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Relation of dietary inorganic arsenic to serum matrix metalloproteinase-9 (MMP-9) at different threshold concentrations of tap water arsenic

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Abstract

Arsenic (As) exposure is associated with cancer, lung and cardiovascular disease, yet the mechanisms involved are not clearly understood. Elevated matrix metalloproteinase-9 (MMP-9) levels are also associated with these diseases, as well as with exposure to water As. Our objective was to evaluate the effects of dietary components of inorganic As (iAs) intake on serum MMP-9 concentration at differing levels of tap water As. In a cross-sectional study of 214 adults, dietary iAs intake was estimated from 24-h dietary recall interviews using published iAs residue data; drinking and cooking water As intake from water samples and consumption data. Aggregate iAs intake (food plus water) was associated with elevated serum MMP-9 in mixed model regression, with and without adjustment for covariates. In models stratified by tap water As, aggregate intake was a significant positive predictor of serum MMP-9 in subjects exposed to water As ≤10 μg/l. Inorganic As from food alone was associated with serum MMP-9 in subjects exposed to tap water As ≤3 μg/l. Exposure to iAs from food and water combined, in areas where tap water As concentration is ≤10 μg/l, may contribute to As-induced changes in a biomarker associated with toxicity.

Keywords

MMP-9; arsenic; dietary exposure; aggregate exposure; biomarker of toxicity

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

INTRODUCTION

Arsenic (As), an abundant element in the earth's crust, occurs naturally and from anthropogenic sources in soils, water and food. Chronic exposure to inorganic As (iAs) is associated with skin, bladder, lung and other cancers,[1–3] chronic lung problems[4–7] and cardiovascular disease and mortality.[8,9] These effects are generally associated with groundwater As concentrations greater than 50 or 100 μg/l, though emerging research is beginning to identify elevated odds of skin lesions,[10,11] cancer,[12] respiratory infections and symptoms,[13,14] blood pressure effects,[15] and mortality from cardiovascular and other chronic diseases[9,16,17] from drinking water concentrations below 50 μg/l.

The mechanisms implicated in As toxicity from relatively low-dose exposure are not clearly understood, but they appear to involve oxidative stress, DNA repair, modification of gene expression and alteration of growth factors that may lead to cancer. Matrix metalloproteinase-9 (MMP-9) is involved in remodeling of the airways[18] and of the vascular wall and myocardium,[19] and is linked to respiratory[20,21] and cardiovascular[19,22–24] disease and to carcinogenesis.[25,26] Previously, we reported associations between sputum MMP-9 and the ratio of urinary monomethylarsonic acid to iAs (MMA:iAs)[27] and between serum MMP-9 and iAs concentrations in tap water and urine[28] in different populations.

In regions where As concentration in drinking water is below the recommended maximum contaminant level (MCL) of 10 μg/l (ppb),[29] food is the predominant source of exposure to iAs.[30] Recent studies indicate that dietary iAs intake is significantly associated with urinary As biomarkers.[31–37] There are only a few studies, however, that have specifically considered potential effects of dietary iAs exposure on biomarkers of toxicity or health outcomes. In these studies, high dietary intake, primarily from rice, is associated with elevated genotoxicity,[38] an increase in prevalent skin lesions,[36,37] and elevated lung cancer risk in men.[39]

This study evaluates the effect of dietary sources of iAs intake on serum concentration of MMP-9 in subjects with household tap water As concentrations above and below 10, 5 and 3 μg/l, to determine whether dietary intake alone or aggregate exposure at these low exposure thresholds might impact the concentration of this biomarker of As toxicity. We account for various factors that may influence metabolism of iAs, such as body mass index, protein and folate intake. In a cross-sectional study of 214 adult subjects living in Arizona communities with varying levels of As in tap water, 24-h diet recall interviews were analyzed for iAs using published residue data,[30,40] and As in cooking and drinking water was estimated from multisource water samples and self-reported consumption data.[41]

MATERIALS AND METHODS

Study Population

The Binational Arsenic Exposure Survey in Arizona (BAsES-AZ) was a cross-sectional survey of four communities (Tucson, New River, Ajo and San Manuel) selected *a priori* to represent a range of exposures to As in groundwater. Recruitment of the study population was through random-digit dialing in each community. In addition, recruitment letters were

mailed to all households in the rural community of New River. Potential participants were eligible if they were over 17 years of age and had lived in their current homes continuously for a minimum of 1 year. Multiple members of some households participated in the study, but individual responses on the use of specific water sources for drinking and cooking were collected for analysis. Participants received information about the study and gave informed consent following the requirements of the University of Arizona Human Subjects Protection Program. During household visits, trained technicians obtained anthropometric measures, administered demographic, health and 24-h dietary recall questionnaires, and collected multiple water samples from all of the sources used for drinking and/or food preparation. A phlebotomist collected blood samples at the household visit.

Dietary Data

The methods used for collecting and analyzing dietary data in the BAsES population have been described in detail elsewhere.[30,41] For the dietary recall, participants were instructed to describe everything they had eaten or drunk during the previous 24 h, how it was prepared and the amount consumed. Portion-size models were used to facilitate the estimation of quantities consumed. The 24-h dietary recalls were sent to the Arizona Diet, Behavior and Quality of Life Assessment Lab at the Arizona Cancer Center for data entry and dietary As and nutrient analysis. Dietary total and iAs were determined using published As residue data from a market basket survey of food commodities.[40] U.S. Department of Agriculture (USDA) recipes were used to estimate the major components of composite foods (e.g., white bread was 56% wheat flour, 36% milk, 4% vegetable oil, and smaller amounts of sugar, yeast and salt), and As values were then assigned based on total and iAs values for these commodities as reported in Schoof et al.[40] Furthermore, certain vegetables, fruits and other food items not included in the study by Schoof et al. were estimated based on average As content of similar food types.[30] The computer-based Minnesota Nutrition Data System-Research (NDS-R) Version software system was used for nutrient analysis.[42]

Water As

Participants completed questionnaires regarding frequency of use of all household water sources used for drinking and/or food preparation (including kitchen tap, private wells, filtered tap, bottled and other sources). Water samples were stored on ice for transport, aliquoted and stored at −80° C for subsequent analysis of total As, using inductively coupled plasma mass spectroscopy, by the University of Arizona Southwest Hazardous Waste Program, Hazard Identification Core. A weighted mean total As concentration was calculated separately for drinking and cooking water, based on an ordinal scale of reported frequency of use —rare, moderate, or frequent. As exposure from drinking water was computed from the weighted mean concentration times the self-reported quantity consumed per day.[41] As exposure from cooking water was calculated from the weighted mean As concentration of the cooking water times the number of grams of water added during preparation.[34] As in water added during cooking or food preparation was estimated only for specific foods, such as rice, pasta, dry beans, homemade soups, beverages and foods from concentrate or powdered mixes, and so on, and the number of grams of water added was based on the percent of water reported in these foods in the NDS-R software.[42]

The limit of detection for total As in water was 0.1 μg/l. The limit of detection for total and iAs in food was 3.6 and 2.0 μg/kg, respectively.[40] When As values in water or food were below the limit of detection, a value of half the limit of detection was used to calculate the exposure.

Blood Draw and Serum MMP-9

On the day after the dietary recall, a non-fasting blood sample was collected for MMP-9 analysis in 10-ml red-top (serum) tubes (Becton Dickinson, Franklin Lakes, NJ, USA). The sample was allowed to clot at room temperature for 15 min and was then stored at 0–8 °C for up to 4 h prior to centrifuging at 1000 × g for 15 min. Serum was separated into 2.0 ml aliquots and stored at −80 °C until assayed for MMP-9 using an ELISA (R&D Systems, Minneapolis, MN, USA). Standards and controls were assayed in duplicate with an automated microplate reader, Model ELx808 (BioTek Instruments, Winooski, VT, USA). The assay limit of detection was 0.156 ng/ml. MMP-9 concentration in samples was determined from the standard curve using a four parameter algorithm for best fit (KC4, BioTek). Testing of all samples was done at the University of Arizona.

Statistical Analyses

Only participants who completed the 24-h dietary recall questionnaire and were not missing information on serum MMP-9 concentration were included in these analyses. Stata 11.2 statistical package (StataCorp, College Station, TX, USA). Distribution and frequency of population characteristics and dependent and independent variables were evaluated. Measures of As exposure and MMP-9 were log(10)-transformed to approximate a normal distribution for use in all statistical tests; geometric means are reported in descriptive analyses.

Univariate and multivariable mixed model regression analyses were used to model the relation of serum MMP-9 and As intake, accounting for intra-correlation within households and/or communities. Potential confounders, including sex, age, ethnicity (Hispanic/non-Hispanic), body mass index, current smoking status, self-reported physician-diagnosed diabetes, dietary total protein intake and dietary total folate intake, were included as covariates in the multivariable models.

Two sets of models were run, an aggregate iAs intake model and an iAs components model, on the total population sample and in analyses stratified by tap water As concentration above and below thresholds of 3, 5 and 10 μg/l. Aggregate iAs intake was calculated as the sum of drinking water, cooking water and dietary exposure to iAs, in microgram per day. The components model included each source of iAs exposure (drinking water, cooking water and food) as a separate covariate in the models. Likelihood ratio tests were used to compare the fit of nested models. A two-tailed hypothesis test with a significance level of $P<0.05$ was considered statistically significant.

RESULTS

The study population consisted of 214 adults aged 19–87 years who participated in the BAsES-AZ study and had completed dietary recall interviews and provided water and blood

samples for analysis. As shown in Table 1, approximately 58% of the population was female, 23% was Hispanic and 77% non-Hispanic white. The geometric mean household tap water As concentration was 7.5 μg/l and ranged from 0.45 to 1004 μg/l. Mean tap water As was significantly higher in non-Hispanic than in Hispanic households (8.7 *vs* 4.6 μg/day, respectively, $P<0.001$). Drinking water As intake averaged 5.1 μg/day, but ranged from 0.03 to 2230 μg/day. Mean aggregate total As and iAs intake were estimated at 53.6 and 19.8 μg/day; aggregate iAs was significantly higher among non-Hispanics ($P=0.005$). Serum MMP-9 averaged 324 ng/ml and was significantly lower in Hispanics as compared with non-Hispanics (250 *vs* 351 ng/ml, respectively, $P = 0.004$). The prevalence of self-reported, physician-diagnosed diabetes in this population was 14% overall and 22% among Hispanics.

Unstratified Models

In crude models of log(10) serum MMP-9 in the total population sample (Table 2), dietary iAs intake was not a significant predictor of serum MMP-9 ($P = 0.142$), but tap water As concentration ($P<0.001$), drinking water As intake ($P = 0.001$), cooking water As intake ($P = 0.045$), dietary total protein intake ($P = 0.043$) and aggregate iAs intake ($P<0.001$) showed positive associations with serum MMP-9 concentration. Hispanic ethnicity ($P = 0.006$), diabetes ($P = 0.011$), age ($P = 0.012$) and body mass index ($P = 0.045$) were negatively associated with MMP-9 and sex, current smoking status and dietary total folate showed no relation in crude analyses.

After adjustment for potential confounders, aggregate iAs intake ($P<0.001$) and dietary total protein ($P = 0.034$) were positive predictors of serum MMP-9 in the total population sample, and dietary folate ($P = 0.002$), Hispanic ethnicity ($P = 0.036$) and age ($P = 0.041$) were negative predictors (Table 2). In contrast, none of the individual components of iAs exposure (dietary, drinking water or cooking water) were significantly associated with serum MMP-9 in the components model, after adjustment (not shown).

Models Stratified by Tap Water As

Aggregate iAs intake, in the stratified adjusted models, was consistently associated with serum MMP-9 among subjects exposed to tap water As ≤10 and ≤5 μg/l, but not above (Table 3). In the components models, only subjects exposed to household tap water As ≤3 μg/l showed a relationship between serum MMP-9 and iAs intake from food alone ($P = 0.022$); neither drinking nor cooking water As intake was a significant predictor in any strata. Dietary folate intake showed a statistically significant inverse relationship to serum MMP-9, regardless of tap water As level.

DISCUSSION

In this cross-sectional study of aggregate iAs exposure in U.S. adults, we report a relationship between aggregate exposure and a biomarker of toxicity among subjects with household tap water As concentrations below the EPA's maximum contaminant level of 10 μg/l. In unstratified models, aggregate iAs has a positive linear relationship to serum MMP-9 that is lessened by folate intake and amplified by dietary protein intake. The association

between serum MMP-9 and dietary iAs exposure is seen among subjects living in households with tap water As concentrations ≤3 μg/l.

We estimated aggregate iAs intake based on 24-h dietary recall interviews, analysis of As in multiple source water samples used for drinking and/or cooking, and estimates of the quantity of drinking and cooking water consumed during that same 24-h period. In a previous study based on both U.S. and Mexican populations that participated in the BAsES study, we reported that drinking water As concentration was a better predictor than urinary As sum of species (iAs+methylated compounds) of serum MMP-9.[28] The analyses presented in the current manuscript are limited to U.S. residents in BAsES, because of differences in food consumption patterns between Sonora, Mexico and Arizona and no available data on iAs in foods purchased and consumed in Sonora.

As toxicity and its relation to a wide variety of diseases —cancers, cardiovascular, pulmonary and so on — is not well understood.[43] Tissue remodeling is one of the several proposed mechanisms of toxicity, and As is thought to induce remodeling via methylation of genes and the expression of mediators and enzymes involved in organization of extracellular matrix. Tissue remodeling occurs in early development, in wound repair, and in respiratory and cardiovascular disease.[43] MMP-9 is also involved in the degradation of extracellular matrix proteins and is associated with carcinogenesis,[44–47] airway remodeling[18,48,49] and cardiovascular disease.[50] MMP-9 is present in low concentrations in serum in healthy adults, but increases within hours of disease onset.[51] Increased secretion of MMP-9 has been observed in As-treated cells, leading to As-induced carcinogenesis possibly regulated by Nrf2[52] or other key signaling pathways.[53,54] Olsen et al.[18] demonstrated an inhibition of wound repair associated with the upregulation of MMP-9 in human lung epithelial cells exposed to As concentrations as low as 30 μg/l.[18] A cross-sectional study in two communities in Arizona reported an effect of low-level As exposure on the ratio of MMP-9 to tissue inhibitor of metalloproteinase 1 (an antiproteinase) in induced sputum, suggesting As-induced lung inflammation from drinking water concentrations of approximately 20 μg/l.[27] Although little is known about the time course of MMP-9 in relation to As exposure in humans, *in vitro* studies have shown increased MMP-9 production within 24 h.[18,53]

Few papers have been published on either low-dose As effects or dietary As effects on disease biomarkers. In general, low-dose effects have been extrapolated from studies of high-dose exposures,[10,55] yet in a comparison of the effects of high *vs* low As on gene expression in treated human bronchial epithelial cells, there was little overlap in expression profiles, that is, different groups of genes were affected at each exposure level.[56] Another study of human cell cultures by Andrew et al.[57] found an increase in DNA damage and a decrease in the expression of an excision repair component of DNA repair processes with exposure to drinking water As ≥6 μg/l as compared with <6 μg/l.[57] In mice, prenatal exposure to drinking water As at the MCL influenced both birth weight and lung mechanics in early life,[58] and *in utero* exposure to As in a New Hampshire birth cohort, at levels well below the MCL, was associated with epigenomic changes (increased methylation) in CpG islands.[59] The Health Effects of Arsenic Longitudinal Study (HEALS) in Bangladesh has also shown increasing odds of skin lesions,[10] elevated pulse pressure[60] and proteinuria[61] with increasing quintiles of drinking water As exposure (in the range of <8.1 to 864 μg/l).

Although few studies thus far have focused on the impact of dietary As on health, this is beginning to change. Besides the studies mentioned earlier on cooked rice intake in Japan and Bangladesh,[36,39] there have been several studies from the New Hampshire Birth Cohort Study that report effects of prenatal exposure to As (measured in urine) on infant infections,[13] placental gene expression associated with birth weight[62] and differential DNA methylation in cord blood.[59] Although these studies did not directly measure maternal dietary As intake, Gilbert-Diamond et al.[32] found that rice consumption and tap water, which averaged 1 μg/l, were statistically significant predictors of urinary As in that study population.[32]

Micronutrients may interact with the absorption, metabolism, binding and/or excretion of As, or with other mechanisms that induce toxicity.[63] Both folate and protein are involved in the metabolism of iAs through the 1-carbon metabolic pathway. Folate is associated with increased urinary As methylation,[64,65] and protein intake with increased methylation[66] and total As excretion.[67] These nutrients were included in the models because in previous analysis of BAsES data, we found a negative impact of dietary protein on the relationship between dietary and water As exposure and urinary sum of iAs and methylated As species, and a negative trend for dietary folate intake.[34] Although neither dietary protein nor folate were associated with MMP-9 in univariate analyses, they were positively correlated with each other. When both were included in a marginal model of MMP-9, protein was a significant positive predictor and folate a negative predictor with borderline significance. Folate might mitigate the potential effects of aggregate iAs intake on serum MMP-9 through its role as a methyl donor, but the mechanism for the additive effect of dietary protein with iAs is unclear. Equally unclear is the negative relation between Hispanic ethnicity and MMP-9, although dietary and lifestyle factors may contribute.

BAsES was a cross-sectional study that evaluated self-reported food and water intake from a single day and serum concentrations of MMP-9 from a single blood sample. Although inclusion in this study required minimum household residence time of 1 year, longer-term or chronic exposure was not evaluated. Hence, our findings are limited by the fact that the results are based on short-term exposure, albeit carefully assessed, subject-specific estimates, and a potential indicator of short-term toxicity.

In this and the handful of other studies that show a relation between dietary As and health, dietary data tend to be based on a single food frequency questionnaire, diet diary or food sample, and dietary As intake is generally modeled, not measured. On the basis of a secondary analysis of the National Human Exposure Assessment Survey (NHEXAS)-Arizona data, estimates of dietary As intake based on published sources of dietary As residue data showed large discrepancies with measured As from duplicate food samples. However, measured and modeled exposures were highly correlated.[35] Dietary iAs exposure estimates used in this study were modeled using the only published data on iAs residues in the major food commodities consumed in the U.S.[40]

Our results show an association of dietary iAs alone and aggregate iAs exposure with serum MMP-9 only among subjects exposed to lower levels of tap water As. It is unclear why aggregate exposure is not associated with MMP-9 in subjects exposed to >5 or >10 μg/l As

in tap water, unless dietary exposure or a confounder related to diet is independently associated with this biomarker. Testing of multiple hypotheses could also have contributed to false positive findings. The effect of dietary iAs intake on serum MMP-9 levels and other toxic biomarkers needs to be tested in future studies.

Both random and systematic error in dietary assessment is common, especially under-reporting of energy intake, regardless of the method of assessment.[68] Contrary to expectation, geometric mean energy intake based on the dietary recall records in the BAsES study was slightly higher than the expected energy intake (1812 *vs* 1799 kilocalories, respectively) based on standard equations,[69] for both Hispanics and non-Hispanics.

The BAsES-AZ population included Hispanic and non-Hispanic adults only. Although there were no differences in dietary iAs intake between ethnic groups, tap water As and drinking water As intake were higher in non-Hispanic households. The difference in exposure to As in water was likely due to a recruitment protocol that involved *a priori* selection of communities based on ground water As concentrations and differential assortment within these communities by ethnicity. The population in one of the high-exposure communities was predominantly non-Hispanic.

CONCLUSIONS

Aggregate iAs intake from food and water sources, at exposure levels averaging <20 μg/day, may contribute to As-induced changes in serum MMP-9, a biomarker associated with toxicity. Dietary iAs alone was associated with serum MMP-9 at the lowest strata of tap water As, ≤3 μg/l. Until recently, concern about As exposure has been focused almost entirely on contaminated drinking water, which remains a significant problem in many locations around the world. In the U.S., the average tap water As concentration is 2.4 μg/l,[70] well below the current 10 μg/l MCL. The significance of this research is that it implies a significant impact of dietary iAs that is apparent at tap water As concentrations below the MCL. At present, As exposure from food and beverages remains largely unregulated. Our current knowledge of exposure to As compounds in food is sorely lacking and attention has just recently begun to focus on the potential health effects of low-dose exposures.

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Table 1

Population characteristics of the Binational Arsenic Exposure Survey (BAsES): Arizona subjects with complete 24-h dietary recall data and serum MMP-9 data.

	Total Population	Hispanic	Non-Hispanic	*P*-value[a]
Number of participants, *n* (%)	214	50 (23.4)	164 (76.6)	
Male	91 (42.5)	23 (46.0)	68 (41.5)	
Female	123 (57.5)	27 (54.0)	96 (58.5)	
Current smoker, *n* (%)	31 (14.5)	3 (6.0)	28 (17.1)	
Age in years, mean ±SD	55.3 ±15.1	48.9 ±15.5	57.3 ±14.4	
Diabetic, *n* (%)	30 (14.1)	11 (22.0)	19 (11.7)	
BMI, mean ±SD				
Male	29.6 ±6.0	32.4 ±6.4	28.6 ±5.5	
Female	28.4 ±6.4	30.9 ±6.6	27.7 ±6.2	
Serum MMP-9, ng/ml, gmean (min-max)	324 (41.1–1503)	250 (41.1–923)	351 (47.9–1503)	0.004
Drinking water As, μg/day, gmean (min-max)	5.1 (0.03–2230)	3.4 (0.11–44.2)	5.8 (0.03–2230)	0.025
Cooking water As, μg/day, gmean (min-max)	2.5 (0.01–1181)	2.1 (0.04–42.5)	2.6 (0.01–1181)	0.387
Dietary total As, μg/day, gmean (min-max)	33.1 (4.8–495)	33.5 (4.8–456)	32.9 (6.3–495)	0.899
Non-seafood eaters	26.2 (4.8–279)	27.0 (4.8–279)	26.0 (6.2–228)	
Dietary iAs, μg/day, gmean (min-max)	6.0 (0.83–62.8)	6.0 (0.83–62.8)	5.9 (1.78–48.3)	0.903
Aggregate total As intake, μg/day, gmean (min-max)	53.6 (9.6–2459)	43.9 (9.7–468)	57.0 (9.6–2459)	0.076
Aggregate iAs intake, μg/day, gmean (min-max)	19.8 (2.5–2429)	14.5 (4.0–92.3)	21.8 (2.5–2429)	0.005
Household tap water As, μg/l, gmean (min-max)	7.5 (0.45–1004)	4.6 (0.54–43.4)	8.7 (0.45–1004)	<0.001

Abbreviations: As, arsenic; gmean, geometric mean; iAs, inorganic arsenic; MMP-9, matrix metalloproteinase 9; min-max, minimum-maximum; SD, standard deviation.

[a]Two-sample *t*-tests of log-transformed values were used to compare means by ethnicity.

Table 2

Crude and adjusted predictors of log(10)-transformed serum MMP-9 in the BAsES-AZ population, unstratified by household tap water As.

Predictor variables	Crude		Adjusted	
	β (± SE)	*P*-value	β (± SE)	*P*-value
Log(10) tap water As (μg/l)	0.187 (0.04)	<0.001		
Log(10) dietary iAs (μg/day)	0.100 (0.07)	0.142		
Log(10) drinking water As (μg/day)	0.087 (0.03)	0.001		
Log(10) cooking water As (μg/day)	0.049 (0.02)	0.045		
Aggregate iAs intake[a] (μg/day)	0.154 (0.04)	<0.001	0.152 (0.04)	<0.001
Log(10) dietary folate (μg/day)	−0.054 (0.07)	0.447	−0.279 (0.09)	0.002
Log(10) dietary protein (g/day)	0.167 (0.08)	0.043	0.222 (0.10)	0.034
Hispanic ethnicity	−0.144 (0.05)	0.006	−0.114 (0.05)	0.036
Diabetes	−0.143 (0.06)	0.011	−0.105 (0.06)	0.059
Age (years)	−0.004 (0.00)	0.012	−0.003 (0.00)	0.041
Sex, male	0.057 (0.03)	0.079	0.059 (0.00)	0.095
BMI	−0.007 (0.00)	0.045	−0.006 (0.00)	0.085
Current smoker	0.043 (0.06)	0.452	−0.003 (0.05)	0.958

[a]Aggregate iAs intake is the sum of dietary, drinking water and cooking water inorganic As.

Table 3

Parameter estimates (± standard error) for the increase in $\log_{10}$-transformed serum MMP-9 in aggregate iAs intake models and component models[a], stratified by household tap water As.

Predictors ($\log_{10}$-transformed)	**≤10 μg/l (*n* = 154)**	**>10 μg/l (*n* = 60)**	**≤5 μg/l (*n* = 83)**	**> 5 μg/l (*n* = 131)**
	β (± SE)	**β (± SE)**	**β (± SE)**	**β (± SE)**
Aggregate models				
Total iAs	0.300 (0.095)**	0.050 (0.042)	0.368 (0.122)**	0.038 (0.043)
Dietary folate	−0.412 (0.128)**	−0.226 (0.102)*	−0.309 (0.172)	−0.327 (0.091)#
Dietary protein	0.290 (0.136)*	0.133 (0.140)	0.082 (0.186)	0.338 (0.112)**
Component models				
Dietary iAs	0.114 (0.101)	0.108 (0.143)	0.145 (0.121)	0.135 (0.113)
Drinking water As	0.088 (0.052)	0.029 (0.042)	0.035 (0.073)	0.028 (0.037)
Cooking water As	0.028 (0.048)	0.007 (0.033)	0.112 (0.067)	−0.032 (0.033)
Dietary folate	−0.345 (0.138)*	−0.257 (0.119)*	−0.332 (0.195)	−0.344 (0.104)**
Dietary protein	0.222 (0.145)	0.138 (0.155)	0.146 (0.201)	0.312 (0.117)**
Predictors ($\log_{10}$-transformed)		≤3 μg/l (*n* = 37)		>3 μg/l (*n* = 177)
		β (± SE)		β (± SE)
Aggregate models				
Total iAs		0.475 (0.163)**		0.092 (0.042)*
Dietary folate		−0.621 (0.274)*		−0.229 (0.087)**
Dietary protein		−0.047 (0.329)		0.286 (0.104)**
Component models				
Dietary iAs		0.381 (0.166)*		0.101 (0.093)
Drinking water As		0.086 (0.120)		0.038 (0.035)
Cooking water As		0.025 (0.095)		−0.003 (0.032)
Dietary folate		−0.598 (0.290)*		−0.222 (0.099)*
Dietary protein		−0.126 (0.381)		0.257 (0.109)*

*P<0.05,

**P<0.01,

#P<0.001

[a]Adjusted for ethnicity, age, sex, BMI, diabetes and current smoking.