Arsenic speciation and concentration in the urine of infants in Xiamen, China：A cross-sectional survey

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Abstract

Background

A dearth of knowledge regarding toxicity markers of Arsenic(As)exposure in infants exists. Thus, the study aimed to identify the reference value for the total As content in urine and the toxicity markers of As exposure and to analyze the factors influencing urinary As (UAs) levels in infants.

Methods

In total, 895 urine samples were collected from infants in Xiamen, China and analyzed for total UAs using inductively coupled plasma coupled with mass spectrometry (ICP-MS). Ninety-four of the samples were randomly selected for the analysis of As species using ICP-MS. The relationship of lifestyle and diet with UAs levels was analyzed by ordered logistic regression analysis.

Results

The total UAs level was found to be 42.60 ± 148.48 μg/gCr, and the 95% upper limit was 962.35 μg/gCr. The unmethylated proportion of UAs was 38.57% (24.67–64.95%). The combined toxicity of different As species multiplied by the corresponding population detection rate was the highest for $iAs^{\square}$+DMA^{V}+$iAs^{\square}$. The total UAs was positively associated with age in 6–36-month-old infants; The intakes of breast milk, seafood, meat, vegetable, and canned beverage were identified as factors contributing to elevated total UAs.

Conclusions

We concluded that the reference value for UAs in infants in Xiamen was 962.35 μg/gCr. $iAs^{\square}$+DMA^{V}+$iAs^{\square}$ was a better combination to evaluate the combined effects of As exposure in infants. The intake of As-contaminated food by mothers and infants, which might be the main cause of high UAs in infants.

1. Background

Arsenic (As) is a metal-like element commonly found in the environment. It occurs in nature in different oxidation states and salts and can enter the human body through the respiratory or digestive tract or the skin[1]. Organic As is most commonly found in seafood, as arsenobetaine(AB)and is considered nontoxic [2]. Inorganic As which is highly toxic, is present in the environment in the form of trivalent inorganic As (iAs^{III}) and pentavalent inorganic As (iAs^{V}) [3]. In addition to drinking water, bioavailability of inorganic As in food is also considered to be high [4], and harmful to health [5].The metabolism of As is a complex process that occurs mainly through the oxidative methylation of As in the liver [6].This was previously

thought to be a detoxification process [1, 7]. However, studies [8, 9] have now shown that the metabolism of As is closely related to its toxicity. Inorganic As is commonly metabolized into monomethylarsonic acid (MMA), and dimethylarsinic acid (DMA). Inorganic As species are found to be more toxic than organic As, and trivalent As compounds are more toxic than pentavalent As compounds. Among them, MMA^{III} is the most toxic, followed by iAs^{III}, iAs^{V}, MMA^{V}, and DMA^{V} [10–12].

Chronic arsenic exposure is a serious public health problem and As contamination has been reported in many countries like Bangladesh [13], China [14], the USA [15] and Chile [16]. Epidemiological studies have shown that chronic As exposure can lead to cancer [17], diabetes [18], skin lesions [19], cardiovascular disease [20], and genital damage [21] among other adverse effects. As toxicity is particularly a great concern in children, because prolonged exposure to As can affect their motor and behavioral abilities, cognitive function, intelligence [22], and nervous system development [23], and early exposure to arsenic in children has long-term health effects [24]. Epidemiological studies have shown that high levels of exposure to As in the uterus and/or early life are associated with higher rates of mortality due to cancer, and cardiovascular and respiratory diseases [25] .

Xiamen is near the coastal and is one of the main marine polluted areas of China [26]. Long-term and large-scale users of common vegetables, fruits, seafood and meat in Xiamen will lead to excessive intake of arsenic. [27]. However, it is unclear whether food consumption increases the risk of As exposure and if this As exposure causes an increase in As metabolite levels. Different exposure routes and exposed population have an impact on the content and form of arsenic metabolites [22], a specific combination of As species in the body that can serve as a marker of As exposure has not been identified.

Most studies on urinary arsenic in China focus on populations with high As environments, and there is a relatively lack of surveys on urinary arsenic levels in Chinese infants and young children[28]. Therefore, the purpose of this study was to evaluate the total UAs concentration and species in infants in Xiamen, and to propose the reference value of total UAs in infants. The study also aimed to analyze the exposure to different As species and the related toxicity of different combinations of As species, and to explore the possible factors influencing total UAs levels, to provide a reference value for the epidemiological characteristics of As exposure in infants in coastal areas.

2. Materials And Methods

2.1 Human subjects and urine samples

The subjects were selected from 10 community hospitals by random cluster sampling method from June to August 2018. In total, 905 infants participated in the study,10 infants without urine sample were excluded. Finally, 895 infants (99.22% of them were Han Chinese) aged from 1 to 36 months old were included.

Inclusion criteria: the subjects included in the study were permanent residents of Xiamen, with on hasn't birth defects. Mela and female, age range from 0–36 mouths old, Parents or legal guardians sign informed consent.

Exclusion criteria: 1) Birth defects; 2) Severe liver and renal dysfunction (serum aspartate aminotransferase, alanine aminotransferase over three-folds of upper limit of the normal range, Glomerular filtration rate ≤ 30ml/min/1.73m^2).3) No urine was collected and the questionnaire information was incomplete.

The infants were divided into different groups according to the age (0–3, 3–6, 6–12, 12–24, and 24–36 months old). The average height and weight of the subjects was 63.09 cm and 11.21 kg, respectively. Signed informed consent was obtained from the parents before the participation of the infants in the study, and the Ethics Committee of the School of Medicine, Xiamen University approved the study. After overnight fasting, parents took their infants to community hospitals. Investigators explain to parents the dos of collecting urine. With the help of parents, urine samples of infants were collected in the plastic toilet device, and investigators would transfer urine to 100 mL acid-washed polypropylene containers in the morning, and samples were immediately stored at or below − 20°C. The polypropylene containers were soaked in 30% nitric acid solution for more than 8 hours and washed with ultrapure water before being used.

2.2 Questionnaire

Parents reported infants' diets with a food frequency questionnaire (FFQ). The diet parameters that were studied included intake frequency (frequency in Supplemental Material, Table S2) of breast milk, vegetables, meat, seafood (fish, crustaceans, shellfish, and cephalopods), milk, and canned goods (drinks, food). The parameters to assess lifestyle included family socioeconomic status (parents' educational background, occupation, and income) and living environment (distance of the house from the road, residential floor, year of housing construction, housing within 1 km distance from a factory, and housing within 1 km from a source of soot pollution)were added to FFQ. Trained staff measured infants' weight (kg) and height (cm) to calculate the Kaup index in kg/cm^2. At the same time the urine samples were collected following standard protocols.

2.3 Determination of total arsenic and arsenic species in urine

2.3.1 Total As content

Aliquots of 500 µL urine sample were diluted with 1% nitric acid to 100 mL. A 0.45-µm filter was used to remove particles and microbes. Ultrapure water (500 µL) drained with 1% nitric acid to 10 mL was used as a blank control.

The 1000 µg/LAs standard solution was diluted with 1% nitric acid to the following concentrations: 0 µg/L, 2 µg/L, 4 µg/L, 8 µg/L, 16 µg/L, 32 µg/L, and the solutions were analyzed by inductively coupled

plasma mass spectrometry (ICP-MS)[29]. Because urine creatinine (Cr) adjustment was widely considered to be a practical approach to correct metal concentrations for the hydration-driven dilution effects[30, 31], such as a person who drinks more fluids than another person may have a higher but more diluted urine output, and the Cr-correction can partially adjust for differences in lean body mass or renal function among individuals. The data of UAs in urine were normalized using Cr levels. The concentrations of Cr in urine samples were determined using a Creatinine Determination Kit (Enzymatic Method) (DICT-500, Bioassay Systems, USA).

2.3.2 Separation and detection of iAs^{III}, iAs^{V}, MMA^{V}, and DMA^{V}

Sample aliquots of 500 μL were mixed with 500 μL of 40 mmol/L–10 mmol/L H_3BO_3-$Na_2B_4O_7$ buffer and centrifuged. Separation of the four As species was performed using inductively coupled plasma mass spectrometry (ICP-MS)[29]. The separation voltage was 13 kV and the injection time was 14 s. The As species standard sample was made every five needles to achieve the monitoring and revising the arsenic signal detection signal throughout the experiment.

2.3.3 Determination of combined toxicity of As species

Based on the principle of half lethal dose (*LD50*) of mixed toxins, the combined toxicity (*ct*) of different As species in the urine was calculated. The *ct* value was equal to the sum of the results for each valence concentration divided by each valence threshold dose.

$ct = iAs^{III}$ /threshold dose + iAs^{V} /threshold dose + MMA^{V} /threshold dose + DMA^{V} /threshold dose

Because threshold dose in various arsenic species has not been recognized, the threshold dose is replaced by the *LD50* of various arsenic species. Based on the previous studies. the *LD50* values for $iAs^{\square}$, $iAs^{\square}$, MMA^{V} and DMA^{V} are found to be 14 mg/kg, 20 mg/kg, 200–1800 mg/kg, and 200–2600 mg/kg [32, 33], respectively. $iAs^{\square}$ is 1.5, 71.4, and 100 times as toxic as $iAs^{\square}$, MMA^{V} and DMA^{V}, respectively. Therefore $ct = iAs^{\square}+MMA^{V}/71.4 + DMA^{V}/100 + iAs^{\square}/1.5$.

The toxicity of arsenic speciation combination in the urine of each infant was obtained by the above formula. However, the detection rate (*dt*) of different As species combinations was different, we didn't only consider the toxicity intensity, but also consider the frequency of different arsenic speciation combinations when the exposure toxicity of the population was evaluated. Finally, we used the average level of *ct* of each As speciation combination in the population multiplied by *dt* of the combination in the population (*ct*dt*) to compare the degree of exposure toxicity of different As speciation combinations in the population.

2.4 Quality control

There are strict quality control requirements in sample collection, questionnaire survey and sample testing. Before the formal investigation, we will train researchers and conduct research publicity. All

investigators must be trained and qualified to conduct on-the-job investigations. The questionnaire survey was completed by one-on-one, face-to-face question-and-answer method, and supervisors were set up to supervise the detection of physical indicators and sampling specifications, and to check the improvement of the questionnaire information. After the survey, 10% of the questionnaires were selected for repeated surveys, and the questionnaires were entered by double entry.

In the process of sample testing, quality control measures including the analysis of reagent blanks, parallel samples, spiked samples, standard samples, and detection limit. The mean response of three replicates for each concentration was used to generate the standard curve. The limits of UAs and four As species (iAs^{III}, iAs^{V}, MMA^{V}, and DMA^{V}) were 0.4 μg/L, 0.3 μg/L, 0.4 μg/L, 0.4 μg/L, and 0.5 μg/L, respectively. The coefficient of variation for the parallel measurements was less than 5.2%, and the recovery rate of the spiked samples ranged from 95.5–105.5%.

2.5 Statistical analysis.

The data are expressed as the mean, median, standard deviation, and percentiles. Normality test was used to determine UAs distribution. Spearman rank correlation analysis was used to analyze the influence of individual and family factors (age, sex, birth weight, Kaup index, parents' educational background, parents' smoking history, family's monthly income, and parental occupation), environmental factors (distance of the house from the road, residential floor, year of housing construction, housing within 1 km distance from a factory, and housing within 1 km from a source of soot pollution), and dietary habits (breast mike, vegetables, meat, fish, crustaceans, shellfish, cephalopods, canned beverages, canned food, milk, and bone soup) on total UAs concentration in infants. Ordered logistic regression models were used to analyze the risk factors contributing to high total UAs levels. Non-parametrictest was used to test differences in UAs concentrations, ct, and unmethylated proportion. The probability level of for hypothesis tests was set at $\alpha = 0.05$. All analyses were carried out with SPSS software for IBM SPSS Statistics 22.0(IBM Corp. Armonk, NY, USA).

3. Results

3.1 Subject characteristics

The distribution of sex, age, nationality, Kaup index, birth weight, monthly household income, and parents'educational history has been presented in Supplemental Material, Table S1. The average height and weight recorded were 63.09 cm and 11.21 kg, respectively. Most parents had a junior high school degree or above. In total, 23.49% of parents had an occupation with a risk of As exposure.

3.2 Analysis of urine As levels in infants

3.2.1 Total urinary As levels

The total concentration of As in the urine of the subjects showed an obvious positively skewed distribution (SKEW 7.852, KURT 96.014). The median ± interquartile (M ± Q) range for total UAs levels was

42.60 ± 148.48 μg/gCr (unadjusted Cr, 7.51 ± 27.42 μg/L). The mean total As level in the urine of male and female infants was subjects was 38.66 ± 131.94 μg/gCr (unadjusted Cr, 8.61 ± 24,81 μg/L), and 48.43 ± 159.88 μg/gCr (unadjusted Cr, 7.26 ± 29.81 μg/L), respectively. The 95% percentiles of total As levels in the urine of infants from Xiamen was 962.35 μg/gCr (unadjusted Cr, 209.56 μg/L), and there was no significant difference between male and female infants (Table 1).

Table 1
Total UAs in Infants

Gender	N	creatinine-adjusted*	M ± Q	Max	Min	95%CI
Male	483	No	8.16 ± 24.81	1101.60	0.01	191.48
		Yes	38.66 ± 131.94	4803.47	0.15	804.27
Female	412	No	7.26 ± 29.81	990.80	0.06	224.56
		Yes	48.43 ± 159.37	8691.58	0.39	1136.91
Total	895	No	7.51 ± 27.42	1101.60	0.01	209.56
		Yes	42.60 ± 148.48	8691.578	0.15	962.35
*unadjusted (μg/L) and creatinine-adjusted (μg/gCr)						

3.2.2 As speciation in urine

We detected four As species in urine: iAs^{III}, iAs^{V}, MMA^{V} and DMA^{V}. Their detectable amounts in urine were 87 (92.55%), 54 (57.45%), 86 (91.49%), and 29 (30.85%), respectively. The detection rates for iAs^{III} and DMA^{V} were higher than those for iAs^{V} and MMA^{V}, and iAs^{III} had the highest detection rate. DMA^{V} had a mean concentration of 19.22 μg/gCr. The mean concentration of iAs^{III} was 15.03 μg/gCr, which was higher than that of iAs^{V} and MMA^{V}. The As concentration of the four species, from highest to lowest, was DMA^{V} (10.45 μg/gCr), iAs^{III} (8.95 μg/gCr), MMA^{V} (1.81 μg/gCr), and iAs^{V} (1.64 μg/gCr) (Table 2).

Table 2
Arsenic Speciation and Concentrations in urine

Distribution of As	Positive detection number	Positive detection rate (%)	Content (μg/gCr)				Content of As (μg/gCr)
			M ± Q*	max	min	95%CI	
$iAs^{Ⅲ}$	87	92.55	15.03 ± 28.47	601.55	0.43	33.49	8.95
$iAs^{Ⅴ}$	54	57.45	3.30 ± 5.71	202.56	0.40	6.28	1.64
MMA	29	30.85	3.38 ± 5.75	313.55	0.45	5.11	1.81
DMA	86	91.49	19.22 ± 38.06	333.46	0.52	73.81	10.45

* "M ± Q" means median ± interquartile

3.2.3 Different combinations of As speciation in infant urine

The four As species ($iAs^{Ⅲ}$, $iAs^{Ⅴ}$, MMA^{V}, and DMA^{V}) could theoretically form 16 combinations, and 10 of these combinations were detected in the urine of 94 infants. These included two-species, three-species, and four-species combinations accounting for 33.0%, 33.0% and 25.5% of the samples, respectively. Overall, 2.10% of the samples showed no detectable As species. Out of the 31 samples that tested positive for two-species combinations, the $iAs^{Ⅲ}$+DMA^{V} species combination was detected in 27. Similarly, $iAs^{Ⅲ}$+DMA^{V}+$iAs^{Ⅴ}$ was the most common three-species combination to be detected (22 of 31 samples) (Table 3). The number of detectable As species was positively correlated with total UAs levels (r_s=0.227, P = 0.031).

3.2.4 Combined toxicity of As speciation in infants

Different As species had different toxicity, and thus, a combination of As species would show varied toxicity. The *ct* values for different As combinations were sorted from highest to lowest as follows: $iAs^{Ⅲ}$+DMA^{V}+$iAs^{Ⅴ}$ > $iAs^{Ⅲ}$+DMA^{V}+MMA^{V} > $iAs^{Ⅲ}$+DMA^{V} > $iAs^{Ⅲ}$+DMA^{V}+MMA^{V}+$iAs^{Ⅴ}$ > $iAs^{Ⅲ}$>DMA^{V}. The result of *ct*dt* value of different As combinations was sorted from highest to lowest as follows: $iAs^{Ⅲ}$+DMA + $iAs^{Ⅴ}$ > $iAs^{Ⅲ}$+DMA > $iAs^{Ⅲ}$+DMA + MMA + $iAs^{Ⅴ}$ > $iAs^{Ⅲ}$+DMA + MMA > $iAs^{Ⅴ}$ > DMA^{V}. The difference in the degree of exposure toxicity was found to be statistically significant (P = 0.014) (Table 3).

Table 3
Combinations of As species in infant urine(N = 94)

Detectable amount of As species in urine	Combination of As species	Positive detection number	Sum of positive detection number	Positive detection rate(%)	*Ct**	*Ct* × *Dt***
Zone	None	2	2	2.1	-	-
One	$iAs^{Ⅲ}$	3	6	6.4	23.31 ± 13.98	1.49 ± 0.52
	DMA	3			0.16 ± 0.14	0.02 ± 0.01
Two	$iAs^{Ⅲ}$+DMA	27	31	33.0	31.9 3 ± 8.69	10.62 ± 3.16
	$iAs^{Ⅲ}$+MMA	1			-	-
	$iAs^{Ⅲ}$+$iAs^{Ⅴ}$	1			-	-
	DMV + $iAs^{Ⅴ}$	2			-	-
Three	$iAs^{Ⅲ}$+DMA + $iAs^{Ⅴ}$	27	31	33.0	49.24 ± 17.22	16.25 ± 5.68
	$iAs^{Ⅲ}$+DMA + MMA	4			35.50 ± 18.85	1.51 ± 0.40
Four	$iAs^{Ⅲ}$+DMA + MMA + $iAs^{Ⅴ}$	24	24	25.5	25.69 ± 7.63	6.42 ± 1.91

***** Ct **means the combined toxicity (ct) of different As species**

****** Dt **means the detection rate (dt) of different As species combinations**

3.3 Unmethylated proportion of As in infants

The unmethylated proportion represents the proportion of urinary As remaining in the unmethylated form. The metabolism of iAs involves a series of reductive and oxidative methylation processes catalyzed by the enzyme arsenic-methyltransferase with S-adenosylmethionine as the methyl group donor that results in the formation of the MMA^{V} and DMA^{V} that are primarily excreted in the urine [34]. MMA^{V} and DMA^{V} potentially posing less toxic effects [35], therefore, the unmethylated proportion could be used to evaluate the metabolism of As, and it equals As content of inorganic As to the total As content of inorganic As and organic As. Based on the formula, inorganic As (%) = ($iAs^{Ⅲ}$+$iAs^{Ⅴ}$)/($iAs^{Ⅲ}$+ $iAs^{Ⅴ}$+MMA + DMA)*100, we calculated the unmethylated proportion of 94 samples. The result showed that the median (lower quartile, upper quartile; $M[Q_L, Q_U]$) of unmethylated proportion was 38.57%(24.67–64.95%)among all infants, but

it was higher in female infants than in males infants ($P = 0.027$) and higher in 0–6-month-old infants than in 6–36 months infants ($P = 0.003$). The unmethylated proportion for different As speciation combinations was sorted from highest to lowest as follows: $iAs^{\square}$+DMA^{V}+$iAs^{\square}$ > $iAs^{\square}$+DMA^{V} > $iAs^{\square}$+DMA^{V}+MMA^{V}+$iAs^{\square}$ (Table 4).

Table 4
The unmethylated proportion of As in infant urine

		N	Unmethylated As M(QL,QU)*□%	Kruskal-Wallis Test *P* (2-tailed)
Gender	Male	56	31.95(21.79, 57.59)	0.027
	Female	48	51.00(32.10, 70.80)	
Mouths age	0–6	36	55.09(35.47, 68.94)	0.003
	6–36	58	32.41(20.55, 56.19)	
Combinations of As species	$iAs^{\square}$+DMA	27	46.15(19.77, 63.91)	0.000
	$iAs^{\square}$+DMA + $iAs^{\square}$	27	57.77(36.24, 72.28)	
	$iAs^{\square}$+DMA + MMA + $iAs^{\square}$	23	31.56(24.67, 37.53)	
Total sample		94	38.57(24.67, 64.95)	——

*"M(QL,QU)" means the median (lower quartile, upper quartile)

3.4 Potential factors influencing total UAs in infants

Subjects were divided into three groups based on their total UAs levels: group Y1 (< 320 μg/gCr), group Y2 (320–640 μg/gCr) and group Y3(≥ 640 μg/gCr). All variables are shown in Supplemental Material Table S2.

3.4.1 Relationship between individual and family factors, and total UAs in infants

The total UAs was higher in 0–3-month-old infants but lower in 3–6-month-old infants; at 6 to 36 months of age, the levels became higher again. The total UAs level was negatively correlated with birth weight

(r_s=-0.260, P = 0.000), father's education (r_s=-0.135, P = 0.000),and family's monthly income (r_s=-0.066, P = 0.049) (Table 5).

3.4.2 Relationship between living environment and total UAs in infants

Both order correlation analysis (Table 5) and logistic regression (Table 6) showed that there was no significant relationship between the living environment and total UAs level.

3.4.3 Relationship between diet and total UAs in infants

The intake of breast mike, vegetables, meat, fish, shellfish, cephalopod, canned food, canned drinks, milk, and bone soup was positively correlated with total UAs levels (Table 5). The almost daily intake compared with intake < 2 times per year, the almost daily intake of breast milk (odds ratio (*OR*), 1.003–2.507, P = 0.048), fish(*OR*, 4.263–21.607, P = 0.000), crustaceans (*OR*, 1.448–6.360, P = 0.003), shellfish(*OR*, 1.392–7.531, P = 0.006), cephalopods(*OR*, 1.898–7.965, P = 0.000), meat(*OR*, 3.536–21.542, P = 0.000), vegetables(*OR*, 3.536–21.542, P = 0.000), and canned drinks (*OR*, 1.232–6.987, P = 0.015) was associated with a higher risk of high total UAs after adjusting for factors (age, sex, birth weight, parents' educational background, and monthly family income) (Table 6).

Table 5
Sperman rank correlation analysis between influencing factors and total UAs in infants

	Influencing factors	r_s	*P* (2-tailed)
Individual	0–36 Mouths age	-0.127	0.000
	0–3 Mouths age	0.119	0.095
	3–6 Mouths age	-0.170	0.076
	6–36 Mouths age	0.142	0.000
	Gender	0.054	0.114
	birth weight	-0.260	0.000
	Kaup Index (kg/cm^2)	-0.021	0.639
Lifestyle	Mother's education background	-0.019	0.663
	Father's education background	-0.135	0.000
	Father smoking	0.060	0.070
	Monthly household income (RMB)	-0.066	0.049
	Parental occupation	-0.001	0.970
	Distance of the house from the road (m)	0.006	0.885
	Residential floor	0.050	0.138
	Year of Housing Construction	0.007	0.883
	Housing within 1 km distance from a factory	-0.008	0.808
	Housing within 1 km distance from a source of soot pollution	0.020	0.564
Diets	Breast mike	0.072	0.028
	Vegetables	0.129	< 0.001
	Meat	0.112	0.001
	Fish	0.169	< 0.001

	Influencing factors	r_s	*P* (2-tailed)
	Crustaceans	0.172	< 0.001
	Shellfish	0.158	< 0.001
	Cephalopod	0.161	< 0.001
	Canned food	0.117	< 0.001
	Canned beverage	0.105	0.029
	Milk	0.118	< 0.001
	Bone soup	0.096	0.004

Table 6
An ordered Logistic regression analysis of influencing factors and total UAs in infants

Influencing factors (A *vs* B)*	Model**	*OR and* 95%*CI*	*P* (2-tailed)
Distance of the house from the road (Street Room *vs* Stay away)	Model1	1.251 (0.875–1.788)	0.218
	Model2	1.141 (0.796–1.634)	0.473
	Model3	1.239 (0.867–1.722)	0.241
Residential floor(Cottage *vs* ≥ 7th floor)	Model1	0.536 (0.156–1.840)	0.321
	Model2	0.495(0.143–1.709)	0.266
	Model3	0.590 (0.169–2.065)	0.409
Housing within 1 km distance from a factory(Yes *vs* No)	Model1	2.046 (0.344–12.170)	0.432
	Model2	1.813 (0.304–10.837)	0.514
	Model3	1.012 (0.131–7.807)	0.991
Year of Housing Construction (After the 1980s *vs* before the 1980s)	Model1	0.906 (0.656–1.251)	0.549
	Model2	0.883 (0.636–1.226)	0.458
	Model3	0.976 (0.694–1.372)	0.889
Housing within 1 km distance from a source of soot pollution (Yes *vs* No)	Model1	1.859 (0.054– 64.328)	0.732
	Model2	1.713 (0.049–59.442)	0.766
	Model3	1.749 (0.050– 61.375)	0.758
Breast mike (Totally *vs* Never)	Model1	1.584 (1.020–2.460)	0.041
	Model2	1.595 (1.018–2.499)	0.042
	Model3	1.586 (1.003– 2.507)	0.048
Vegetables (Almost every day *vs* < 2 times/year)	Model1	3.967 (1.933– 8.142)	0.000
	Model2	6.910 (3.271–14.600)	0.000
	Model3	6.653 (3.536–21.542)	0.000
Meat (Almost every day *vs* ≤ 2 times/year)	Model1	5.669 (2.394–3.437)	0.432

* "A vs B" means compared to factor B, the risk that factor A causes an increase in total UAs

** "Model" which including three different models. Model1 represents univariate regression results, Model2 represents regression results for adjusting month age, birth weight, and gender, and Model3 represents regression results for adjusting month age, birth weight, gender, father's educational background, and monthly household income.

Influencing factors (A *vs* B)*	Model**	*OR and* 95%*CI*	*P* (2-tailed)
	Model2	9.272 (3.827–22.466)	0.000
	Model3	8.723 (3.536–21.542)	0.000
Fish	Model1	5.807 (2.718–12.416)	0.000
(Almost every day *vs*	Model2	9.915 (4.513–21.758)	0.000
< 2 times/year)	Model3	9.593 (4.263–21.607)	0.000
Crustaceans	Model1	3.452 (1.548–7.698)	0.002
(Almost every day *vs*	Model2	3.364 (1.578–7.164)	0.002
< 2 times/year)	Model3	3.034 (1.448– 6.360)	0.003
Shellfish	Model1	2.807 (1.290–3.258)	0.009
(Almost every day *vs*	Model2	3.310 (1.502– 7.301)	0.003
< 2 times/year)	Model3	3.323 (1.392–7.531)	0.006
Cephalopod	Model1	2.954 (1.495–5.386)	0.000
(Almost every day *vs*	Model2	3.225 (1.616–6.437)	0.001
< 2 times/year)	Model3	3.896 (1.898–7.965)	0.000
Canned food	Model1	0.672 (0.087–1.944)	0.457
(Almost every day *vs*	Model2	0.269 (0.457–0.996)	0.996
< 2 times/year)	Model3	1.014 (0.462–2.228)	0.973
Canned beverage(Almost every day *vs*	Model1	2.866 (1.298–6.322)	0.009
< 2 times/year)	Model2	3.056 (1.368–6.828)	0.006
	Model3	2.936 (1.232–6.987)	0.015
Milk	Model1	2.54×10^{-06} (1.60×10^{-06}–4.42×10^{-06})	0.000
(Almost every day *vs*			
< 2 times/year)			

***** "A vs B" means compared to factor B, the risk that factor A causes an increase in total UAs

****** "Model" which including three different models. Model1 represents univariate regression results, Model2 represents regression results for adjusting month age, birth weight, and gender, and Model3 represents regression results for adjusting month age, birth weight, gender, father's educational background, and monthly household income.

Influencing factors (A *vs* B)*	Model**	*OR and* 95%*CI*	*P* (2-tailed)
	Model2	3.58×10^{-06} (2.10×10^{-06}–6.11×10^{-06})	0.000
	Model3	3.87×10^{-06}(2.15×10^{-06}–6.98×10^{-06})	0.000
Bone soup (Almost every day *vs* < 2 times/year)	Model1	4.77×10^{-07} (2.40×10^{-07}–9.90×10^{-07})	0.000
	Model2	4.72×10^{-07} (2.02×10^{-07}–9.70×10^{-07})	0.000
	Model3	4.79×10^{-07} (2.29×10^{-07}–9.96×10^{-07})	0.000
* "A vs B" means compared to factor B, the risk that factor A causes an increase in total UAs			
** "Model" which including three different models. Model1 represents univariate regression results, Model2 represents regression results for adjusting month age, birth weight, and gender, and Model3 represents regression results for adjusting month age, birth weight, gender, father's educational background, and monthly household income.			

4. Discussion

As exposure has been an important public health problem in many countries, causing several adverse effects at different stages of life [24]. There are few reports on UAs in infants, and the reference limits of urinary As are not uniform owing to differences in regions, diets and levels of environmental pollution. In this research, our results here showed that the UAs levels did not follow a normal distribution. Therefore, we identified the upper limit of the total UAs content as 962.35 μg/gCr (unadjusted Cr, 209.56 μg/L). This value was higher than the upper limit of the UAs found in 2–10 years old children in China's interior (27.51 μg/L or 55.88 μg/gCr) [28] and in other countries (Canada (18 μg/L)[36], the USA(65.4 μg/L) [37], , and Chile (125 μg/L) [38]). Most of the studies were aimed at children over 2 years old, while infants had higher urinary arsenic levels than children, so further attention should be paid to the health problems of foods exposed to As in infants.

We found three major factors affecting total UAs in infants. Breast feeding could affect UAs in infants. Rebelo and Caldas reviewed the studies conducted from 2000 to 2016 to assess the risk of As exposure in breast milk and found that As levels in breast milk were higher among those living in As-contaminated areas [39]. Regional studies in Lebanon have shown that As contamination in breast milk was mainly associated with intake of cereals and fish [40]. Additionally, according to a Chinese study, inorganic As in

breast milk posed a health risk in newborns, and thus, breast feeding was a risk factor for elevated UAs [41]. This study also found that breast-feeding was a risk factor for elevated UAs, suggesting that breast-feeding mothers exposed to higher levels of As may be through the transfer of As from breast milk to infants. Since the presence of As in breast milk influences exposure to As among infants, it should be considered as a health problem. Breastfeeding mothers need to be made aware of the As contamination in different food to avoid excessive exposure to As.

Food As contamination could affect total UAs in infants. Xiamen is the main polluted area near the coast of Fujian, and owing to serious marine pollution, marine life is exposed to pollutants. These pollutants enter the food chain, and in turn the human body, through consumption of seafood. Studies showed that the Japanese seabass (*Lateolabrax japonicus*) and red seabream (*Pagrus major*) in the coastal waters of south Fujian revealed that the As level in the muscle of the both species was generally higher than Chin's national standard (1.0 microg/g), and The contents of total mercury and total arsenic in most of the marine cultured oysters in Xiamen Bay were significantly higher than those in other sea areas along the southern coast of Fujian [42, 43]. The detection of vegetable, fruit, seafood and meat consumption and heavy metal content of Xiamen residents showed that arsenic poses the greatest health risk. For residents who consume a large scale of fruits, vegetables and seafood, the carcinogenic risk of arsenic deserves attention [27, 44, 45]. While most studies found that from 2007 to 2015, the survey results on the drinking water quality of Xiamen residents showed that the arsenic content of Xiamen residents' drinking water did not exceed the drinking water national health standard limit (0.5mg/L). The arsenic intake of Xiamen residents mainly comes from food[46–49]. In this study, dietary habits were found to be associated with UAs levels in infants. The higher the intake of seafood, the higher the UAs content. Pollution of the marine environment and contamination of seafood in Xiamen[45] are reflected in the UAs level in infants, and they might cause chronic harm to all inhabitants of Xiamen, including infants.

The fluctuations in UAs content with age in infants are related to food sources. The urinary As content among infants aged 1–3 months was significantly higher than that among those aged 3–6 months, which may be because breast milk was the main food source at this stage, and lactating women consume more seafood contaminated with As. An explanation for the positive correlation between the age and total UAs for 6–36-month-old infants is that there may be an increased exposure to exogenous As due to direct consumption of seafood, vegetable, meat and so on, even though their exposure to As from breast milk was reduced. Other studies also found increased urinary As concentrations in infants to be associated with increased exposure to As during the transition to solid food, suggesting the need to minimize exposure during this critical developmental period[50, 51].

In this study, four As species (iAs, iAs, MMA^V, and DMA^V) were detected in the urine samples. Different sources of As exposure, exposure dose and exposure population affect As metabolites, and the toxicity of As varies greatly with its valence state. From the experimental results (Refer Table 2), the As content of DMA^V was relatively high, but iAs had the highest detection rate and its toxicity was found to be much higher than that of DMA^V (185 times higher). Therefore, considering the detection rate, toxicity, and As content of iAs, it could be used as a marker for As exposure. The detection rate and combined toxicity of

different As forms are different because the amount and levels of these species might differ in each infant. Although the detection rates for $iAs^{Ⅲ}$+$DMA^{Ⅴ}$ and $iAs^{Ⅲ}$+$DMA^{Ⅴ}$+$iAs^{Ⅲ}$ were similar, the toxicity of $iAs^{Ⅲ}$+$DMA^{Ⅴ}$+$iAs^{Ⅲ}$ was the highest. We also found that the unmethylated rate for $iAs^{Ⅲ}$+$DMA^{Ⅴ}$+$iAs^{Ⅲ}$ was also the highest. Therefore, $iAs^{Ⅲ}$+$DMA^{Ⅴ}$+$iAs^{Ⅲ}$ was found to be the most important combination for evaluating the combined toxicity of As exposure in infants.

This study calculated the unmethylated proportion in infants to be 38.57%, It was observed that the lower the age, the higher the concentration of non-methylated As species. However, the the unmethylated proportionin adults ranges from 20–25%, regardless of exposure level [52]. The concentration of non-methylated As species was found to be higher in infants, indicating that infants have a weaker metabolic capacity [53]. The correlation analysis showed that the amount of detectable As species in urine was positively correlated with UAs concentrations. The higher the amount of detectable As species, the lower the unmethylated proportion. A study on the correlation between seafood intake and UAs levels found that seafood intake was a significant factor contributing to the increase in total urinary As and DMA[54]. Hence, in addition to the methylation ability of infants, the intake of seafood may affect the As transformation as well as the total UAs levels in infants[55].

As metabolism is closely related to toxicity, and it exerts its toxicity by inhibiting approximately 200 enzymes involved in cellular energy pathways and DNA synthesis and repair[56]. As metabolic toxicity in processes involved in cardiovascular dysfunction, diabetes development, neurotoxicity, hepatotoxicity, and nephrotoxicity by increasing production of reactive oxygen species (ROS), thereby increasing lipid peroxidation and cell damage[1, 56, 57]. Since the methylation capacity is lower than that of adults, the effect of As toxicity on the growth and development of infants deserves attention. Long-term ingestion of arsenic in food or water will inhibit the immune function of infants, resulting in slow growth and development[58], weight loss and underweight[59]; some studies have found that the neurotoxicity of As will affect the intelligence of adult children, possibly by affecting acetylcholinease activity at synapses[60, 61]. We need to further strengthen the monitoring of metal content in the food intake of infants and nursing mothers, and at the same time, we need to strengthen the effect of environmental arsenic pollution on the accumulation of As in food, and control the risk of As exposure from the food source.

5. Conclusions

Infants in Xiamen had high total UAs levels. The reference value of UAs of Xiamen infants was found to be 962.35 μg/gCr. Our results also showed that in addition total UAs content, analysis of UAs in infants should also focus on the detection of $iAs^{Ⅲ}$. $iAs^{Ⅲ}$+$DMA^{Ⅴ}$+$iAs^{Ⅲ}$ is the most important combination for evaluating the combined toxicity of As species in infants, which is very important to monitor the risk of As toxicity in the population. The As transformation ability of infants is weak, and their As methylation capacity is lower than that of adults. Finally, our results show that the diet may be the major source of As exposure in infants. Because Xiamen is a polluted area, is located on the coast, excessive intake of

contaminated food by mothers or infants themselves may be the main cause of the high urinary total arsenic levels in infants. Hence, the levels of As in breast milk and the food in the area must be monitored, and limits should be set. Moreover, breastfeeding mothers must be made aware of the risks of As exposure to infants due to the intake of foods such as seafood.

6. Limitation

Owing to shortcomings in the sample, this study had some limitations. Food samples of infants were not collected for arsenic testing, and no attention was paid to maternal food consumption and arsenic in breast milk. We did not ask the parents of infants for detailed information such as the name of the food, intake, and preparation process.

Abbreviations

AB, arsenobetaine;

As, arsenic;

Cr, creatinine;

ct, combined toxicity;

DMA^{V}, dimethylarsinic acid;

dt, detection rate;

$iAs^{\square}$, trivalent inorganic As;

$iAs^{\square}$, pentavalent inorganic As;

ICP-MS, inductively coupled plasma mass spectrometry;

LD50, half lethal dose;

MMA^{V}, monomethylarsonic acid;

UAs, urinary As

Declarations

[Ethics approval and consent to participate]

This is an observational study. This study was approved by the Ethics Committee of the School of Medicine, Xiamen University according to the recommendations of the World Medical Association

Declaration of Helsinki Ethical Principles and the Council of International Medical Scientific Organizations, and the relevant regulations of the National Science Foundation of China. In the course of the implementation of this project, informed consent was strictly made, the use of biological samples of the sample source was informed, the personal information and medical information of the sample source will not be publicly disclosed, and every effort will be made to protect the personal medical information, disease information, life information and basis of the sample source, to the extent permitted by law. The ethical approval number: XDYX202008. The detail could refer to the PDF of Ethics Committee.

[Consent for participate]

Written informed consent was obtained from the parents or legal guardian.

[Consent for publication]

No applicable

[Competing interests]

The authors have no relevant financial or non-financial interests to disclose.

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[Author's contributions]

All authors contributed to the study conception and design. Wei Zhang : Investigation, Formal analysis, Data Curation, Writing - Original Draft preparation, Writing- Reviewing and Editing**. Hongwei Li**: Methodology, Supervision, Project administration,Writing- Reviewing and Editing. **Hanying Zheng**: Visualization, Investigation. **Hui Lan**: Investigation, Validation. **Yingying Zhuang:** Investigation, Writing-Reviewing and Editing.

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[Availability of date and materials]

The datasets generated during and/or analysed during the current study are not publicly available due to including personal medical and life information. But the datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

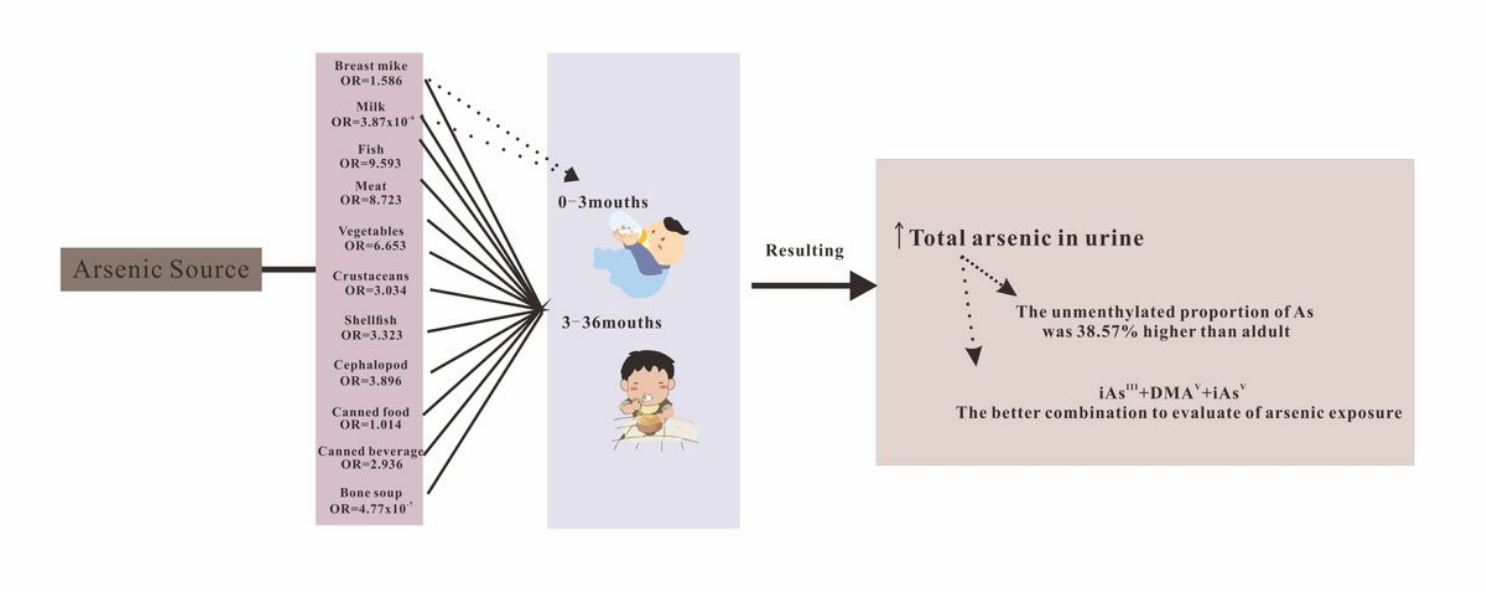

Figure 1

Graphical Abstract

Supplementary Files

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