HHS Public Access

Author manuscript

Environ Res. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

Environ Res. 2016 November ; 151: 445–450. doi:10.1016/j.envres.2016.08.015.

Dietary micronutrient intake and its relationship with arsenic metabolism in Mexican women

Lizbeth López-Carrillo[a], **Brenda Gamboa-Loira**[a], **Wendy Becerra**[a], **César Hernández-Alcaraz**[a], **Raúl Ulises Hernández-Ramírez**[a,1], **A. Jay Gandolfi**[b], **Francisco Franco-Marina**[c], and **Mariano E. Cebrián**[d]

[a]Instituto Nacional de Salud Pública, Av. Universidad 655, Col. Santa María Ahuacatitlán, C.P. 62100, Cuernavaca, Morelos, México

[b]Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona, Tucson, AZ 85721, USA

[c]Instituto Nacional de Enfermedades Respiratorias, Calz. Tlalpan 4502, Col. Sección XVI, Del. Tlalpan, C.P. 14080, D.F., México

[d]Departamento de Toxicología, Centro de Investigación y de Estudios Avanzados del IPN, Av. Instituto Politécnico Nacional 2508, Col. San Pedro Zacatenco, Del. Gustavo A. Madero, C.P. 07360, D.F., México

[1]Raúl Ulises Hernández-Ramirez, Yale University, New Haven, CT 06520, USA

Abstract

Introduction—Concentrations of inorganic arsenic (iAs) metabolites in urine present intra-and interindividual variations, which are determined not only by the magnitude of exposure to iAs, but also by differences in genetic, environmental and dietary factors.

Objective—To evaluate whether differences in dietary intake of selected micronutrients are associated with the metabolism of iAs.

Methods—The intake of 21 micronutrients was estimated for 1027 women living in northern Mexico using a food frequency questionnaire. Concentration of urinary metabolites of iAs was determined by high performance liquid chromatography inductively coupled plasma mass spectrometry (HPLC-ICP-MS) and the proportion of iAs metabolites was calculated (%iAs, monomethylarsonic acid [%MMA] and dimethylarsinic acid [%DMA]), as well as ratios corresponding to the first (MMA/iAs), second (DMA/MMA) and total methylation (DMA/iAs).

Results—After adjustment for covariates, it was found that methionine, choline, folate, vitamin B12, Zn, Se and vitamin C favor elimination of iAs mainly by decreasing the %MMA and/or increasing %DMA in urine.

Corresponding author: Lizbeth López-Carrillo, Dr. PH. Instituto Nacional de Salud Pública, Av. Universidad 655, Col. Santa María Ahuacatitlán, C.P. 62100, Cuernavaca, Morelos, México. Phone: (52) 777 3293000 (2501). lizbeth@insp.mx.

Conclusions—Our results confirm that diet contributes to the efficiency of iAs elimination. Further studies are needed to assess the feasibility of dietary interventions that modulate the metabolism of iAs and the consequent risk of diseases related to its exposure.

Keywords

Inorganic arsenic; arsenic metabolism; micronutrients; northern Mexico

1. INTRODUCTION

Inorganic arsenic (iAs) is metabolized and excreted in urine in its monomethylated (15–25%) and di-methylated forms (40–75%) and as iAs (20–25%) (Agency for Toxic Substances and Disease Registry, 2007). A greater proportion of monomethylarsonic acid (MMA), and a lower of dimethylarsinic acid (DMA) increase the risk of various cancers, skin lesions and diseases of the circulatory system among others (Steinmaus et al., 2010).

The concentrations of iAs metabolites in urine present intra-and interindividual variations, determined not only by the amount of iAs exposure but also by differences in genetic, environmental and dietary factors, such as the intake of several nutrients involved in one carbon metabolism, a series of oxidation-reduction reactions that provide methyl groups needed for arsenic methylation (Tseng, 2009).

Several studies undertaken in different human populations exposed to iAs, have consistently shown a negative association between urinary %MMA and dietary intake and/or plasma levels of some micronutrients (selenium [Se], zinc [Zn], calcium [Ca], folate, methionine, vitamin C and B6). In some studies, an increase in %DMA has been observed in relation to the consumption of these nutrients (Basu et al., 2011; Gamble et al., 2006, 2005; Hall et al., 2009; Heck et al., 2007; Steinmaus et al., 2005a). Likewise, the intake of certain pro-vitamins and vitamins (β-carotene, B2, B6, B12, A, C, E and folic acid) have been associated with a reduced risk of diseases linked to iAs exposure (skin cancer, hyperkeratosis diseases, melanosis and changes in blood pressure) (Chen et al., 2007; Hsueh et al., 1997; Zablotska et al., 2008).

In north Mexico, iAs is naturally found In drinking water In concentrations exceeding the limit (10 μg/L) recommended by the World Health Organization (Camacho et al., 2011). Recently, our research group reported an increased risk of breast cancer in women living in the area, who had reduced ability to metabolize iAs, expressed by higher %MMA and lower %DMA in urine (López-Carrillo et al., 2014). The aim of the present study is to evaluate whether differences in the dietary intake of micronutrients related to one carbon metabolism, as well as other selected nutrients, could explain variations in iAs metabolism among clinically healthy control women participating in the above mentioned study.

2. MATERIALS AND METHODS

2.1. Study population

A cross-sectional study was undertaken among 1027 healthy Mexican women aged at least 20 years and resident for at least one year in any of the following states: Chihuahua,

Coahuila, Durango, Nuevo Leon and Sonora, during the period 2007 to 2011 (López-Carrillo et al., 2014). The women were identified with the Master Sampling System for National Health Surveys in Mexico, which provides a list of homes located in both urban and rural areas, grouped into city blocks and also into basic geostatistical areas (BGA). A certain number of BGAs and city blocks were randomly selected, where homes were systematically visited in order to identify an eligible woman. In homes where no eligible woman was found, or if she did not consent, we proceeded to locate a new home; when there was more than one eligible woman, we randomly selected one. The response rate was 99.6% (1027/1031). The project was approved by the Research, Biosecurity and Bioethics Committees at the National Institute of Public Health (Mexico).

2.2. Interviews

Pending informed consent, participants were interviewed face to face in one occasion, at their homes by trained interviewers about sociodemographic characteristics, diet, alcohol, and tobacco consumption. Anthropometric measurements for calculating the body mass index were also obtained [BMI = body weight (kg)/height (m^2)]. All interviews were made in the period of 2007 to 2009.

2.3. Urinary arsenic determination

Participants donated a first morning void urine sample, not necessarily the same day of interview. Samples were collected in a sterile disposable polypropylene urine collection cup, stored in a fridge and maintained at least for two years at −70 °C until analysis. Concentrations (μg/L) of urinary species for arsenite (As^{3+}), arsenate (As^{5+}), monomethylarsonic acid (MMA^{5+}), dimethylarsinic acid (DMA^{5+}) and arsenobetaine (AsB) were determined by high performance liquid chromatography coupled with mass spectrometry (HPLC-ICP-MS), according to methodology previously described (Gilbert-Diamond et al., 2011). Measurements below the limit of detection (LOD) (AsB: 24.25%; As^{3+}: 19.28%; As^{5+}: 56.28%; MMA^{5+}: 1.95%; DMA^{5+}: 0.49%) were given the corresponding LOD: AsB: 0.08; As^{3+}: 0.15; As^{5+}: 0.41; MMA^{5+}: 0.12 and DMA^{5+}: 0.12, divided by two (LOD/2), as suggested by Barr et al. (2006). The urinary concentration of creatinine (mg/dL) was measured using an enzymatic method kit (Randox, Antrim County, UK). Coefficients of variation were: MMA^{5+}= 8%, DMA^{5+}= 9%, As^{3+}= 8% and creatinine= 2.76%.

In order to evaluate iAs metabolism, we calculated: 1) iAs concentration from the sum of As^{3+} and As^{5+}; 2) Total As (TAs) as a result of the sum of iAs, MMA^{5+} (MMA), DMA^{5+} (DMA) and AsB; 3) proportions of iAs, MMA and DMA based on the total sum of these; 4) methylation ratios: first= MMA/iAs; second= DMA/MMA; and total= DMA/iAs.

2.4. Micronutrient intake evaluation

Daily consumption over the last year of 119 foods and 14 dishes was estimated using a validated semi-quantitative food frequency questionnaire, which included predetermined portions for each food, with 10 response options from “never” to “six or more times per day” (Galván-Portillo et al., 2011). Fruits and vegetables frequency of consumption was

adjusted according to their availability throughout the year; for example, half the reported plum consumption was assumed because they are only available six months of the year.

Previously, our work group identified the specific foods contained in our questionnaire, with those in the reference tables for nutrient composition No. 20 of the United States Department of Agriculture (USDA). Based on the frequency of food consumption reported by participants, the daily intake of total energy was estimated, as well as that of the following micronutrients: retinol, vitamin C, α-tocopherol, thiamine, riboflavin, niacin, vitamin B6, folate, vitamin B12, choline, methionine, betaine, phosphorus (P), magnesium (Mg), iron (Fe), copper (Cu), sodium (Na), potassium (K), Ca, Zn and Se.

2.5. Statistical analysis

Sociodemographic characteristics, proportions and methylation ratios of iAs metabolites, as well as nutrient intakes in the study population were described using measures of central tendency and dispersion. The percentage of women with consumption below the Daily Recommended Intake (DRI) was calculated using the values reported for Mexican women of 19–70 years (Bourges et al., 2009), and when the corresponding information was not available, that suggested for American women was taken as reference (Institute of Medicine, 2006).

The associations between each nutrient of interest with each urinary As metabolite were determined by multiple linear regression models. The proportions and iAs methylation ratios were transformed to log scale to improve their normality. Nutrient intakes of interest were adjusted for total energy intake, according to the residual method proposed by Willett et al. (1997). We included as covariates those that first: correlated significantly with any of the proportions or methylation ratios of iAs; second: correlated significantly with energy-adjusted nutrients of interest; third: were not significantly correlated with each other. Those covariates were: age (years), total energy intake (kcal/day) and TAs-AsB (μg/l). BMI was not included because it was highly correlated with total energy intake.

3. RESULTS

On average, participants in the study were 54 years old, with 6 years of education, a BMI on the margin of obesity (30 kg/m^2) and 48 years of residence in the selected states (Table 1). Most women did not smoke (85%) or consume alcohol (89%) (Data not included in Table 1).

There was a high iAs exposure in our study population, since at least half of the women had urinary TAs concentrations of about 26 μg As/g of creatinine and 10% had concentrations higher than 150 μg As/g of creatinine. These values were higher than the median values reported for American nonsmoker adults (7.17 μg As/g of creatinine) and the percentile 90 (33.7 μg As/g of creatinine) in the National Health and Nutrition Examination Survey for the years 2011–2012 (Centers for Disease Control and Prevention, 2015). In our study, less than 4% of TAs was present as AsB (Table 2).

In general terms, women in our study had daily dietary intakes lower than the DRI for retinol, folate, vitamin B12, choline, betaine, vitamin C, α-tocopherol, Ca, Fe, Zn and K. In particular, potassium, retinol, choline and calcium intakes were lower than the DRI in 90% of the women (Table 3). Except for Ca, most nutrients were significantly correlated with each other (data not included).

The daily intake of methionine, choline, folate, vitamin B12, vitamin C, Fe, Zn, Se and Na was significantly associated with the parameters favoring iAs elimination (reduction of %iAs, and/or %DMA increase, and/or DMA/MMA increase, and/or increase of DMA/iAs). The intakes of Ca and α-tocopherol were associated with the parameters reducing iAs elimination (increase of %MMA and/or MMA/iAs (Table 4).

4. DISCUSION

Our results show that dietary intake of several micronutrients (methionine, choline, folate, vitamin B12, vitamin C, Fe, Zn, Se, Na, Ca and α-tocopherol) play an important role in the metabolism of iAs.

In particular, our findings suggest that methionine, choline, folate and vitamin B12 dietary intakes improve iAs elimination by increasing urinary %DMA, which confirms the results of an epidemiological observational study performed in U.S.A (Steinmaus et al., 2005a); however, were not in agreement with the findings from two studies performed in Bangladesh (Heck et al., 2007; Hall et al. 2009). In a randomized clinical trial, supplementation of folic acid in adults was significantly associated with higher %DMA and lower %MMA in urine (Gamble et al., 2006), as well as with lower concentrations of iAs and MMA in blood (Gamble et al., 2007). In addition, mice exposed to As^{3+} and fed methionine, showed a decrease in %iAs and an increase in %DMA blood levels (Jin et al., 2010). Methionine, folate, vitamin B12 and B6, choline, betaine, among other nutrients participate in the one-carbon metabolism, where methionine is activated to S-adenosylmethionine (SAM), the main donor of methyl groups for iAs methylation. In the event of high iAs exposure and limited availability of methyl groups, SAM is used primarily for MMA synthesis, rather than for DMA synthesis (Hall and Gamble, 2012; Howe et al., 2014)

Additionally, we found that Zn dietary intake was associated with a significant pattern of increased iAs elimination: decreased %MMA and %iAs as well as increased %DMA, DMA/MMA and DMA/iAs. This elimination pattern was also observed with the Fe intake, with the exception of the increase in %DMA. These results were in agreement with those from a study conducted among US adults (Steinmaus et al., 2005a), but not with another study undertaken in pregnant Bangladeshi women (Li et al., 2008). A possible explanation, could be that the effects of Zn, as well as of the various micronutrients that participate in the one-carbon metabolism, may be less obvious in pregnancy, due to the greater efficiency for iAs methylation during this period (Li et al., 2008; Tseng, 2009). In rodents, administered with As and Zn there was less accumulation in tissues and increased removal of iAs, when compared with the control group (Kamaluddin and Misbahuddin, 2006; Kreppel, 1994). Zn participates in the one-carbon cycle as a component of the active site of betaine-homocysteine methyltransferase, which catalyzes methionine synthesis by transferring a

methyl group from betaine to homocysteine, in an alternative route to the transfer of 5-methyltetrahydrofolate to homocysteine (Evans et al., 2002; Millian and Garrow, 1998). Even if the above mechanism could explain the effects of Zn on iAs methylation, there is no similar information available for Fe.

Our results also showed a significant negative association between Se intake and %iAs as well as positive with DMA/iAs, in agreement with findings from studies in Taiwan and Chile, where urinary Se was evaluated (Christian et al., 2006; Hsueh et al., 2003). Additionally, blood levels of Se have been linked to a reduction in urinary TAs concentrations (George et al., 2013), and %MMA in urine (Basu et al., 2011) and blood (Pilsner et al., 2011). Notwithstanding, a recent study showed non-linear relationships between Se and As metabolites, that deserve further attention (Yoshida et al., 2015). To our knowledge, no information is available on the relationships between dietary intake of Se and methylation ratios, which could be compared with the increase in DMA/iAs observed in the present study. Some foods, such as lentils, are sources of Se, usually present as selenomethionine (Thavarajah et al., 2007). Rats fed with lentils and exposed to iAs showed higher total excretion of As in feces and urine (Sah et al., 2013). It is possible that the mechanism underlying these findings involves Se participation in the thioredoxin (Trx)/ thioredoxin reductase (TR) system, since Trx provides reducing equivalents for the reduction of MMA^{5+} to MMA^{3+}, which is subsequently converted to DMA^{5+}. TR is dependent on Se and decreases its activity at low concentrations of this metalloid, with a consequent reduction in Trx production (Hill et al., 1997).

Regarding the effect of vitamin C on As metabolism, we have identified a positive association between vitamin C intake and urinary %DMA and DMA/iAs, which is consistent with a recent epidemiological study performed in Japan (Ilmiawati et al., 2013). Both findings are in agreement with *in vivo* studies showing that vitamin C and α-tocopherol improved reduced glutathione (GSH) levels (Ramanathan et al., 2005), which in turn promoted As methylation and urinary elimination (Wang et al., 2015). In addition, individuals deficient in vitamin C have shown low GSH levels (Johnston et al., 1993). Furthermore, the ratio GSH/GSSG (oxidized glutathione) was significantly associated with increased urinary %MMA, decreased %DMA and higher TAs in blood in folate-deficient individuals (Niedzwiecki et al., 2014). Nevertheless, we identified a significant positive association between α-tocopherol and MMA/iAs, for which we do not have a feasible biological explanation.

Likewise, we identified isolated associations between Ca, K and Na intake and specific iAs metabolites which do not enable identification of a pattern for iAs elimination.

Results from this study should be interpreted considering methodological limitations and strengths. Most studies suggest that women have a better methylation capacity than men, then it would be difficult to extrapolate our results to men (Tseng, 2009). The presence of random errors due to the way diet is measured is possible, therefore we accept that our results may represent a conservative approximation, since this type of error underestimates associations, which may be the case for retinol, thiamine, riboflavin, niacin, vitamin B6, betaine, P, Mg and Cu. In contrast, the possibility of a differential measurement error in the

concentrations of iAs species, in terms of women's diet, is negligible, since both interviewers and participants were unaware of the study hypothesis, as well as of their As levels in urine at the time of interview. In addition, a high percentage of iAs values that were below the LOD were imputed, whereas this situation may misrepresent the results, the sole use of detectable values would reduce the statistical power. We did a sensitivity analysis using only detectable values and found that most of our results remained (Table 1, supplementary material). Also, to reduce the likelihood of type I error due to multiple comparisons, those that resulted significant at $p<0.001$ were considered to be robust.

It has been considered that evaluation of the efficiency of iAs elimination with a single urine sample is a good estimate of chronic exposure, considering that the source of exposure is from daily water intake, coupled with evidence showing the existence of stable patterns of methylation over time (Steinmaus et al., 2005b) with small variations during the day (<5%) (Concha et al., 2002).

We also controlled for possible confounders that could influence the elimination efficiency of iAs such as age, total energy intake and magnitude of exposure to As (represented by TAs in urine) (Tseng, 2009). Varying dilution of urine samples may also distort the results. The concentration of creatinine, an indicator of dilution, has been associated with the efficiency of iAs elimination (Basu et al., 2011). However, the use of creatinine to control for potential concentration/dilution issues is a matter of debate: some authors suggest dividing urinary concentrations of the metabolite of interest by the respective concentration of creatinine, whereas others recommend its inclusion as an adjustment variable in multivariate models (Barr et al., 2004; Basu et al., 2011). Under these considerations, firstly, by using proportions and ratios of As metabolites in the present study, the value of creatinine concentration was mathematically eliminated; secondly, because its concentration was highly correlated with several important covariates, it was not included in the final models.

Additionally, the median intake of total energy, protein, carbohydrates, total fat, vitamin C, Fe, Zn, Ca and folate in women under study were similar to those reported for women aged 20–59 years in the Mexico National Survey for Health Nutrition, 2006 (ENSANUT 2006) (Barquera et al., 2009), which reduces the probability of having studied an atypical sample of Mexican women.

In conclusion, our results support the hypothesis that diet contributes to the efficiency of iAs elimination. Further studies are needed to assess the feasibility of dietary interventions in Mexico that could modulate the metabolism of iAs and the consequent risk of diseases related to As exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by CONACYT Fondo Sectorial de Investigación en Salud y Seguridad Social 2005-2-14373, 2009-1-111384 y 2010-1-140962 and by The Superfund Basic Research Program Grant to the University of Arizona (NIH ES-04940). The analyses for arsenic metabolites were performed by the Analytical

Section of the Hazard Identification Core, College of Pharmacy, University of Arizona. We wish to acknowledge Michael Kopplin for performing the analyses and Rosa María Hernández for technical support.

References

Agency for Toxic Substances and Disease Registry. Toxicological profile for arsenic. U.S. Department of Health and Human Services, Public Health Service; Atlanta, GA: 2007.

Barquera S, Hernández-Barrera L, Campos-Nonato I, Espinosa J, Flores M, J AB, Rivera Ja. Energy and nutrient consumption in adults: analysis of the Mexican National Health and Nutrition Survey 2006. Salud Publica Mex. 2009; 51(Suppl 4):S562–73. [PubMed: 20464232]

Barr DB, Landsittel D, Nishioka M, Thomas K, Curwin B, Raymer J, Donnelly KC, McCauley L, Ryan PB. A survey of laboratory and statistical issues related to farmworker exposure studies. Environ Health Perspect. 2006; 114:961–968. [PubMed: 16760001]

Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, Pirkle JL. Urinary Creatinine Concentrations in the U.S. Population: Implications for Urinary Biologic Monitoring Measurements. Environ Health Perspect. 2004; 113:192–200.

Basu A, Mitra S, Chung J, Guha Mazumder DN, Ghosh N, Kalman D, von Ehrenstein OS, Steinmaus C, Liaw J, Smith AH. Creatinine, diet, micronutrients, and arsenic methylation in West Bengal, India. Environ Health Perspect. 2011; 119:1308–13. [PubMed: 21652291]

Bourges RH, Casanueva E, Rosado J. Recomendaciones de Ingestión de Nutrimentos para la población mexicana. Bases Fisiológicas. Médica Panamericana. 2009:664.

Camacho LM, Gutiérrez M, Alarcón-Herrera MT, Villalba MDL, Deng S. Occurrence and treatment of arsenic in groundwater and soil in northern Mexico and southwestern USA. Chemosphere. 2011; 83:211–25. [PubMed: 21216433]

Centers for Disease Control and Prevention. Fourth national report on human exposure to environmental chemicals. Updated tables. Feb. 2015 Available from: www.cdc.gov/biomonitoring/pdf/FourthReport_UpdatedTables_feb2015.pdf (Accessed 05 June 2015)

Chen Y, Factor-Litvak P, Howe GR, Graziano JH, Brandt-Rauf P, Parvez F, van Geen A, Ahsan H. Arsenic exposure from drinking water, dietary intakes of B vitamins and folate, and risk of high blood pressure in Bangladesh: a population-based, cross-sectional study. Am J Epidemiol. 2007; 165:541–52. [PubMed: 17164464]

Christian WJ, Hopenhayn C, Centeno JA, Todorov T. Distribution of urinary selenium and arsenic among pregnant women exposed to arsenic in drinking water. Environ Res. 2006; 100:115–22. [PubMed: 16337848]

Concha G, Vogler G, Nermell B, Vahter M. Intra-individual variation in the metabolism of inorganic arsenic. Int Arch Occup Environ Health. 2002; 75:576–80. [PubMed: 12373320]

Evans JC, Huddler DP, Jiracek J, Castro C, Millian NS, Garrow TA, Ludwig ML. Betaine-Homocysteine Methyltransferase. Structure. 2002; 10:1159–1171. [PubMed: 12220488]

Galván-Portillo M, Torres-Sánchez L, Hernández-Ramírez RU, Anaya-Loyola MA. Validity and reproducibility of a food frequency questionnaire to estimate folate intake in a Mexican population. Salud Publica Mex. 2011; 53:237–46. [PubMed: 21829889]

Gamble MV, Liu X, Ahsan H, Pilsner JR, Ilievski V, Slavkovich V, Parvez F, Chen Y, Levy D, Factor-Litvak P, Graziano JH. Folate and arsenic metabolism: a double-blind, placebo-controlled folic acid-supplementation trial in Bangladesh. Am J Clin Nutr. 2006; 84:1093–101. [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 Perspect. 2005; 113:1683–8. [PubMed: 16330347]

Gamble MV, Liu X, Slavkovich V, Pilsner JR, Ilievski V, Factor-Litvak P, Levy D, Alam S, Islam M, Parvez F, Ahsan H, Graziano JH. Folic acid supplementation lowers blood arsenic. Am J Clin Nutr. 2007; 86:1202–9. [PubMed: 17921403]

George CM, Gamble M, Slavkovich V, Levy D, Ahmed A, Ahsan H, Graziano J. A cross-sectional study of the impact of blood selenium on blood and urinary arsenic concentrations in Bangladesh. Environ Health. 2013; 12:52. [PubMed: 23816141]

Gilbert-Diamond D, Cottingham KL, Gruber JF, Punshon T, Sayarath V, Gandolfi AJ, Baker ER, Jackson BP, Folt CL, Karagas MR. Rice consumption contributes to arsenic exposure in US women. Proc Natl Acad Sci U S A. 2011; 108:20656–60. [PubMed: 22143778]

Hall MN, Gamble MV. Nutritional manipulation of one-carbon metabolism: effects on arsenic methylation and toxicity. J Toxicol. 2012; 2012:595307. [PubMed: 22523489]

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. Environ Health Perspect. 2009; 117:825–31. [PubMed: 19479028]

Heck JE, Gamble MV, Chen Y, Graziano JH, Slavkovich V, Parvez F, Baron Ja, Howe GR, Ahsan H. Consumption of folate-related nutrients and metabolism of arsenic in Bangladesh. Am J Clin Nutr. 2007; 85:1367–74. [PubMed: 17490975]

Hill KE, McCollum GW, Boeglin ME, Burk RF. Thioredoxin reductase activity is decreased by selenium deficiency. Biochem Biophys Res Commun. 1997; 234:293–5. [PubMed: 9177261]

Howe CG, Niedzwiecki MM, Hall MN, Liu X, Ilievski V, Slavkovich V, Alam S, Siddique AB, Graziano JH, Gamble MV. Folate and Cobalamin Modify Associations between S-adenosylmethionine and Methylated Arsenic Metabolites in Arsenic-Exposed Bangladeshi Adults. J Nutr. 2014; 144:690–7. [PubMed: 24598884]

Hsueh Y, Chiou H, Huang Y. Serum beta-carotene level, arsenic methylation capability,and incidence of skin cancer. Cancer Epidemiol Biomarkers Prev. 1997; 6:589–596. [PubMed: 9264271]

Hsueh YM, Ko YF, Huang YK, Chen HW, Chiou HY, Huang YL, Yang MH, Chen CJ. Determinants of inorganic arsenic methylation capability among residents of the Lanyang Basin, Taiwan: arsenic and selenium exposure and alcohol consumption. Toxicol Lett. 2003; 137:49–63. [PubMed: 12505432]

Ilmiawati C, Ogawa M, Sasaki S, Watanabe T, Kayama F. Urinar y arsenic excretion profiles and associated dietar y factors in Japanese women from a coastal area in Chiba Prefecture. Jichi Med Univ J. 2013; 36:1–11.

Institute of Medicine. Dietary reference intakes: the essential guide to nutrient requirements, Dietary Reference Intakes. :2006.

Jin Y, Zhao F, Zhong Y, Yu X, Sun D, Liao Y, Lv X, Li G, Sun G. Effects of exogenous GSH and methionine on methylation of inorganic arsenic in mice exposed to arsenite through drinking water. Environ Toxicol. 2010; 25:361–6. [PubMed: 19449390]

Johnston CS, Meyer CG, Srilakshmi JC. Vitamin C elevates red blood cell glutathione in healthy adults. Am J Clin Nutr. 1993; 58:103–5. [PubMed: 8317379]

Kamaluddin M, Misbahuddin M. Zinc supplement on tissue arsenic concentration in rats. Bangladesh Med Res Counc Bull. 2006; 32:87–91. [PubMed: 17867273]

Kreppel H. Zinc-Induced Arsenite Tolerance in Mice. Fundam Appl Toxicol. 1994; 23:32–37. [PubMed: 7958560]

Li L, Ekström EC, Goessler W, Lönnerdal B, Nermell B, Yunus M, Rahman A, El Arifeen S, Persson LA, Vahter M. Nutritional status has marginal influence on the metabolism of inorganic arsenic in pregnant Bangladeshi women. Environ Health Perspect. 2008; 116:315–21. [PubMed: 18335097]

López-Carrillo L, Hernández-Ramírez RU, Gandolfi AJ, Ornelas-Aguirre JM, Torres-Sánchez L, Cebrian ME. Arsenic methylation capacity is associated with breast cancer in northern Mexico. Toxicol Appl Pharmacol. 2014; 280:53–59. [PubMed: 25062773]

Millian NS, Garrow TA. Human betaine-homocysteine methyltransferase is a zinc metalloenzyme. Arch Biochem Biophys. 1998; 356:93–8. [PubMed: 9681996]

Niedzwiecki MM, Hall MN, Liu X, Slavkovich V, Ilievski V, Levy D, Alam S, Siddique AB, Parvez F, Graziano JH, Gamble MV. Interaction of plasma glutathione redox and folate deficiency on arsenic methylation capacity in Bangladeshi adults. Free Radic Biol Med. 2014:67–74.

Pilsner JR, Hall MN, Liu X, Ahsan H, Ilievski V, Slavkovich V, Levy D, Factor-Litvak P, Graziano JH, Gamble MV. Associations of plasma selenium with arsenic and genomic methylation of leukocyte DNA in Bangladesh. Environ Health Perspect. 2011; 119:113–8. [PubMed: 21205583]

Ramanathan K, Anusuyadevi M, Shila S, Panneerselvam C. Ascorbic acid and alpha-tocopherol as potent modulators of apoptosis on arsenic induced toxicity in rats. Toxicol Lett. 2005; 156:297–306. [PubMed: 15737492]

Sah S, Vandenberg A, Smits J. Treating chronic arsenic toxicity with high selenium lentil diets. Toxicol Appl Pharmacol. 2013; 272:256–62. [PubMed: 23800687]

Steinmaus C, Carrigan K, Kalman D, Atallah R, Yuan Y, Smith AH. Dietary Intake and Arsenic Methylation in a U.S. Population. Environ Health Perspect. 2005a; 113:1153–1159. [PubMed: 16140620]

Steinmaus C, Yuan Y, Kalman D, Atallah R, Smith AH. Intraindividual variability in arsenic methylation in a U.S. population. Cancer Epidemiol Biomarkers Prev. 2005b; 14:919–24. [PubMed: 15824164]

Steinmaus C, Yuan Y, Kalman D, Rey Oa, Skibola CF, Dauphine D, Basu A, Porter KE, Hubbard A, Bates MN, Smith MT, Smith AH. Individual differences in arsenic metabolism and lung cancer in a case-control study in Cordoba, Argentina. Toxicol Appl Pharmacol. 2010; 247:138–45. [PubMed: 20600216]

Thavarajah D, Vandenberg A, George GN, Pickering IJ. Chemical form of selenium in naturally selenium-rich lentils (Lens culinaris L.) from Saskatchewan. J Agric Food Chem. 2007; 55:7337–41. [PubMed: 17685630]

Tseng CH. A review on environmental factors regulating arsenic methylation in humans. Toxicol Appl Pharmacol. 2009

Wang D, Lin L, Li X, Sun GF. Effects of glutathione on the in vivo metabolism and oxidative stress of arsenic in mice. J Toxicol Sci. 2015; 40:577–583. [PubMed: 26354374]

Willett WC, Howe GR, Kushi LH. Adjustmentfor total energyintake in epidemiologic studies. Am J Clin Nutr. 1997; 65:1220–8.

Yoshida N, Inaoka T, Sultana N, Ahmad SA, Mabuchi A, Shimizu H, Watanabe C. Non-monotonic relationships between arsenic and selenium excretion and its implication on arsenic methylation pattern in a Bangladeshi population. Environ Res. 2015; 140:300–7. [PubMed: 25885118]

Zablotska LB, Chen Y, Graziano JH, Parvez F, van Geen A, Howe GR, Ahsan H. Protective Effects of B Vitamins and Antioxidants on the Risk of Arsenic-Related Skin Lesions in Bangladesh. Environ Health Perspect. 2008; 116:1056–1062. [PubMed: 18709164]

Table 1

Selected characteristics of the study population (n= 1027)

Characteristics	Mean ± S.D.	Median (p10, p90)
Age (years)	53.74 ± 12.66	54 (37, 71)
BMI (kg/m^2)	30.61 ± 6.2	29.95 (23.44, 38.54)
Education (years)	5.86 ± 3.89	6 (1, 11)
Residence (years)	47.92 ± 13.82	48 (30, 66)
Age at menarche (years)	13.02 ± 1.58	13 (11, 15)
Parity (number)	5.46 ± 3.41	4 (2, 10)
Age at first birth (years)	20.16 ± 4.35	19 (16, 26)
Total breastfeeding (months)	61.32 ± 65.73	36 (0, 156)

Table 2

Urinary arsenic metabolites (n= 1027)

Arsenic metabolites	Median	p10	p90
Total As-AsB (μg As/g creat[a])	19.96	6.40	98.41
Total As[b] (μg As/g creat)	25.90	7.17	152.94
iAs	1.95	0.63	9.96
MMA	1.82	0.58	9.37
DMA	15.62	4.87	75.22
AsB	0.85	0.08	37.74
Metabolites[c] (%)			
iAs	10.15	5.39	18.87
MMA	9.84	5.64	15.28
DMA	79.68	68.01	87.40
Methylation ratios[d]			
MMA/iAs	1.00	0.50	1.79
DMA/MMA	8.00	4.52	14.88
DMA/iAs	7.84	3.64	16.12

[a] Creatinine (mg/dL), p10, p50, p90: 18.49, 63.99, 161.5

[b] AsB (μg As/g creat) in Total As= 3.28%

[c] Percentage in Total As

[d] Primary methylation= MMA/iAs, secondary methylation= DMA/MMA, total methylation= DMA/iAs

Table 3

Daily dietary intake of selected nutrients (n= 1027)

Nutrients	Mean ± S.D.	Median (p10, p90)	DRI	% of women <DRI
Retinol (μgRE/day)	222.21 ± 365.91	125.79 (48.33, 446.89)	570[a]	93.48
Vitamin C (mg/day)	62.05 ± 48.15	50.11 (22.05, 109.43)	75[a]	75.17
α-tocopherol (mg/day)	9.87 ± 3.37	9.68 (5.90, 14.01)	13[a]	85.69
Thiamin (mg/day)	1.43 ± 0.69	1.27 (0.74, 2.30)	0.9[a]	21.03
Riboflavin (mg/day)	1.34 ± 0.54	1.28 (0.75, 1.97)	0.9[a]	18.99
Niacin (mg/day)	14.12 ± 6.26	12.93 (7.75, 21.94)	12[a]	43.43
Vitamin B6 (mg/day)	1.62 ± 0.64	1.48 (0.95, 2.41)	1.2[a]	23.37
Folate (μg/day)	338.25 ± 156.45	313.64 (164.63, 542.54)	460[a]	81.60
Vitamin B12 (μg/day)	2.68 ± 3.19	1.82 (0.71, 5.10)	3.0[a]	73.52
Choline (mg/day)	262.88 ± 105.43	245.59 (148.31, 386.51)	425[b]	94.94
Methionine (mg/kg/day)	17.89 ± 7.07	16.75 (9.93, 27.07)	15[bc]	37.78
Betaine (mg/day)	19.81 ± 13.96	17.39 (7.16, 35.37)	–	–
Calcium (mg/day)	705.13 ± 304.53	656.24 (365.97, 1098.89)	1100[a]	90.17
Phosphorus (mg/day)	1762.15 ± 894.43	1524.33 (909.12, 2901.10)	700[a]	2.73
Magnesium (mg/day)	413.53 ± 203.55	358.91 (220.54, 669.43)	260[a]	19.96
Iron (mg/day)	13.11 ± 5.4	12.10 (7.27, 19.78)	16.5[a]	77.99
Zinc (mg/day)	10.11 ± 4.03	9.40 (6.00, 14.75)	11[a]	65.92
Copper (mg/day)	1.43 ± 0.76	1.31 (0.77, 2.14)	0.75[a]	9.15
Sodium (mg/day)	2212.29 ± 987.28	2082.56 (1132.93, 3354.10)	1375[b]	17.92
Potassium (mg/day)	2411 ± 776.81	2295.67 (1517.71, 3432.58)	4700[a]	99.03
Selenium (μg/day)	78.38 ± 33.1	74.00 (40.92, 119.10)	48[a]	16.36
Energy (kcal/day)	2085.48 ± 753.63	1948.58 (1279.16, 3039.00)	–	–

[a] Average for Mexican women aged 19–70 years (Bourges et al., 2009)

[b] Average for U.S. women 19–70 years (Institute of Medicine, 2006)

[c] DRI for methionine + cysteine

Table 4

Regression coefficients ($\times 10^{-3}$)[a] between nutrient intake and urinary arsenic metabolites (n= 1027)

Nutrients (units)	%iAs	%MMA	%DMA	MMA/iAs	DMA/MMA	DMA/iAs
Retinol (μgRE)	−0.04	−0.04	0.03	0.00	0.06	0.07
Vitamin C (mg)	−0.69	−0.04	0.30*	0.64	0.34	0.98*
α-tocopherol (mg)	−10.00	4.19	4.04	14.20*	−0.15	14.10
Thiamin (mg)	−87.20	−18.00	−24.60	69.20	−6.56	62.60
Riboflavin (mg)	−70.70	−2.59	18.60	68.10	21.20	89.30
Niacin (mg)	−7.58	−5.78	−0.95	1.80	4.83	6.63
Vitamin B6 (mg)	23.60	28.10	20.30	4.44	−7.80	−3.36
Folate (400 μg)	−0.35*	−0.08	0.01	0.27	0.09	0.36*
Vitamin B12 (μg)	−14.00*	−7.93	4.89*	6.11	12.80*	18.90*
Choline (mg)	−0.42*	−0.19	0.17*	0.23	0.36*	0.60*
Methionine (g)	−223.00**	−94.80	64.20*	128.00	159.00*	287.00**
Betaine (mg)	−0.70	−0.43	0.25	0.26	0.69	0.95
Calcium (mg)	0.04	0.23**	−0.03	0.19	−0.26*	−0.06
Phosphorus (mg)	0.09	0.04	−0.01	−0.06	−0.04	−0.10
Magnesium (mg)	0.31	0.12	−0.05	−0.19	−0.17	−0.36
Iron (mg)	−26.20**	−15.70*	0.92	10.50	16.60*	27.10*
Zinc (mg)	−37.70***	−24.60***	9.10*	13.10	33.70***	46.80***
Copper (mg)	−41.40	−40.50	15.20	0.92	55.70	56.60
Sodium (mg)	−0.06*	−0.01	0.01	0.04	0.02	0.063*
Potassium (mg)	−0.06	0.02	0.01	0.079*	0.00	0.08
Selenium (μg)	−3.04**	−1.40	0.39	1.64	1.80	3.43*

*p<0.05,

**p<0.01,

***p<0.001

[a]Each model contains only one nutrient adjusted by age (years), total energy intake (kcal/day) and TAs-AsB (μg/l); beta coefficients are log transformed