4 [0.9, 3.9]***
Serum ferritin, ng/mL								
≥ 15	12.7 ± 8.5	Ref.	11.8 ± 6.0	Ref.	9.5 ± 3.5	Ref.	78.7 ± 7.2	Ref.
< 15	11.3 ± 6.4	−1.1 [−3.1, 0.9]	10.6 ± 5.2	−1.5 [−3.0, −0.1]**	10.1 ± 3.5	0.3 [−0.6, 1.2]	79.4 ± 7.2	1.5 [−0.2, 3.2]*
Hemoglobin, g/dL								
< 12.7	12.8 ± 8.7	Ref.	11.2 ± 5.4	Ref.	9.8 ± 3.6	Ref.	79.1 ± 7.2	Ref.
≥ 12.7	11.4 ± 6.6	−1.5 [−3.3, 0.2]*	11.8 ± 6.2	0.7 [−0.6, 2.0]	9.8 ± 3.5	0.1 [−0.7, 0.9]	78.3 ± 7.4	−0.9 [−2.4, 0.6]
Nutrient intake								
Total folate, μg/1000 kcal/day								
< 217	12.3 ± 7.8	Ref.	11.3 ± 6.2	Ref.	10.0 ± 3.7	Ref.	78.7 ± 7.7	Ref.
≥ 217	12.1 ± 8.0	−1.1 [−2.9, 0.7]	11.4 ± 5.5	−0.7 [−2.0, 0.6]	9.5 ± 3.4	−0.9 [−1.7, −0.1]**	79.2 ± 7.0	1.8 [0.2, 1.2]**
% Carbohydrate								
< 57	11.9 ± 7.2	Ref.	11.3 ± 5.6	Ref.	9.6 ± 3.5	Ref.	79.3 ± 7.5	Ref.
≥ 57	12.6 ± 8.5	−0.3 [−2.2, 1.5]	11.9 ± 6.0	0.7 [−0.6, 2.1]	9.9 ± 3.6	0.6 [−0.2, 1.4]	78.6 ± 7.1	−1.5 [−3.1, −0.1]*
% Protein								
< 13	12.2 ± 7.6	Ref.	11.0 ± 5.5	Ref.	10.0 ± 3.6	Ref.	78.9 ± 6.8	Ref.
≥ 13	12.2 ± 8.1	−0.2 [−2.0, 1.6]	11.6 ± 6.1	023 [−1.1, 1.5]	9.5 ± 3.5	−0.7 [−1.5, 0.1]	79.0 ± 7.8	0.6 [−0.9, 2.2]
% Fat								
< 30	12.2 ± 7.8	Ref.	11.8 ± 6.3	Ref.	9.7 ± 3.6	Ref.	78.9 ± 6.8	Ref.
≥ 30	12.3 ± 7.9	1.1 [−0.7, 3.0]	10.9 ± 5.3	−1.2 [−2.5, 0.1]*	9.7 ± 3.5	−0.5 [−1.3, 0.4]	79.0 ± 7.8	1.7 [0.2, 3.3]**

[1] U-As=Sum of inorganic arsenic metabolites, adjusted for mean specific gravity (1.020);

[2] Models adjusted for age (categorized at the median), sex, BMI (continuous variable), household crowding, household possessions (categorized at the median), source of drinking water, and location of the school; nutrient models adjusted for season of recall;

[3] Models additionally adjusted for U-As.