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Demographic Predictors of Urinary Arsenic in a Low-Income Predominantly Hispanic Pregnancy Cohort in Los Angeles

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Abstract

Background: Arsenic (As) is a contaminant of top public health concern, due to its range of detrimental health effects. Arsenic exposure has not been well-characterized among U.S. Hispanic populations and has been particularly understudied in this population during pregnancy.

Methods: As part of the MADRES ongoing pregnancy cohort of predominantly lower-income, Hispanic women in Los Angeles, CA, we examined levels of maternal 1st trimester urinary arsenic (As), including total As and As metabolites (inorganic (iAs), monomethylated (MMA) and dimethylated As (DMA)), in relation to participant demographics, lifestyle characteristics, and rice/seafood consumption, to identify factors that may influence As exposure and its metabolites during pregnancy (N=241).

Results: Total As concentrations ranged from low to high (0.8–506.2 µg/L, mean: 9.0µg/L, SD: 32.9) in our study population. Foreign-born Hispanic women had 8.6% higher %DMA (95% CI: 3.3%, 13.9%) and –7.7% lower %iAs (95% CI: –12.6%, –2.9%), than non-Hispanic women. A similar trend was observed for U.S.-born Hispanic women. Additionally, maternal age was associated with 0.4% higher %iAs (95% CI: 0.1%, 0.6%) and 0.4% lower %DMA (95% CI: –0.7%, –0.1%) per year, which may indicate poor As methylation capacity.

Conclusion: Individual factors may predict As exposure and metabolism in pregnancy, and in turn, greater risk of adverse health effects.

Keywords

pregnancy; arsenic; environment; cohort; Hispanic; health disparities

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Conflicts of Interest

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Introduction

Pregnancy is a vulnerable period for environmental exposures for both a mother and her growing child. Prenatal exposures to environmental contaminants are widely recognized as important contributors to a multitude of adverse impacts on the *in utero* development and subsequent long-term health of the child.^{1–3} While developing children are uniquely vulnerable to prenatal exposures, a growing body of evidence suggests that such exposures may also increase the risk of health effects for the mother, including pregnancy complications such as gestational diabetes and elevated blood pressure.^{4–8}

Arsenic (As) is a contaminant of top public health concern due to its range of detrimental effects on the health of both adults and children.^{9–11} Mounting evidence indicates that, even at relatively low levels of exposure, As may have profound neurological, cardiovascular and developmental effects.^{9–11} Individuals are most commonly exposed to inorganic As (iAs) via drinking and staple foods, such as rice^{12–15}. However, living in urban industrial environments can also contribute to exposure.^{16, 17} Socially and economically-disadvantaged communities tend to be disproportionately burdened by environmental contaminants and may be concentrated in closer proximity to possible industrial sources of As, such as toxic waste sites, legacy contamination, and dense roadway networks.^{18–21} In California, there is evidence of significant environmental exposure disparities, with Hispanic populations being at greatest risk of living in communities burdened by harmful exposures.^{22, 23} Thus, Hispanic individuals living in California have a high risk for toxic chemical exposures and may bear a larger proportion of the health-related impacts. Further, these groups tend to be underrepresented in epidemiological studies and may have greater barriers to participation.^{24, 25}

Exposure to As can be easily and non-invasively assessed using urine samples, which reflects recent exposure, generally within the last few days¹⁵. Several studies have characterized urinary As and major sources of exposure in the general U.S. population^{26–28} and in certain subpopulations in the U.S.^{13, 29–32} Further, characterizing As metabolites in urine may help identify those at increased risk for adverse health effects, as As metabolic profiles can vary greatly between individuals and differences in methylation efficiency have been related to As toxicity.³³ However, levels of total urinary As and its metabolites have not been well studied among Hispanic populations in the urban U.S. and have been particularly understudied in these populations during pregnancy.

Given the increasing awareness of the need to account for the potential impact of sociodemographic, lifestyle and dietary factors as predictors of environmental exposure burdens and in turn, health disparities, we have conducted cross-sectional analyses to examine predictors of urinary As and its metabolites during pregnancy in the Maternal and Developmental Risks from Environmental and Social Stressors (MADRES) study, a low-income, predominantly Hispanic pregnancy cohort in Los Angeles. We hypothesized that the distribution of urinary As and its metabolites would vary by sociodemographic factors, such as ethnicity and acculturation, as well as by dietary factors, such as rice consumption.

Methods

The MADRES cohort

The MADRES study is an ongoing pregnancy cohort of low-income, primarily Hispanic women living in Southern California during pregnancy. Recruitment for the study is ongoing and began in 2015, and the details of this cohort have been described elsewhere.³⁴ Briefly, pregnant women, age 18 and older, are recruited for participation until 30 weeks gestation from three partner community health care facilities serving primarily low-income, Hispanic obstetric patients in urban Los Angeles. Women are not eligible to participate if they have any of the following conditions: 1) HIV positive status; 2) physical, mental, or cognitive disabilities that prevent participation; 3) current incarceration; 4) multiple gestation pregnancy. All study procedures are completed in either English or Spanish, by trained study staff members fluent in both languages, depending on the primary language of the participant. Informed consent and HIPAA authorization to obtain medical records from each participant is obtained at study entry. All protocols and study materials were approved by the University of Southern California's Institutional Review Board.

In-clinic assessment and questionnaires

In this analysis, we focused only on women who enrolled in MADRES prior to 20 weeks gestation, who upon enrollment, completed an initial in-person assessment during the first half of pregnancy with a trained research coordinator to obtain anthropometric measures, biological samples and information on health and lifestyle by interviewer-administered questionnaire. All participants recruited between November 2015 and January 2019 who provided a urine specimen at the initial visit were included in the current analysis (n=241). Maternal standing height was measured twice by stadiometer (Perspectives Enterprises Model PE-AIM-101). A third measurement of weight and/or height was taken if the first two measurements differed by more than 0.1 pounds (0.05 kg) or 1 cm, respectively. Height measures, with self-reported pre-pregnancy weight, were used to calculate pre-pregnancy body mass index (BMI; kg/m²) according to CDC guidelines.³⁵

During the initial study visit, participants completed a series of questionnaires, which were verbally administered by a research coordinator in either English or Spanish to accommodate the varying levels of literacy among this population. Baseline questionnaire measures included assessment of covariates used in these analyses, such as health history, prior pregnancy history, ever smoking status, second hand smoke exposure during the pregnancy, and demographics (e.g., race and ethnicity, country of origin, household income, education level, employment and occupation, marital status and number of children).

Dietary assessment

Rice and seafood consumption patterns during pregnancy were determined by a questionnaire, administered during the second trimester in either English or Spanish, depending on the preferred language of the participant. Questions were designed to capture usual dietary patterns. Participants were asked if they had ever consumed rice during the index pregnancy. If a participant responded yes, she was subsequently asked how frequently she typically consumed rice to understand general rice consumption patterns: 1–6 times per

year, 7–11 times per year, 1 time per month, 2–3 times per month, 1 time per week, 3–4 times per week, 5–6 times per week, 1 time per day, or 2 or more times per day. Additionally, she was asked the amount of rice that she typically consumed: <0.5 cups, 0.5 to 1.5 cups, or >1.5 cups. Participants were also asked if they had ever consumed any of the following types of fish or seafood during the pregnancy: fish sticks, fresh oily fish, other fresh fish, canned tuna, shellfish, or fried shellfish, selecting from the following options: yes, no, or don't know. If a participant responded yes to this first question, she was additionally asked how frequently she consumed that type of fish or seafood: daily, weekly, monthly, rarely, or don't know. Fish sticks were defined as any commercially prepared frozen, boneless, white fish crumbled and fried in oil. Fresh oily fish was defined as fish containing more than 2% fat, such as blue-eyed cod, silver bream, gemfish, blackfish, mullet, orange roughy, pilchards, redfish, yellowtail, Atlantic salmon, southern Bluefin, tuna, blue grenadier, tailor, blue mackerel, tarwhine, and rainbow trout. Other fresh fish was defined as flounder and shark. Shellfish was defined as shrimp, lobster, crabs, crayfish, clams, mussels, and scallops.

Since almost all of the participants (98.1%) reported ever consuming rice during their pregnancy, women were classified into two categories: those who reported consuming rice on a weekly basis, who also reported that they typically consumed at least 0.5 cups of rice, versus all others.

A combined variable with three categories was created to capture any consumption of fish or seafood during the pregnancy: 1) consumed any type of fish or seafood at least weekly, 2) consumed any type of fish or seafood at least monthly, and 3) never or rarely consumed any type of fish or seafood during the pregnancy. A very small number of women reported not knowing whether they had consumed a specific type of fish or seafood during their pregnancy, but reported never consuming all other types of fish; these women were included in the never/rarely consumed fish or seafood category.

Urinary Metals Biomarker Assessment

Women were asked to provide a spot urine sample upon enrollment (median collection time: 12.4 weeks gestation; interquartile range: 10.1–16.6 weeks) and at a 3rd trimester follow-up visit (median: 33.6 weeks gestation; interquartile range: 32.4–34.6 weeks), in a sterile 90-ml specimen container. Of women who enrolled in their 1st trimester, 91.7% provided a urine specimen. Samples were transported to the laboratory for processing within approximately one hour of collection, where they were stored at 4°C for up to 24 hours prior to processing, before being aliquoted and frozen at –80°C until analysis. Urine samples collected at 1st and 3rd trimester were analyzed for bulk unspiciated levels of As, as well as for As species, including arsenite (iAs^{III}), arsenate (iAs^V), monomethylarsonic acid (MMA), dimethylarsinic acid (DMA) and arsenobetaine (AsB) by high-performance liquid chromatography (HPLC) inductively coupled plasma mass spectrometry (ICP-MS) at the University of Arizona Hazard Identification Core.^{36–38} Total urinary As was calculated by summing inorganic (iAs = iAs^{III}+iAs^V) and organic (DMA, MMA) metabolites.³⁹ Arsenobetaine, a form of As found in fish and seafood was excluded, as it is thought to be non-toxic and is excreted into urine unmetabolized.⁴⁰ %As metabolites were calculated as

follows: %iAs: $iAs/(iAs+MMA+DMA)$, %MMA: $MMA/(iAs+MMA+DMA)$, %DMA: $DMA/(iAs+MMA+DMA)$. Limits of detection (LOD) ranged from 0.004 to 0.1302 $\mu\text{g/L}$ for bulk As, while limits of detection for iAs, MMA and DMA metabolites ranged from 0.0879 to 1.6874 $\mu\text{g/L}$. The % of samples below the LOD for each As species and metabolites were as follows: AsIII, 58.5%; AsV, 53.9%; MMA, 23.7%; DMA, 1.2%; and AsB 29.9% (Supplemental Table 1). Values that were below detection were imputed as LOD divided by the square root of 2. Specific gravity, measured by refractometer (Itago), was used to account for urine dilution, using the following formula: $A_c = A \times [(SG_{\text{mean}} - 1)/(SG - 1)]$, where A = the raw As or As metabolite concentration value, A_c = the SG-adjusted As or As metabolite concentration, SG_{mean} = the mean SG value for the study sample, and SG = the SG value of the participant.⁴¹

Statistical Methods

For the purposes of this analysis, we only included women who were recruited prior to 20 weeks gestation with complete covariate information and a urine sample collected during the first half of pregnancy and available for As analysis as of January 28, 2019, for a total of 241 women. Urinary As and metabolites were measured on all 241 women. We also measured As and its metabolites in urine samples collected during the third trimester of pregnancy for a subset of women (N=25). All women had information on maternal age and preferred language (English or Spanish) at minimum. Statistical analyses were conducted in July 2019.

We calculated descriptive statistics for total urinary As excluding AsB and for each of the four major As metabolites (iAs, MMA, DMA, and AsB) at 1st and 3rd trimester and also for demographic and dietary information. We examined Spearman correlations between 1st and 3rd trimester concentrations of total As and each of the As metabolites and also evaluated potential differences between the paired time points using a Wilcoxon test for paired samples. Additionally, given evidence that the greatest changes in As metabolism occur in the 1st trimester⁴², we examined Spearman correlations between the GA at urine sample collection and 1st trimester measures of total As and each of the As metabolites.

In our primary analyses, we ran separate linear regression models to examine the relationship between log-transformed total urinary As (no AsB) and each of the following demographic covariates: age (continuous), pre-pregnancy BMI (continuous), pre-pregnancy BMI (categorical: underweight/normal, overweight, obese), recruitment site (clinic sites A, B or C), marital status, place of birth (U.S. versus not U.S.), preferred language (Spanish versus English), ethnicity, ethnicity by birth place (including foreign-born non-Hispanic participants), ethnicity by birth place (excluding foreign-born non-Hispanic participants), education, employment status during pregnancy, ever smoking status, whether or not the participant was living with a smoker during the pregnancy, and total household income. Then, we ran a multivariable linear regression model including demographic and lifestyle covariates simultaneously in one model. Models were further adjusted either for first trimester tertiles of AsB, a biomarker of fish/seafood consumption, or for rice and fish/seafood consumption where indicated. Variables for preferred language, years living in the U.S., employment status during pregnancy, and total household income were excluded from

the final multivariable models because they either were 1) not strongly related to urine As or the % metabolites in unadjusted models, or 2) not hypothesized to be potential predictors of urine As. Additional variables were excluded, including pre-pregnancy BMI (continuous), place of birth, ethnicity, ethnicity by birth place (excluding foreign-born non-Hispanic participants) because they were closely related to another demographic variable that was included in final models. For example, we chose to only include the ethnicity by birth place (including foreign-born non-Hispanic participants) variable in final adjusted models, as this variable accounts for both ethnicity and place of birth and was strongly related to preferred language (Chi-Square p-value = 2.2×10^{-16}). Secondary analyses evaluated the same linear regression models (unadjusted and adjusted), but examined the %As metabolites (untransformed) as the outcome variables.

In sensitivity analyses, models were run 1) excluding outliers or influential points and 2) restricting to participants who reported never or rarely consuming seafood during the pregnancy. Outliers and influential points were determined using the outlierTest() and influencePlot() functions in the “car” package in R⁴³, and regression coefficients were compared after including versus excluding these observations from each model.

Statistical significance was determined at $p < 0.05$ (two-sided). All analyses were performed in R version 3.5.0.⁴⁴

Results

Demographics

Table 1 presents the demographic characteristics of 241 women who provided a urine specimen prior to 20 weeks gestation and for whom we had assessed urine metals at the time of this analysis. Women were, on average, 28 (SD: 6) years of age upon enrollment. Mean maternal pre-pregnancy BMI was 28.6 (SD: 6.2) kg/m², with approximately two-thirds (67%) of women falling into the overweight or obese categories, according to CDC guidelines.³⁵

Our study sample was predominantly Hispanic (85.5%) and white (86.2%), and about half of participants (48.5%) reported that they were born outside of the US. Most foreign-born women reported their birthplace as Mexico (30.3%) or Central America (15.4%). There was a wide distribution of length of time living in the US, with 14% of foreign-born women having lived in the US for 10 years or less, 18% for 11 to 20 years and 15% for 20 or more years. Spanish was the preferred language of a third (35.3%) of women.

Approximately half (55.2%) of women in our study had a high school education or less. The majority of women reported that they were either married (29.5%) or living with a partner (48.5%). Half of participants reported working during their pregnancy, and 59% reported an annual household income of less than \$30,000. Approximately one-quarter (26.6%) of women in our sample reported ever smoking, and 7.1% reported living with a smoker during their pregnancy, but few (3.3%) reported personal smoking during their pregnancy.

Exposure biomarkers

Table 2 shows descriptive statistics for 1st trimester concentrations of total urinary As and As metabolites among women in our study. Concentrations are shown with and without adjustment for specific gravity. Specific gravity adjustment for urinary dilution only minimally changed mean concentrations of all measures.

Median total As, calculated by summing metabolites and excluding AsB, was 5.7 µg/L, with values ranging from 0.8–506.2 µg/L. The median iAs concentration was 1.1 µg/L, with values ranging from 0.2–59.0 µg/L, and iAs represented 15.8% of the total metabolites in urine. MMA had a median concentration of 0.5 µg/L and represented the smallest proportion of As metabolites in urine (8.0%). DMA represented the greatest percentage of As metabolites in urine (74.8% of the total), with a median concentration of 4.0 µg/L and a range of 0.4–420.3 µg/L. AsB, a metabolite resulting from seafood consumption, which was excluded from the calculation of total As, had the greatest variability, with a median value of 0.4 µg/L, and a range of 0.1 to 482.9 µg/L.

We also compared As concentrations in the 1st versus 3rd trimester among the 25 women for whom we had analyzed paired urine samples (Supplemental Table 2). Median concentrations for total As and its metabolites, expressed as concentrations and percentages, were similar across the two pregnancy time points, and no significant differences were observed. Correlations between As measures from the two time points ranged from weak to moderate (Supplemental Table 3). We also evaluated correlations between GA at urine collection and each of the 1st trimester As measures (N=241). However, no statistically significant correlations were observed (Supplemental Table 4).

Dietary sources of As exposure

Given that rice and fish/seafood consumption are common potential sources of As exposure, we also explored dietary consumption patterns of these major food types during pregnancy (Supplemental Table 5). Rice consumption was very prevalent in this study population, with 98% of women reporting that they had ever consumed rice during their pregnancy and 60% reporting consumption 2 times per week or more (Supplemental Table 5). Most women (56%) reported typically eating servings of 0.5 to 1.5 cups rice. Fish/seafood consumption were less common, with 73.1% of women reporting never or rarely eating fish/seafood during their pregnancy, 16% reporting monthly consumption and 10.8% reporting weekly consumption (Supplemental Table 5). Among women who reported eating fish/seafood during their pregnancy, canned tuna and shellfish were the most commonly consumed.

Predictors of urinary As concentrations

To begin to explore the relationship of maternal demographic and lifestyle characteristics with urinary As concentrations and %As metabolite profiles in mothers' 1st trimester urine samples, we used unadjusted linear regression models (Supplemental Table 6). Then, we further examined urinary As levels in relation to a subset of these demographic and lifestyle variables in multivariable adjusted models, with versus without additional adjustment for any rice or seafood consumption during pregnancy (Tables 3 and 4).

Age.—Maternal age at enrollment was positively, albeit not significantly, related to levels of total As (excluding AsB), such that each year of age was associated with a 1.4% (95% CI: −0.1, 2.8) higher total As concentration (Table 3). This association was attenuated when either AsB or rice and fish/seafood consumption were included in the model. Maternal age was also positively and significantly related to %iAs, with each year of age associated with a 0.4% (95% CI: 0.1, 0.6) higher iAs% and a corresponding −0.4% (95% CI: −0.7, −0.1) lower %DMA (Table 4).

Acculturation, Ethnicity and Place of Birth.—We explored differences in total As (excluding AsB) and %As metabolites by a number of variables that may be proxies for acculturation in this population. In unadjusted models, women who were born in the US were observed to have 3.3% (95% CI: 0.5, 6.1) higher %iAs and correspondingly, a 3.7% (95% CI: −6.8, −0.6) lower %DMA, as compared to those who were foreign-born (Supplemental Table 6). Similarly, in adjusted models, compared to non-Hispanic women, foreign-born Hispanic women had significantly lower %iAs and higher %DMA in their urine. We observed that foreign-born Hispanic women had 7.7% (95% CI: −12.6, −2.9) lower %iAs in their urine and a corresponding 8.6% (95% CI: 3.3, 13.9) higher %DMA (Table 4). These associations remained statistically significant after additional adjustment for AsB (Supplemental Tables 7-9) or for rice and seafood consumption (Supplemental Table 10). Similar trends were observed for US-born Hispanic women, as compared with non-Hispanic women. However, these associations did not reach statistical significance.

Living with a smoker.—Women who reported living with a smoker during their pregnancy had significantly lower %iAs in their urine (−6.5, 95% CI: −12.3, −0.6), with a borderline statistically significant increase in % DMA (6.4, 95% CI: 0.0, 12.8), as compared to women who did not live with a smoker (Table 4). This association remained significant after additional adjustment for AsB (Supplemental Table 7), and after excluding influential observations as part of a sensitivity analysis (Supplemental Table 11), but was attenuated after adjusting for rice and seafood consumption (Supplemental Table 10). We did not observe any statistically significant differences in total uAs or %MMA between women living with smokers and those who did not.

Parity and Marital Status.—Women who reported that this was not their first pregnancy had significantly lower %MMA in their urine (−1.6, 95% CI: −2.9, −0.2), as compared to women in their first pregnancy (Table 4). Women who identified as single or never married had significantly lower %DMA (−4.9, 95% CI: −9.5, −0.3), as compared to individuals who were married (Table 4).

Rice, fish and seafood consumption.—We examined the influence of dietary sources of As on levels of total As and As metabolites in urine. Although rice and seafood consumption were not significantly associated with total urinary As (excluding AsB) (Table 3), women who reported consuming 0.5 cups or more rice at least weekly had 3.5% (95% CI: 0.1, 6.8) higher %DMA levels, compared to women who reported eating less than 0.5 cups of rice weekly or who reported eating rice less frequently (Supplemental Table 10). We also examined the influence of AsB and found that individuals with higher levels of urinary

AsB also had higher levels of total As (tertile 2: 21.6, 95% CI: 3.3, 43.1; tertile 3: 68.2 95% CI: 42.9, 98.0), as compared to individuals with lower tertiles of AsB (Table 3). However, AsB was not related to levels of % metabolites and additional adjustment for AsB in sensitivity analyses did not substantially alter estimates (Supplemental Tables 7-10).

Other covariates.—We also examined the relationship between total As, as well as the %As metabolites, with other variables including employment status, income, pre-pregnancy BMI category, and level of education. However, while some associations were found to be statistically significant in the unadjusted models (Supplemental Table 6), none remained significant in multivariable regression models (Tables 3 and 4).

Sensitivity Analyses.—We performed a number of sensitivity analyses to test the robustness of our results. We identified several outliers and influential points, which consisted of participants with higher total urine As (excluding AsB) concentrations or very high or low %As metabolite levels. The exclusion of these participants from regression models did not impact our estimates or alter our primary findings (Supplemental Table 11 and 12). Given that the majority of participants reported rarely or never consuming fish or seafood during their pregnancy, we also examined whether limiting our analyses to individuals who rarely or never consumed seafood impacted the estimates. However, the results were very similar in this restricted set of participants (Supplemental Table 13).

Discussion

In a sample of the MADRES pregnancy cohort of primarily low-income Hispanic women living in urban Los Angeles, we observed variation in the distribution of urinary As and As metabolites by several demographic predictors. Specifically, we found that maternal age and ethnicity by birthplace were consistently associated with differences in urinary As and/or its metabolites. We found that total As and As metabolite profiles varied significantly by several indicators of ethnicity and acculturation in this population. For example, as compared to non-Hispanic women, both U.S.-born and foreign-born Hispanic women had urinary As metabolite profiles that may be indicative of more efficient As metabolism (i.e., lower %iAs and higher %DMA). We did not observe that rice or fish/seafood consumption were related to total uAs levels in this population. However, rice consumption was associated with some of the %As metabolites (i.e., higher %DMA). While other studies have begun to show that sociodemographic factors are related to differences in As exposure, few studies have focused on urban, primarily Hispanic populations. Given that prenatal As exposure in pregnant women and their children has been related to long-term health consequences^{45–48}, characterizing the levels and predictors of urinary As and its metabolites is of particular importance for public health. This study suggests that consistent with prior evidence that Hispanic individuals living in California have a high risk for toxic chemical exposures^{22, 23}, women within our predominantly Hispanic study population may have somewhat higher levels of exposure, as compared to other US and Canadian studies of pregnant women.^{49–52} However, the overall levels of As exposure are predominately low to moderate, suggesting that women in our study are not widely exposed to disproportionately higher levels of As.

When iAs is ingested, the majority is metabolized via two sequential methylation reactions, yielding first MMA, then DMA, which is rapidly excreted into urine.³³ Arsenic metabolism varies greatly between individuals, and in populations exposed to high levels of iAs in drinking water, a greater proportion of DMA in urine is considered an indicator of more efficient As methylation and therefore As excretion, whereas a higher proportion of MMA is indicative of inefficient methylation.³³ Arsenic methylation capacity has been related to As toxicity. In support of this, numerous observational studies have observed that a higher proportion of MMA and/or a lower proportion of DMA in urine is associated with increased risk for many adverse health effects,³³ although the opposite has also been observed for certain outcomes such as diabetes and metabolic syndrome.^{53, 54} In the current study, when compared to non-Hispanic women, foreign-born Hispanic women had significantly higher %DMA in their urine and a corresponding trend toward lower %iAs. Similar trends were observed for US-born Hispanic women. One potential explanation is that Hispanic women may have more efficient As metabolism than their non-Hispanic counterparts due to a higher prevalence of genetic variants which improve As metabolism.^{33, 55, 56} Indeed, recent work among women of the Argentinian Andes has observed a higher prevalence of genetic variants in the As methyltransferase among populations that originate from As-endemic regions, such as parts of Central and South America, which may help accelerate As metabolism.⁵⁷ It is possible that such variants are more common in Hispanic women and may be protective against some adverse health effects of As exposure. Differences in diet or nutritional status could also play a role, as certain dietary factors (especially folate) have been related to an increased As methylation capacity.^{54, 58–61} However, it is also possible that the %As metabolites do not reflect As metabolism, but rather organic arsenicals from dietary sources, in this population, as some foods, such as rice and seafood, can be sources of specific As species, such as iAs and DMA.^{62–64} However, in the current study, %iAs and %DMA remained significantly associated with ethnicity by birth place even after additional adjustment for rice and seafood consumption, and also after restricting to participants who reported rarely or never consuming fish or seafood.

We also observed that maternal age was associated with a higher iAs% and a lower %DMA. While not statistically significant, maternal age was also associated with higher total As concentrations in urine. Similar trends have been previously reported in the Maternal-Infant Research on Environmental Chemicals (MIREC) pregnancy cohort of Canadian women, such that statistically significant associations between women's age and increased urinary and blood As were observed.^{52, 65} Age-related increases in urinary As and iAs have been observed in other adult populations in the U.S., including in a population of older low-income Hispanic adults in New Mexico⁶⁶ and a population of older adults residing in Nevada.⁶⁷

In order to put the levels of exposure in our cohort into a broader context, we compared the levels of urinary As in MADRES to those measured in other pregnancy cohorts in the US and around the world. Total urinary As (excluding AsB) levels in MADRES participants (mean 9.0 µg/L, range 0.8–506.2 µg/L) were, on the whole, considerably lower than those observed in pregnancy cohorts in As-endemic regions of the world, such as Bangladesh and Chile, where average total urinary As levels have been observed in the 50–100 µg/L range, with some values reaching upwards of 3000 µg/L.^{42, 68–70} Among Mexican women in the

Biomarkers of Exposure to ARsenic (BEAR) pregnancy cohort, levels of total urinary As measured just prior to delivery were higher on average (mean 37.5 µg/L) than those observed in MADRES (mean: 9.0 µg/L), with some individuals' urinary As levels falling within the 100–300 µg/L range.⁷¹ Bulk levels of urinary As (including AsB) that were reported among pregnant women from Mexico City as part of the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) cohort were also generally higher (median 18.7 µg/L)⁷² than in MADRES participants (median 6.2 µg/L). However, urinary As levels in MADRES participants were on par with, if not slightly higher than, several studies in other pregnancy populations in the US. For example, MADRES urinary levels of total As (no AsB) were very similar to those reported in the New Hampshire Birth Cohort Study (NHBCS) (mean 6.05 ± SD: 13.19), which includes women exposed to a wide range of environmental As via well water.⁴⁹ Studies from the NHBCS have observed associations between these low to moderate levels of As exposure and numerous maternal and newborn health effects, including gestational diabetes, elevated blood pressure, birth outcomes, and infant health.^{45, 73–76} Mean total urinary As levels (including AsB) observed in MADRES were also similar to those of post-partum Mexican-American women living in Texas⁵⁰ and to women in their 1st trimester of pregnancy in the Seattle-Tacoma area Omega cohort.⁵¹ Additionally, very similar levels of As metabolites were observed in 1st trimester urine samples from the Spanish Infancia y Medio Ambiente (INMA) pregnancy cohort (median iAs: 0.4 µg/L, MMA: 0.3 µg/L, DMA: 5.7 µg/L).⁷⁷ Lower overall 1st trimester urinary As was reported in MIREC, a pregnancy cohort of Canadian women, with a high percentage (50–92.5%) of As metabolites below the limit of detection (0.75 µg/L), with the exception of DMA, which was detectable, but low in most women (median 2.4 µg/L).⁵² Lastly, the %As metabolite levels observed in MADRES were within the range of what has been observed previously in samples from pregnant women prior to 20 weeks gestation in other studies, including in populations where overall As exposures were greater than those observed in MADRES.^{42, 68, 70}

Evidence from previous studies suggest that As methylation efficiency and urinary As excretion increase in pregnancy.^{42, 68, 70} We therefore also examined possible trends in urinary As across gestation. In a subset of 25 individuals who contributed samples in both early and late pregnancy, we observed no statistically significant differences in As concentrations or the %As metabolites across trimesters. While small, the sample size for this analysis was similar to a previous study in Chile, which did find significant changes in As metabolism across pregnancy.⁷⁰ Given prior evidence suggesting that the largest changes in As metabolism occur in early pregnancy⁴², we additionally examined correlations between GA at urine collection and the 1st trimester As measures in the larger sample of participants (N=241), as urine samples were collected across a relatively wide range of GAs (median: 12.4, interquartile range: 10.1–16.6 weeks gestation). However, none of the correlations were statistically significant. Although the null findings for MADRES contrast with several previous studies that were conducted in more highly exposed populations, such as in Bangladesh and Chile^{42, 68, 70}, they are consistent with the INMA cohort in Spain, which is characterized by low levels of exposure and did not observe differences in total urinary As by trimester.^{78, 79} It is therefore possible that pregnancy-related improvements in As metabolism and urinary As excretion are less pronounced in populations exposed to low

levels of As, possibly due to greater confounding from dietary sources. Consistent with this, a study of pregnant women in Bangladesh observed that GA-associated differences in %MMA and %DMA were stronger after restricting to participants with urine As concentrations ($< 50 \mu\text{g/L}$).⁴²

Strengths of our study included evaluation of a traditionally research and medically-underserved, sensitive population of pregnant women; collection of biospecimens early in pregnancy; and the availability of a broad range of key covariates, collected by individual interview. Importantly, we cannot rule out the possibilities of confounding by unmeasured covariates, including dietary sources of As that were not captured in our questionnaires, such as rice-based cereals and other rice products. Another limitation of this study is that, although we observed reasonably consistent levels of exposure in both the first and third trimesters of pregnancy, urinary levels of As and metabolites primarily reflect recent exposures and these analyses were performed in a small subset of participants ($n=25$). Thus, our study cannot account for possible variability over time due to differences in environmental or dietary exposures. Urinary levels of As also reflect total exposure; therefore, it is not possible to differentiate between potential routes or sources of exposure. Further work is needed to identify the sources of As exposure for this population. Since this study focused on participants seeking prenatal care in urban Los Angeles, private well use is expected to be very low. MADRES participants are therefore likely to be drinking bottled and/or publicly supplied water, so we would not expect drinking water to be a major contributor to As exposure in this population, but we cannot rule out that some exposure may result from drinking tap water and/or using it for other purposes that may lead to consumption, such as cooking, making ice, etc. Los Angeles county water quality reports for 2016 through 2018 indicate that As levels measured at each of the source water plants that supply the county water system were all below the $10 \mu\text{g/L}$ maximum contaminant limit and ranged from below the $2 \mu\text{g/L}$ detection limit for reporting up to $7 \mu\text{g/L}$.⁸⁰ However, water from various sources are commonly mixed to reduce exposures before the water reaches individual home taps. We did not capture information on drinking water source or consumption habits, so a limitation of this work is that we currently cannot account for drinking water exposures in our analyses. Growing evidence indicates that diet is a major source of As exposure, particularly when levels in drinking water are low.^{13, 81, 82} Although we were able to account for women's reported usual intake of rice and fish/seafood, we did not observe significant associations between these major food sources and total urinary arsenic among MADRES participants in our primary analysis. In secondary analyses, which evaluated maternal characteristics associated with As metabolites in models accounting for rice and fish/seafood intake (Supplemental Table 10) we did observe some evidence that rice intake was associated with significantly higher %DMA and a suggestively lower %iAs. Since most participants in this study (~90%) consume rice at least 2–3 times per month or more, differences may only be apparent in those consuming rice very frequently. Further, although dietary questions were designed to capture 'usual diet', rather than actual consumption, these questions were not measured using validated measures. Also, these dietary questions were asked in the second trimester, which may not reflect diet during the first trimester, when urine samples were collected for metals analysis. It is therefore possible that we are not fully capturing the variability and contribution of these dietary sources of As

in our population. Lastly, a large percentage of individuals in our study population had undetectable levels of iAs in their urine, so observations pertaining to iAs levels must be interpreted with caution.

There are a number of key future directions and research needs that will further our understanding of contributors to As exposure among urban Latina women. While we focused the current study on As exposure in early pregnancy, given the hypothesized importance of exposures during this time period for maternal and child health, we are currently collecting samples at the third trimester paired with more detailed dietary information, to examine the contribution of a range of dietary factors to As exposure in pregnancy. Further, while drinking water is not expected to be a primary source of exposure among urban populations that rely primarily on municipal water, we did not collect information on participants' drinking water and future studies should account for this potential exposure source. Additional assessment of other toxic metals and environmental contaminant exposures, which may contribute to adverse health outcomes and health disparities, is an important area of future work as well.

In conclusion, our study is the first to describe urinary biomarkers of As, indicating low to moderate levels of exposure, in a low-income, primarily Latina urban population. These exposure levels indicate that while women within our predominantly Hispanic study population are not likely to be widely exposed to disproportionately higher levels of As, they are exposed to levels that are similar to those observed in other US pregnancy cohorts, such as the New Hampshire Birth Cohort Study, which have linked low to moderate As exposure to maternal and child health outcomes, such as elevated blood pressure during pregnancy, gestational diabetes, birth weight and early life infant infection risk.^{45, 73, 74, 76} Future work should focus on better understanding why the demographic factors identified in the current study are significant predictors of urine As and As metabolites and identifying potential sources of exposure and strategies that can be implemented to modify exposures, particularly during pregnancy, in this vulnerable population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Participant Characteristics (N = 241)

Variable	Mean $\pm$ SD or N (%)
Age, years	28 $\pm$ 6
Median (range)	28 (18–45)
Pre-Pregnancy BMI, kg/m ²	28.6 $\pm$ 6.2
Median (range)	27.8 (17.6–53.6)
Pre-Pregnancy BMI Category	
Underweight (<18.5 kg/m ²)	6 (2.5)
Normal weight (18.5–24.9 kg/m ²)	73 (30.3)
Overweight (25.0–29.9 kg/m ²)	75 (31.1)
Class I Obese (30.0–34.9 kg/m ²)	56 (23.2)
Class II or III Obese ($\geq$ 35.0 kg/m ²)	31 (12.9)
Born in the U.S.	
Yes	124 (51.5)
No	117 (48.5)
Years Lived in the U.S. ^a	
1–10 Years	34 (14.2)
11–20 Years	44 (18.3)
>20 Years	36 (15.0)
Lifetime U.S. Resident	124 (51.7)
Inconsistent Response	2 (0.8)
Preferred Language	
English	156 (64.7)
Spanish	85 (35.3)
Ethnicity by Birth Place	
Non-Hispanic	35 (14.5)
U.S. Born Hispanic	94 (39.0)
Foreign Born Hispanic	112 (46.5)
Birth Place	
U.S.	124 (51.5)
Mexico	73 (30.3)
Central America	37 (15.4)
South America	2 (0.8)
Other	5 (2.1)
Race ^b	
White	206 (86.2)
Black	24 (10.0)
American Indian or Alaska Native	3 (1.3)

Variable	Mean $\pm$ SD or N (%)
Asian	2 (0.8)
More than One Race	4 (1.7)
Education	
Less than 12 th grade	72 (29.9)
Completed 12 th grade	61 (25.3)
Some college/technical school	82 (34.0)
Completed college and/or some graduate training	26 (10.8)
Marital Status	
Married	71 (29.5)
Living together, not married	117 (48.5)
Never married, single	53 (22.0)
Working Status During Pregnancy ^a	
Ever Worked	121 (50.4)
Never Worked	119 (49.6)
Employment Status During Pregnancy	
Homemaker	72 (29.9)
Student	18 (7.5)
Employed	113 (46.9)
Temporary Medical Leave	1 (0.4)
Unemployed	37 (15.4)
Birth Order of Baby	
1st	83 (34.4)
2nd	74 (30.7)
3rd	45 (18.7)
4th or more	39 (16.2)
Lifetime Cigarette Smoking Status	
Ever Smoked	64 (26.6)
Never Smoked	177 (73.4)
Cigarette Smoking Status During Pregnancy	
Ever Smoked	8 (3.3)
Never Smoked	233 (96.7)
Living with Cigarette Smoker During Pregnancy	
Yes	17 (7.1)
No	224 (92.9)
Total Household Income	
Don't Know	43 (17.8)
<\$15,000	64 (26.6)
\$15,000–\$29,000	78 (32.4)
\$30,000–\$49,999	44 (18.3)

Variable	Mean $\pm$ SD or N (%)
\$50,000–\$99,999	11 (4.6)
\$100,000	1 (0.4)

Sample sizes vary due to missingness or restriction.

^aN=240,

^bN=239

Table 2.

First Trimester Arsenic and Arsenic Metabolite Concentrations (N = 241)

Arsenic Measure	Mean ± SD	Percentile						
		Min.	5 th	25 th	50 th	75 th	95 th	Max.
Total As (no AsB) ^a , µg/L	9.0 ± 32.9	0.8	2.2	3.7	5.7	8.0	18.0	506.2
SG-Adjusted Total As (no AsB) ^b	8.2 ± 21.4	1.7	3.1	4.4	5.6	7.5	14.0	323.6
iAs, µg/L	1.4 ± 4.5	0.2	0.2	0.6	1.1	1.2	2.2	59.0
SG-Adjusted iAs	1.5 ± 3.9	0.2	0.3	0.6	1.0	1.3	2.9	55.5
MMA, µg/L	0.8 ± 3.1	0.1	0.2	0.2	0.5	0.7	1.4	47.8
SG-Adjusted MMA	0.7 ± 2.0	0.1	0.2	0.3	0.5	0.7	1.3	30.6
DMA, µg/L	6.9 ± 27.1	0.4	1.2	2.5	4.0	6.2	15.4	420.3
SG-Adjusted DMA	6.0 ± 17.3	0.8	2.0	3.0	4.1	5.6	11.4	268.7
AsB, µg/L	5.4 ± 33.6	0.1	0.1	0.1	0.4	1.7	13.9	482.9
SG-Adjusted AsB	5.2 ± 32.5	0.0	0.1	0.2	0.5	1.9	14.7	480.2
%iAs	18.4 ± 11.1	3.3	5.5	10.0	15.8	23.3	39.0	64.8
%MMA	8.8 ± 4.4	1.5	3.8	6.0	8.0	10.3	17.1	26.5
%DMA	72.8 ± 12.3	22.5	51.4	65.9	74.8	81.6	89.1	93.7

Abbreviations used: As, arsenic; AsB, arsenobetaine; DMA, dimethyl arsenic; iAs, inorganic arsenic; MMA, monomethyl arsenic; SG, specific gravity; SD, standard deviation

^aTotal As is calculated as the sum of As metabolites iAs, MMA and DMA, excluding AsB.

Table 3.

Multivariable linear regression models of maternal characteristics associated with total As in 1st trimester urine samples.

Maternal Characteristics	Base Model ^d (N=241)		Base Model + Adjustment for Urinary Arsenobetaine ^b (N=241)		Base Model + Adjustment for Rice and Seafood Consumption ^c (N=211)	
	Estimated %Difference in Total As (95% CI) ^d	P ^e	Estimated %Difference in Total As (95% CI) ^d	P ^e	Estimated %Difference in Total As (95% CI) ^d	P ^e
Maternal Age	1.4 (-0.1, 2.8)	0.06	1.1 (-0.2, 2.5)	0.10	1.4 (-0.3, 3.1)	0.11
Maternal Ethnicity by Birthplace						
Non-Hispanic ^f	Ref.	--	Ref.	--	Ref.	--
U.S. Born Hispanic	20.0 (-5.7, 52.7)	0.14	24.5 (-0.4, 55.6)	0.05	12.4 (-15.6, 49.8)	0.42
Foreign-Born Hispanic	20.5 (-5.7, 53.9)	0.13	21.9 (-2.9, 52.9)	0.09	18.2 (-11.4, 57.7)	0.25
Education						
Less than 12 th grade	Ref.	--	Ref.	--	Ref.	--
Completed grade 12	-10.5 (-26.6, 9.2)	0.28	-14.9 (-29.3, 2.3)	0.09	-6.5 (-25.5, 17.2)	0.56
Some college/technical school	-3.2 (-19.9, 17.1)	0.45	-7.6 (-22.6, 10.2)	0.38	-3.5 (-22.0, 19.3)	0.74
Marital Status						
Married	Ref.	--	Ref.	--	Ref.	--
Living Together, Not Married	12.3 (-6.0, 34.1)	0.20	17.9 (-0.1, 39.0)	0.05	15.4 (-5.2, 40.5)	0.15
Never Married, Single	19.0 (-3.7, 47.1)	0.11	20.5 (-1.0, 46.6)	0.06	25.2 (-1.5, 59.2)	0.07
Smoking Status						
Never	Ref.	--	Ref.	--	Ref.	--
Ever	-3.3 (-17.9, 13.9)	0.69	-4.9 (-18.3, 10.7)	0.52	3.0 (-14.5, 24.2)	0.75
Living with a Smoker						
No	Ref.	--	Ref.	--	Ref.	--
Yes	10.0 (-18.1, 47.7)	0.53	6.4 (-19.0, 39.8)	0.65	-4.6 (-32.7, 35.3)	0.79
BMI Category						
Normal/Underweight	Ref.	--	Ref.	--	Ref.	--
Overweight	3.7 (-13.7, 24.7)	0.69	2.1 (-14.0, 21.2)	0.81	0.6 (-17.9, 23.3)	0.95
Obese	1.4 (-15.2, 21.2)	0.88	0.9 (-14.5, 19.0)	0.92	4.7 (-14.7, 28.4)	0.66

Maternal Characteristics	Base Model ^a (N=241)		Base Model + Adjustment for Urinary Arsenobetaine ^b (N=241)		Base Model + Adjustment for Rice and Seafood Consumption ^c (N=211)	
	Estimated %Difference in Total As (95% CI) ^d	P ^e	Estimated %Difference in Total As (95% CI) ^d	P ^e	Estimated %Difference in Total As (95% CI) ^d	P ^e
Parity						
First Pregnancy	Ref.	--	Ref.	--		
Not First Pregnancy	6.9 (-10.0, 27.0)	0.44	10.7 (-5.7, 29.9)	0.21	6.1 (-12.9, 29.3)	0.55
Urinary Arsenobetaine						
Tertile 1 (<0.23 µg/L)	Ref.	--	Ref.	--	Ref.	--
Tertile 2 (0.23 & <1.16 µg/L)	--	--	21.6 (3.3, 43.1)	0.02	--	--
Tertile 3 (1.16 µg/L)	--	--	68.2 (42.9, 98.0)	<0.01	--	--
Rice Consumption						
<½ Cup Less Than Weekly	Ref.	--	Ref.	--	Ref.	--
½ Cup or More At Least Weekly	--	--	--	--	4.9 (-10.7, 23.2)	0.56
Any Seafood Consumption						
Never, Rarely, or Don't Know	Ref.	--	Ref.	--	Ref.	--
Monthly	--	--	--	--	6.1 (-16.1, 34.1)	0.62
At Least Weekly	--	--	--	--	-2.4 (-25.0, 27.0)	0.85

^a All covariates were included simultaneously in the base model, including age, recruitment site, ethnicity by birthplace, education, marital status, smoking status, second hand smoke exposure, BMI category and parity.

^b Base model with additional adjustment for arsenobetaine.

^c Base model with additional adjustment for any rice or seafood consumption

^d Coefficients reflect percent change in total As (excluding AsB). Outcomes were natural log-transformed. Regression coefficients were back-transformed to represent the % difference in the outcome for a unit difference in the predictor using the following formula: $((e^{\beta}) - 1) * 100$

^e Bolded values are statistically significant at $p < 0.05$.

^f Includes foreign-born non-Hispanic women

Multivariable linear regression models of maternal characteristics associated with percentage of As metabolites^a in 1st trimester urine samples (n=241).

Table 4.

Maternal Characteristics	Estimated Difference in %iAs (95% CI) ^c	P	Estimated Difference in %MMA (95% CI) ^c	P	Estimated Difference in %DMA (95% CI) ^c	P
Maternal Age	0.4 (0.1, 0.6)	0.01	0.0 (-0.1, 0.1)	0.93	-0.4 (-0.7, -0.1)	0.02
Maternal Ethnicity by Birthplace						
Non-Hispanic ^e	Ref.	--	Ref.	--	Ref.	--
U.S. Born Hispanic	-4.1 (-8.8, 0.7)	0.09	-0.9 (-2.8, 0.9)	0.33	5.0 (-0.2, 10.3)	0.06
Foreign-Born Hispanic	-7.7 (-12.6, -2.9)	<0.01	-0.9 (-2.8, 1.1)	0.38	8.6 (3.3, 13.9)	<0.01
Education						
Less than 12 th grade	Ref.	--	Ref.	--	Ref.	--
Completed grade 12	0.3 (-3.7, 4.2)	0.89	-0.9 (-2.4, 0.7)	0.28	0.6 (-3.8, 4.9)	0.80
At least some college/technical school	-1.7 (-5.4, 2.1)	0.38	-1.0 (-2.5, 0.5)	0.20	2.6 (-1.5, 6.8)	0.21
Marital Status						
Married	Ref.	--	Ref.	--	Ref.	--
Living Together, Not Married	2.8 (-0.8, 6.3)	0.12	0.3 (-1.1, 1.7)	0.67	-3.1 (-6.9, 0.8)	0.12
Never Married, Single	4.2 (0.0, 8.4)	0.05	0.7 (-0.9, 2.4)	0.39	-4.9 (-9.5, -0.3)	0.04
Smoking Status						
Never	Ref.	--	Ref.	--	Ref.	--
Ever	1.3 (-1.9, 4.6)	0.42	0.5 (-0.8, 1.8)	0.47	-1.8 (-5.4, 1.8)	0.32
Living with a Smoker						
No	Ref.	--	Ref.	--	Ref.	--
Yes	-6.5 (-12.3, -0.6)	0.03	0.1 (-2.2, 2.4)	0.94	6.4 (0.0, 12.8)	0.05
BMI Category						
Normal/Underweight	Ref.	--	Ref.	--	Ref.	--
Overweight	0.5 (-3.2, 4.1)	0.79	-1.2 (-2.6, 0.3)	0.11	0.7 (-3.3, 4.7)	0.73
Obese	1.3 (-2.3, 4.8)	0.42	-0.9 (-2.3, 0.5)	0.20	-0.4 (-4.3, 3.5)	0.85
Parity						
First Pregnancy	Ref.	--	Ref.	--	Ref.	--

Maternal Characteristics	Estimated Difference in %iAs (95% CI) ^c	P	Estimated Difference in %MMA (95% CI) ^c	P	Estimated Difference in %DMA (95% CI) ^c	P
Not First Pregnancy	-0.7 (-4.1, 2.7)	0.68	-1.6 (-2.9, -0.2)	0.02	2.3 (-1.5, 6.0)	0.23

^a All covariates were included simultaneously in one model (age, recruitment site, ethnicity by birthplace, education, marital status, smoking status, second hand smoke exposure, BMI category and parity).

^b Percentage of metabolites calculated percent of total As (excluding AsB).

^c Coefficients reflect the change in the % metabolites.

^d Bolded values are statistically significant at p<0.05.

^e Includes foreign-born non-Hispanic women