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Arsenic Metabolites and Methylation Capacity Among Individuals Living in a Rural Area with Endemic Arseniasis in Inner Mongolia, China

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Abstract More than 0.3 million individuals are subject to chronic exposure to arsenic via their drinking water in Inner Mongolia, China. To determine arsenic methylation capacity profiles for such individuals, concentrations of urinary arsenic metabolites were measured for 548 subjects using high-performance liquid chromatography and a hydride generator combined with inductively coupled plasma-mass spectrometry. Mean urinary concentrations of dimethylarsonic acid (DMA), monomethylarsonic acid (MMA), inorganic arsenic (iAs), and total arsenic (TAs) were 200.50, 46.71, 52.96, and 300.17 μg/L, respectively. The %iAs, %DMA, and %MMA were 15.98, 69.72, and 14.29 %. Mean urinary %iAs and %MMA were higher in males, while urinary %DMA was higher in females. There was a strong positive correlation between %iAs and %MMA, with negative correlations between %iAs and %DMA, and %iAs and %MMA. In addition, %iAs and %MMA were positively associated with total arsenic in drinking water (WAs), while %DMA was negatively related with WAs. Regression analysis indicated that the primary methylation index (PMI) and secondary methylation index (SMI) generally decreased with increasing WAs. Females had a higher arsenic methylation capacity compared to males. Younger subjects had lower primary arsenic methylation capacity. However, the secondary arsenic methylation capacity was hardly affected by age. Moreover, both primary and secondary arsenic methylation capacities were negatively related to WAs.

Keywords Arsenic · Methylation capacity · Arsenic metabolites · Drinking water

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Introduction

Millions of people throughout the world suffer from chronic exposure to arsenic via their drinking water [1]. Even moderately elevated concentrations of inorganic arsenic (iAs) in drinking water pose a serious public health problem [2]. Previous epidemiological studies of individuals exposed to high arsenic levels in drinking water suggest that chronic arsenic exposure via drinking water is widely associated with a higher risk of skin lesions, hypertension, diabetes, cardiovascular diseases, and cancer of the skin, lungs, bladder, liver, and possibly kidneys [2–12]. Therefore, the World Health Organization guideline for arsenic in drinking water is 10 μg/L [13].

Arsenic in drinking water is dominated by iAs as pentavalent (As^{V}) and trivalent arsenite (As^{III}) [14, 15]. In humans, the primary iAs metabolic pathway is methylation, which involves reduction and oxidative methylation [16–18]. After its ingestion in drinking water, iAs is readily absorbed by the gastrointestinal tract and methylated via oxidation to monomethylarsonic acid (MMA) in a process termed primary arsenic methylation. MMA can be further methylated to dimethylarsonic acid (DMA) in secondary arsenic methylation [12, 19]. Arsenic species differ in their toxicity, and iAs

is more toxic than organic arsenic. Therefore, arsenic methylation has been considered a detoxification mechanism because of the relatively low toxicity of MMA and DMA [20–23]. However, recent investigations suggest that MMA^{III} and DMA^{III} are more toxic than iAs arsenite [24, 25].

Urinary arsenic speciation is typically used as an indicator of arsenic metabolism in evaluating arsenic methylation capacity [26] in terms of the primary methylation index (PMI, defined as (MMA+DMA)/total arsenic (TAs)) and secondary methylation index (SMI, defined as DMA/(MMA+DMA)) [20, 27]. Numerous epidemiological studies have revealed that the risk of adverse health effects is associated with arsenic methylation capacity. A high percentage of MMA (%MMA) in urine is positively related to cancer risk [28, 29]. Kile et al. [1] reported that a higher proportion of MMA in urine was correlated with a greater risk of skin lesions. Lindberg et al. [26] and Li et al. [30] confirmed that a higher proportion of MMA and a lower proportion of DMA in urine indicated a higher risk of arsenic-related skin lesions. Moreover, exposure of individuals with a low arsenic methylation capacity to high arsenic levels might confer a higher risk of carotid atherosclerosis [31]. Inefficient arsenic methylation and higher urinary MMA might be related to hypertension risk [10, 18]. Chen et al. [15] suggested that incomplete methylation of arsenic is associated with a higher risk of heart disease. Several other studies showed positive correlations between the %MMA in urine and the prevalence of arsenic-related toxic effects [32–34].

Urinary arsenic metabolite concentrations and arsenic methylation capacity are significantly associated with human health effects. Therefore, we measured urinary arsenic metabolites for 548 residents of a rural area in Inner Mongolia where tube well water is widely contaminated with arsenic. The aim of the study was to estimate concentrations and percentages of arsenic metabolites in urine. The arsenic methylation capacity of the study subjects was assessed, and factors affecting arsenic methylation capacity were analyzed.

Materials and Methods

Study Area and Subjects

The study area, the Bameng region, is located north of the Yellow River in western Inner Mongolia, People's Republic of China. The groundwater in this area typically contains high arsenic concentrations of up to 1354 μg/L [35, 36]. Residents typically use high-arsenic groundwater for drinking water.

Individuals who had ingested seafood in the previous week, pregnant women, and children younger than 10 years were excluded from the study cohort. Consequently, 548 residents (389 females and 159 males) living in eight villages were selected for the study. All the subjects signed informed consent forms agreeing to participation in the study before specimen collection and interview. The interview questionnaire collected data on gender, age, living conditions, dietary habits, smoking, alcohol consumption, and illness for all the subjects. The average age was 37.8 years (range 10–65) for females and 36.2 years (range 12–61) for males. Table 1 lists demographic data for the subjects. Among the male participants, approximately 64.15 % smoked and 35.85 % consumed alcohol. The corresponding rates for female participants were 12.85 and 1.29 %.

Sample Collection

Tube well water was pumped for approximately 5 min to remove water at the tip of the tap before samples were collected. Approximately 100 mL of water was collected into a clean polyethylene bottle for each sample. Samples were stored at −20 °C.

Approximately 50 mL of first-morning-void urine was collected in a 100-mL polypropylene tube for each subject. Urine samples were immediately placed on ice and transferred to the Inner Mongolia Center for Endemic Disease Control and Research in Hohhot within 8 h, where they were stored at −20 °C.

Urine and water samples were kept on dry ice and transported to the laboratory for arsenic analysis in the Institute of Geographic Sciences and Natural Resources Research (Beijing, China) and stored in a low-temperature refrigerator until analysis. Collection of urine and water samples was completed before a water improvement program was initiated in the study area.

Determination of Urinary Arsenic Species

To investigate arsenic metabolism and methylation profiles for individuals exposed to high levels of arsenic in drinking water, urinary arsenic metabolites were separated on a high-performance liquid chromatography (HPLC) system equipped with a hydride generator [30, 37]. Concentrations of iAs (including As^{III} and As^{V}), MMA, and DMA in urine samples were determined by inductively coupled plasma-mass spectrometry (ICP-MS). TAs concentrations in water samples were determined by HPLC and ICP-MS after filtration through 0.45-μm membranes. The detection limit of this method for As species was 1 ng. A standard reference material containing 1000 mg/L iAs, MMA, and DMA (National Center for Standard Reference Materials) was used to check the validity of urinary arsenic species measurement. The reliability of the arsenic species determination was evaluated in terms of the analytical recovery rate for added arsenic species. The

Table 1 The demographic characteristics of study subjects

Item	*N*	Min	Max	Mean	Smoking (%)	Alcohol consumption (%)
Total	548	10	65	37.3	21.74	11.31
Female	389	10	65	37.8	12.85	1.29
Male	159	12	61	36.2	64.15	35.85

recovery rate was 83–94 % for iAs, 91–97 % for MMA, and 90–102 % for DMA.

Statistical Analysis

The TAs concentration in urine was calculated as the sum of iAs+MMA+DMA. Arsenic methylation indices were defined as the percentages of respective arsenic species in urine samples. Moreover, PMI was calculated as (MMA+DMA)/TAs and SMI as DMA/(MMA+DMA) [27].

SPSS version 18.0 for Windows was used for descriptive statistics, regression analysis, and correlation analysis. Linear regression analysis was used to estimate correlations between TAs concentrations, percentage of arsenic metabolites in urine, and total arsenic content in drinking water (WAs). Pearson correlation coefficients were calculated. In addition, the Student's *t* test was applied to evaluate differences in urinary arsenic metabolites between males and females. Differences in urinary arsenic metabolites among age groups and arsenic levels in water were analyzed by ANOVA.

Results

Concentrations of Arsenic Metabolites in Urine

Arsenic concentrations in drinking water ranged from 0. 34 to 824.70 μg/L. Results for arsenic metabolites in urine and PMI and SMI are listed in Table 2. For the total cohort, mean urinary DMA, MMA, iAs, and TAs concentrations were 200.50, 46.71, 52.96, and 300.17 μg/L, and %iAs, %DMA, and %MMA were 15.98, 69.72, and 14.29 %, respectively. Arsenic methylation capacity was estimated using PMI and SMI, which had mean values of 0.84 and 0.83, respectively. Mean urinary DMA, MMA, iAs, and TAs concentrations were generally higher for males than for females. Mean

Table 2 Statistical data of arsenic metabolites in urine and methylation capacity index in the subjects (μg/L)

	DMA	MMA	iAs	TAs	%iAs	%DMA	%MMA	PMI	SMI
Total (*N*=548)									
Mean	200.50	46.71	52.96	300.17	15.98	69.72	14.29	0.84	0.83
Median	116.75	22.15	24.20	168.45	14.48	71.05	13.73	0.85	0.84
Min	2.90	0.50	0.50	4.30	2.56	25.64	0.95	0.40	0.54
Max	1430.40	450.80	516.90	2063.50	59.50	89.73	29.67	0.97	0.99
SD	227.78	62.18	71.80	346.45	7.65	9.38	4.44	0.08	0.06
Female (*N*=389)									
Mean	193.81	40.51	45.83	280.14	14.77	71.61	13.62	0.85	0.84
Median	105.50	19.70	21.20	149.40	13.27	72.74	13.21	0.87	0.85
SD	224.09	52.79	64.32	326.82	7.18	8.69	4.16	0.07	0.05
Min	2.90	0.50	0.50	4.30	2.56	25.64	0.95	0.40	0.60
Max	1430.40	316.90	516.90	1936.60	59.50	89.73	26.11	0.97	0.99
Male (*N*=159)									
Mean	219.32	62.27	70.75	352.35	18.92	65.16	15.92	0.81	0.80
Median	143.70	34.70	37.40	213.70	17.71	64.67	15.982	0.82	0.81
SD	236.49	78.72	85.02	386.53	7.96	9.47	4.71	0.08	0.06
Min	10.40	1.40	1.70	15.40	4.06	34.31	5.97	0.50	0.54
Max	1191.10	450.80	421.60	2063.50	49.83	82.70	29.67	0.96	0.93
Student's *t* test between female and male									
P	0.234	0.002	0.001	0.039	0.000	0.000	0.000	0.000	0.000

Min minimum, *Max* maximum, *SD* standard deviation

urinary %iAs and %MMA were also higher for males, while urinary %DMA was higher for females.

Urinary Arsenic Metabolites by Age Group

The urinary arsenic concentrations, percentages, and methylation capacity might vary among different age groups. Therefore, the subjects were divided into six groups according to their age: <20, 21–30, 31–40, 41–50, 51–60, and >60 years. Among females, the mean DMA, MMA, and TAs concentration in urine generally increased with age, while the mean iAs decreased (Table 3). The mean %iAs in urine decreased significantly with increasing age for both males and females. By contrast, the mean %DMA and %MMA largely increased with age. In terms of the arsenic methylation capacity among females, PMI increased from 0.82 for those aged <20 years to 0.89 for those aged >60 years. However, SMI varied slightly among the age groups. The highest value (0.85) was observed for those aged 21–30 years. For males, the mean urinary DMA, MMA, and TAs concentrations increased with age, whereas the mean iAs decreased with increasing age.

Table 3 shows that mean DMA, MMA, iAs, and TAs concentrations in urine were much higher for females than for males for subjects aged <20 years. By contrast, mean concentrations of these arsenic metabolites in urine were lower for females than for males among the other age groups. Moreover, the mean urinary %iAs and %MMA were lower for females than for males and the mean %DMA was significantly higher for females among all age groups. PMI and SMI were much higher for females than for males. The highest PMI values for both females and males (0.89 and 0.85) were among subjects aged >60 years, while the lowest PMI values (0.82 and 0.78) were among those aged <20 years. The highest SMI values for females and males (0.85 and 0.81) were in those aged 21–30 and <20 years.

Urinary Arsenic Metabolite Levels in Relation to Arsenic Levels in Drinking Water

Different levels of arsenic in drinking water might significantly affect arsenic metabolite profiles and arsenic methylation capacity among individuals. Therefore, the concentrations and percentages of arsenic metabolites were calculated. The results are listed in Table 4. WAs levels were categorized as <10, 10–50, 50–100, 100–150, 150–200, 200–250, 250–300, 300–350, 350–400, 400–450, 450–500, and >500 μg/L. In general, urinary DMA, MMA, iAs, and TAs concentrations significantly increased with WAs. Similarly, %iAs and %MMA increased with WAs. However, %DMA decreased with increasing WAs (Table 4). Regression analysis results also indicate that %iAs and %MMA were positively associated with WAs, while %DMA was negatively correlated

Table 3 Arsenic metabolites and methylation capacity index among the age groups (μg/L)

Age	<20 years		21–30 years		31–40 years		41–50 years		51–60 years		>60 years		*P* (ANOVA)	
	F, *N*=62	M, *N*=32	F, *N*=50	M, *N*=23	F, *N*=107	M, *N*=36	F, *N*=96	M, *N*=40	F, *N*=61	M, *N*=27	F, *N*=12	M, *N*=1	F	M
DMA	170.33	127.33	172.95	180.39	182.06	221.32	211.96	276.07	195.4	277.46	348.23	147.94	0.172	0.088
MMA	33.83	32.92	37.13	61.56	38.82	54.22	45.47	81.04	39.43	81.43	67.85	39.06	0.371	0.116
iAs	52.92	50.91	47.55	63.94	45.08	59.51	49.93	92.66	31.18	84.04	46.5	32.62	0.502	0.305
TAs	257.8	211.16	257.63	305.89	265.96	335.05	307.37	449.76	266.01	442.93	462.56	219.62	0.387	0.114
%iAs	17.66	21.97	16.6	18.64	15.13	16.32	13.67	19.32	12.09	18.59	10.77	14.85	0.000	0.108
%DMA	69.46	63.25	70.89	65.2	71.01	67.93	72.61	64.12	73.35	65.11	75.05	67.36	0.067	0.430
%MMA	12.88	14.77	12.51	16.15	13.87	15.74	13.72	16.56	14.56	16.3	14.18	17.79	0.097	0.693
PMI	0.82	0.78	0.83	0.81	0.85	0.84	0.86	0.81	0.88	0.81	0.89	0.85	0.000	0.108
SMI	0.84	0.81	0.85	0. 80	0.84	0.81	0.84	0.79	0.83	0.80	0.84	0.79	0.858	0.884

F female, *M* male

Table 4 Arsenic metabolites and methylation capacity index among different levels of arsenic in drinking water (μg/L)

	N	DMA	MMA	iAs	TAs	%iAs	%DMA	%MMA
Total								
<10	103	37.76	7.19	9.03	53.98	14.05	73.46	12.49
10–50	89	60.96	11.58	11.75	84.30	14.16	72.24	13.60
50–100	64	112.74	21.27	19.78	153.79	13.23	73.18	13.59
100–150	45	143.58	31.00	35.21	209.81	16.46	68.65	14.89
150–200	60	192.81	43.25	43.88	279.93	15.83	69.12	15.06
200–250	32	280.46	61.23	65.35	407.04	15.88	68.99	15.13
250–300	39	306.42	69.77	82.35	458.55	17.72	67.69	14.58
300–350	34	405.07	98.23	112.22	615.53	18.34	65.77	15.88
350–400	23	527.51	129.17	147.75	804.41	17.45	66.97	15.57
400–500	25	447.67	114.63	127.44	689.75	20.73	63.12	16.16
>500	34	508.58	135.84	172.35	816.74	22.68	61.48	15.83
P		0.000	0.000	0.000	0.000	0.000	0.000	0.000
Female								
<10	72	35.92	6.53	7.28	49.74	12.34	75.38	12.28
10–50	74	61.69	11.14	11.15	83.99	13.53	73.30	13.17
50–100	50	112.15	20.04	18.91	151.10	13.16	73.56	13.28
100–150	29	146.87	30.92	32.81	210.61	15.55	69.43	15.02
150–200	36	196.58	36.79	40.26	273.62	14.75	71.83	13.43
200–250	21	268.89	52.66	61.24	382.78	15.29	70.65	14.05
250–300	28	302.02	61.34	73.29	436.65	16.48	70.16	13.34
300–350	24	415.38	90.41	98.13	603.92	16.91	68.40	14.69
350–400	16	470.74	102.86	119.24	692.83	16.15	68.70	15.14
400–500	17	493.22	110.66	105.92	709.81	16.31	68.27	15.42
>500	22	514.00	123.57	169.50	807.06	22.33	62.64	15.03
P		0.000	0.000	0.000	0.000	0.000	0.000	0.020
Male								
<10	31	42.03	8.74	13.09	63.84	18.02	69.02	12.96
10–50	15	59.90	14.41	15.39	89.72	17.41	66.82	15.77
50–100	14	114.87	25.66	22.87	163.42	13.49	71.83	14.68
100–150	16	137.64	31.16	39.55	208.38	18.10	67.24	14.66
150–200	24	187.16	52.93	49.32	289.40	17.45	65.05	17.50
200–250	11	302.55	77.60	73.18	453.35	16.98	65.82	17.20
250–300	28	317.62	91.24	105.42	514.28	20.88	61.41	17.71
300–350	11	380.31	117.00	146.03	643.39	21.79	59.47	18.74
350–400	7	657.26	189.29	212.91	1059.4	20.42	63.03	16.55
400–500	9	357.71	116.47	160.63	634.84	28.02	54.90	17.08
>500	12	498.63	158.32	177.58	834.48	23.33	59.36	17.31
P		0.000	0.000	0.000	0.000	0.002	0.000	0.004

to WAs (Fig. 1). The trends for urinary arsenic metabolites among females and males were similar to the trends for the entire cohort (Table 4).

Correlations Among Urinary Arsenic Metabolites, PMI, and SMI

Correlation coefficients for arsenic metabolites, PMI, SMI, and WAs are listed in Table 5. There are strong positive correlations between WAs and urinary DMA, MMA, iAs, and TAs. The %iAs and %MMA are significantly correlated with urinary concentrations of arsenic metabolites. There is a positive correlation between %iAs and %MMA and significantly negative correlations between %iAs and %DMA, and %MMA and %DMA. In addition, %iAs and %MMA are positively associated with WAs, while %DMA is negatively associated with WAs. PMI and SMI are negatively correlated with urinary

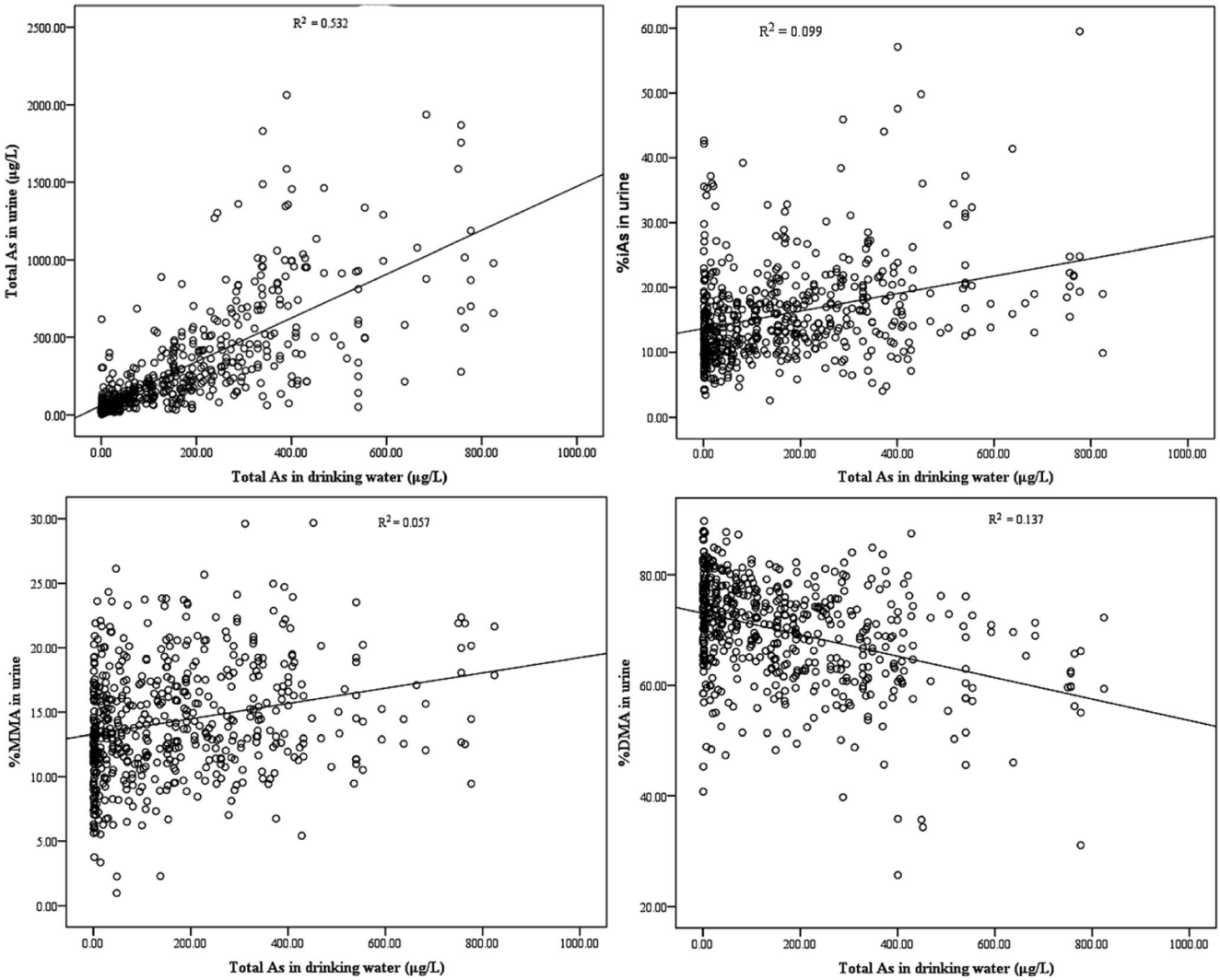

Fig. 1 Correlations between WAs and TAs and percentages of arsenic metabolites in urine

concentrations of arsenic metabolites, WAs, %iAs, and %MMA. However, PMI and SMI are positively correlated with %DMA. Regression analysis results also indicate that PMI and SMI decrease with increasing WAs (Fig. 2). Figure 3 shows that PMI and SMI for both females and male were negatively associated with WAs.

Table 5 Correlation coefficients among concentrations and percentages of arsenic metabolites in urine, PMI, SMI, and WAs

	DMA	MMA	iAs	TAs	%iAs	%DMA	%MMA	PMI	SMI	WAs
DMA	1	0.898**	0.793**	0.983**	0.079	−0.148**	0.177**	−0.079	−0.178**	0.698**
MMA		1	0.867**	0.949**	0.200**	−0.365**	0.426**	−0.200**	−0.450**	0.684**
iAs			1	0.884**	0.485**	−0.521**	0.265**	−0.485**	−0.401**	0.715**
TAs				1	0.189**	−0.271**	0.247**	−0.189**	−0.281**	0.730**
%iAs					1	−0.0883**	0.144**	−1.000**	−0.442**	0.315**
%DMA						1	−0.591**	0.883**	0.807**	−0.370**
%MMA							1	−0.144**	−0.943**	0.239**
PMI								1	0.442**	−0.315**
SMI									1	−0.315**
WAs										1

*Significant value $p \leq 0.05$; **significant value $p \leq 0.01$

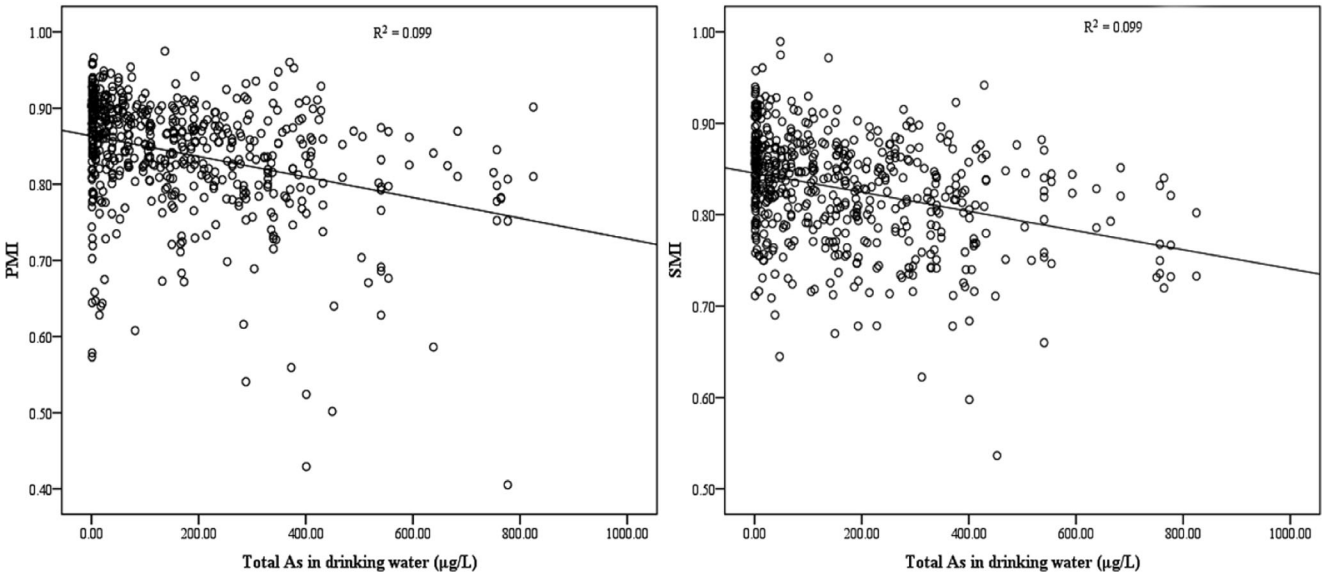

Fig. 2 Correlations between WAs and arsenic methylation capacity index of human

Discussion

Mean urinary concentrations of DMA, MMA, iAs, and TAs were higher among the study subjects than among subjects not exposed to high WAs levels (>50 μg/L). Saoudi et al. [38] reported that the geometric mean concentration of iAs + MMA + DMA was 3.75 μg/L for the adult population living in France [38]. Mean urinary concentrations of DMA, MMA, iAs, and TAs were also significantly higher in the total cohort than among subjects exposed to low WAs levels (<10 μg/L). Table 4 shows that mean urinary DMA, MMA, iAs, and TAs concentrations increased with the level of arsenic in drinking water ingested by subjects. Correlation analysis revealed significant positive correlations between WAs and arsenic metabolite concentrations in urine (Table 5), indicating a positive association between urinary arsenic metabolites and WAs. Agusa et al. [39, 40] reported that iAs concentrations in human urine are strongly dependent on iAs intake. Higher mean urinary DMA, MMA, iAs, and TAs concentrations among males suggest that the frequency of water ingestion might be higher for males than for females [39].

Percentages of arsenic metabolites in urine are typically used to provide insight into arsenic methylation capacity in humans [21, 41]. A typical urinary arsenic metabolite profile contains 10–30 % iAs, 10–20 % MMA, and 60–80 % DMA [29, 40, 42]. The urinary arsenic metabolite percentages observed for females and males in this study are consistent with previous studies. Higher urinary %DMA and lower urinary

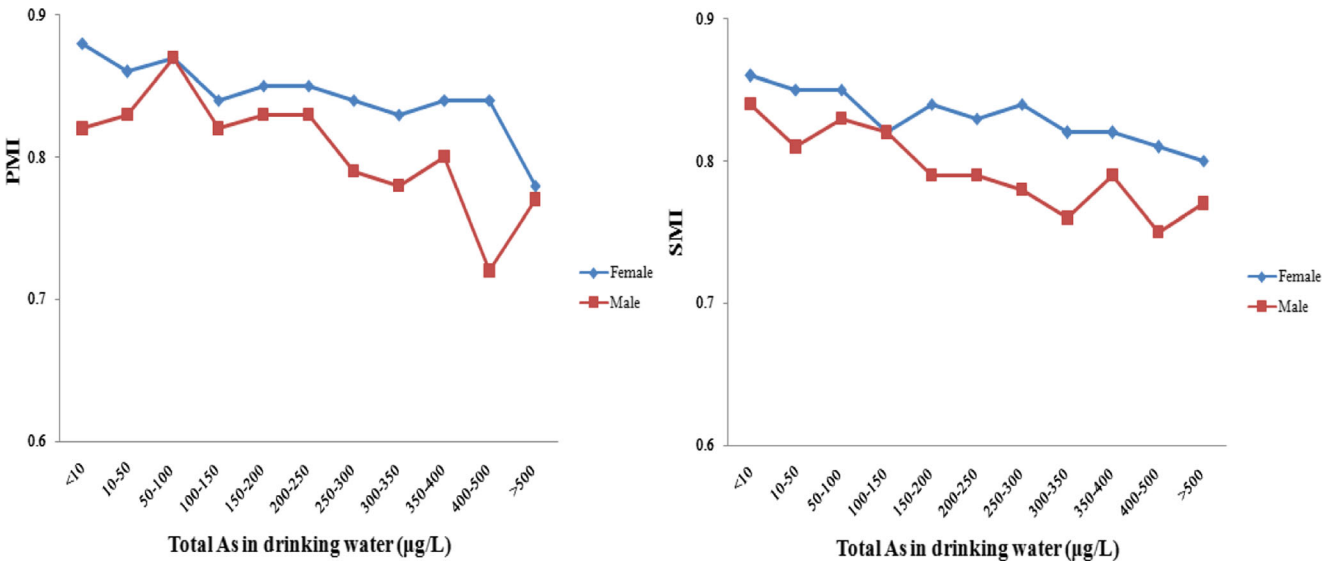

Fig. 3 The changes of PMI and SMI for both female and male with arsenic levels in drinking water

%iAs and %MMA among females suggest that female metabolism may be influenced by sex steroids, resulting in more efficient arsenic methylation compared to males, in agreement with previous studies [30, 43]. Previous investigations revealed that younger individuals had more efficient arsenic methylation [21]. However, the lower %iAs and higher %DMA and %MMA observed for older groups in our study imply that older individuals had a higher arsenic methylation capacity than younger subjects. This might be because arsenic exposure influenced age-dependent urinary excretion of arsenic and methylation capacity [22]. A series of studies suggested that a higher proportion of MMA in urine might indicate retention of high-toxicity MMA^{III} in body tissues and increase the risk of arsenic-related health effects [6, 44, 45]. Our results suggest that iAs might be excreted more quickly by younger people than by older individuals.

Exposure to different levels of arsenic in drinking water might affect the percentage of urinary arsenic metabolites. We found that higher WAs levels obviously increased urinary %iAs and %MMA and decreased %DMA (Table 4). Strong positive correlations between WAs and urinary %iAs and %MMA and negative correlations between WAs and %DMA confirm that arsenic levels in drinking water significantly affected iAs transformation to organic arsenic and arsenic methylation capacity. Previous studies also revealed that arsenic exposure levels negatively influence iAs metabolism [46].

PMI and SMI are typically used to estimate human arsenic methylation capacity [47]. In our study, PMI and SMI were generally higher among females than among males, indicating that females from the study area had a higher arsenic methylation capacity. This is consistent with previous investigations [45, 46]. Several studies have revealed that the arsenic methylation capacity is widely influenced by age [12]. In our study, PMI clearly increased with age among females. Among males, PMI also increased with age up to 40 years. This suggests that older subjects have a higher primary arsenic methylation capacity. However, SMI varied slightly among the age groups for both females and males, indicating that the secondary arsenic methylation capacity of subjects might be not associated with age. These results differ from those of previous studies. Zhang et al. [12] reported that older people had a lower arsenic methylation capacity (lower %DMA and SMI).

The study subjects were exposed to different levels of arsenic in their drinking water and thus ingested different doses of arsenic. Significantly negative correlations between arsenic levels in drinking water and PMI and SMI for the whole cohort and for both females and males confirm that human primary and secondary arsenic methylation capacities are both significantly negatively affected by high arsenic levels in drinking water. In addition, higher PMI and SMI in females suggest that females have higher primary and secondary arsenic methylation capacities compared to males. Other studies have also revealed that higher arsenic concentrations are correlated with lower arsenic methylation capacity. This might be attributable to saturation of the arsenic metabolic pathway [48].

Conclusions

The results of this study indicate that the arsenic methylation capacity of humans exposed to arsenic in drinking water is affected by gender, age, and arsenic levels in drinking water. Urinary concentrations of iAs, MMA, DMA, and TAs were generally higher in males than in females. Females had a higher arsenic methylation capacity compared to males. Younger subjects had a lower primary arsenic methylation capacity, while the secondary arsenic methylation capacity was hardly affected by age. Moreover, exposure to higher arsenic levels in drinking water was correlated with lower primary and secondary arsenic methylation capacities.

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Conflict of Interest The authors declare they have no competing financial interests.

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