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Arsenic methylation capacity and obesity are associated with insulin resistance in obese children and adolescents

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ABSTRACT

The goal of the present study was to compare the arsenic methylation capacities in elementary school and junior high school students in an area of Taiwan with low arsenic exposure, and explore the influence of both arsenic methylation capacity and obesity on insulin resistance in these children and adolescents using the HOMA-IR index. We recruited 303 elementary school students and 319 junior high school students in Taipei City from September 2007 to November 2011. Concentrations of inorganic arsenic (arsenite + arsenate), monomethylarsonic acid (MMA^V) and dimethylarsinic acid (DMA^V) were determined by a high-performance liquid chromatography-linked hydride generator and atomic absorption spectrometry. Insulin resistance was determined by HOMA-IR. Elementary school students had significantly lower inorganic arsenic percentage and a higher DMA^V percentage than junior high school students. It seems that the former had better arsenic methylation capability than the latter. The HOMA-IR value was significantly and positively related to the sum of the urinary inorganic and methylated arsenic (TotalAs) concentrations and also the BMI Z score, with the regression coefficients (β) being 0.058 ($p < 0.001$) and 0.001 ($p = 0.027$), respectively. The higher BMI values and higher TotalAs concentration were associated with higher HOMA-IR values in children and adolescents in Taiwan.

1. Introduction

One of the first studies on inorganic arsenic and diabetes reported that chronic exposure to inorganic arsenic in drinking water was associated with the occurrence of diabetes in the Blackfoot disease hyperendemic area of Southwestern Taiwan (Lai et al., 1994). A cohort study then reported a dose–response relationship between long-term arsenic exposure and the incidence of type 2 diabetes in the same area (Tseng et al., 2000). Moreover, several epidemiological studies continued to report that arsenic exposure was related to diabetes in arsenic endemic areas of Mexico and Bangladesh (Del Razo et al., 2011; Islam et al., 2012). These findings suggest that ingestion or inhalation of arsenic may predispose an individual to the development of diabetes. However, a National Toxicology Program Workshop Review reported that evidence is insufficient to conclude that arsenic is associated with diabetes in cases of low to moderate arsenic exposure (<150 μg/L drinking water) (Kuo et al., 2013; Maull et al., 2012). Further studies which use large sample sizes, a prospective design, and better measures of outcome and exposure need to be conducted to fully explore the relationships between arsenic exposure and insulin resistance.

The differences in susceptibility to arsenic toxicity may be due to the variability in the metabolic biotransformation of inorganic arsenic in the body. Absorbed arsenate is reduced to arsenite and undergoes methylation to form monomethylarsonic acid (MMA^V) and dimethylarsinic acid (DMA^V), which have low toxicity (Yamauchi and Fowler, 1994) and are excreted by the kidneys (Vahter, 2002). However, toxicity studies conducted *in vitro* have suggested that monomethylarsonous acid (MMA^{III}) and dimethylarsenious acid (DMA^{III}) are more toxic than inorganic arsenite (Styblo et al., 2000; Tokar et al., 2013), although epidemiologic data were not available. Our previous prospective study found that MMA^V percentage

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(MMA^V%) increased and DMA^V percentage (DMA^V%) decreased significantly with age (Huang et al., 2008), suggesting that a decrease in arsenic methylation capacity is associated with aging. It is an interesting issue as to whether or not arsenic methylation capacity is varied in early childhood. Fortunately we have an opportunity to test differences in arsenic methylation capacity between elementary school and junior high school students.

Obesity is rapidly becoming a leading cause of morbidity in all age groups. Recent research shows that obesity in children and adolescents is associated with multiple risk factors for cardiovascular disease (Dhuper et al., 2013). Children who are obese have been shown to have a significantly increased risk of insulin resistance (Guerrero-Romero et al., 2013). The homeostasis model assessment of insulin resistance (HOMA-IR) is widely employed as a marker of insulin resistance (Matthews et al., 1985). A recent study found that 48-hour exposure to low concentrations of arsenite and trivalent methylated metabolites of inorganic arsenic inhibited glucose-stimulated insulin secretion (Douillet et al., 2013). These findings suggested that arsenic or inorganic arsenic metabolites and obesity contribute to the development of diabetes by impairing pancreatic β-cells function, particularly insulin synthesis and secretion. In addition, our recent study found that obese children with high insulin levels had significantly higher MMA^V% and significantly lower DMA^V% than obese adolescents with low insulin (Su et al., 2012). It implies that obesity and high insulin levels were associated with a worse arsenic methylation capacity in adolescents. Whether urinary arsenic profiles and obesity can also affect glucose metabolism and insulin resistance, altering blood glucose regulation in adolescents even with low arsenic exposure, is unknown. Therefore, the goal of the present study was to compare the arsenic methylation capacities in elementary school and junior high school students in an area of Taiwan with low arsenic exposure, and explore the influence of both arsenic methylation capacity and obesity on insulin resistance in these children and adolescents using the HOMA-IR index.

2. Materials and methods

2.1. Study participants

Two cross-sectional studies were conducted. The first study was performed using ~ 3500 students at eight elementary schools, including San Sing, Wu Sing, Sin Yi, Ding Si, Sin He, Shuang Cheng, Yong He, and An Keng Elementary Schools in Taipei City or New Taipei City from September 2007 to September 2009. Ten percent of all elementary school students were randomly invited to attend Taipei Medical University Hospital for a detailed health examination. A total of 303 (86.57%) elementary students volunteered to receive health examinations, which were conducted from September 2009 to December 2009 (Su et al., 2012). A second study was performed with ~ 319 junior high school students from Chengde and Young-Ji Junior High Schools in Taipei City from October 2010 to November 2011. All participants came from Taipei City or New Taipei City. All study participants provided either their parents' or their own written informed consent form before participating in questionnaire interviews, or providing biological specimens. The Research Ethics Committee of the Taipei Medical University, Taipei, Taiwan, approved the study, which was conducted in agreement with the standards specified in the World Medical Association Declaration of Helsinki. The anthropometric measurements of weight and height were collected for all elementary school students and junior high school students according to standard guidelines by two research assistants who had received 6 hours of specialized training. Standing height and weight were measured in a rigid vertical position, using a standard medical balance scale, with participants not wearing shoes, and in light clothes. Height was measured to the nearest 0.5 cm, and weight was measured to the nearest 100 g. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Categories of overweight, obesity, and lower than normal weight were defined according to guidelines developed by the Department of Health, Executive Yuan, Taiwan (Department of Health, 2011) based on WHO Child Growth Standards (de Onis et al., 2007), and a modified locally weighted method (Chen et al., 2003) designed for use with children and adolescents based on BMI, age, and gender. A commercially available bioelectrical impedance analyzer (Maltron BioScan 920 analyzer, Maltron International Ltd) was used to obtain two measurements of body fat as a percentage of weight. The majority of study participants (>80%) lived in Taipei City and drank tap water from the Taipei Water Department of the Taipei City Government. The average arsenic concentration of tap water in Taipei City is 0.7 μg/L, but concentrations range from nondetectable to 4.0 μg/L.

2.2. Questionnaire interview

A face-to-face interview using a structured questionnaire executed by well-trained interviewers was conducted to collect information. Demographics and socioeconomic characteristics, lifestyle behaviors of parents, such as cigarette smoking and alcohol consumption, and personal and family disease history were included in the questionnaire.

2.3. Biological specimen collection

Peripheral blood specimens (5–8 mL) were collected using vacuumed syringes at the time of recruitment. The blood samples were then separated into red blood cells and serum and frozen at –80 °C for the measurements of biochemical indices and homocysteine. Concurrently, spot urine samples (20 mL) were collected and immediately transferred to a –20 °C freezer until needed for urinary arsenic species analyses.

2.4. Urinary arsenic species measurement

The analytical methods for the determination of urinary arsenic species have been described previously (Hsueh et al., 1998). Briefly, urine samples were thawed at room temperature ultrasonically mixed and filtered through a Sep-Pak C18 column (500 mg 40 μm APD, 60 Å; JT Baker). A 200-μL sample of treated urine was injected into high-performance liquid chromatography (HPLC), linked with a hydride generator and atomic absorption spectrometer (HG-AAS) to measure the concentrations of arsenite (iAs^{III}), arsenate (iAs^V), MMA^V and DMA^V. Recovery rates of the four arsenic species were calculated by (sample spiked standard solution concentration – sample concentration)/standard solution concentration × 100. The detection limits for iAs^{III}, DMA^V, MMA^V and iAs^V were 0.02, 0.08, 0.05 and 0.07 μg/L respectively, and the recovery rates ranged from 93.8% to 102.2%. The standard reference material (SRM 2670) was obtained from the National Institute of Standards and Technology (NIST) and contained 480 ± 100 μg/L of inorganic arsenic. SRM 2670 was used as a quality standard and analyzed along with urine samples. The mean value of SRM 2670 determined by our system was 507 ± 17 μg/L (n = 4). Both arsenobetain and arsenocholin come from seafood and are excreted without metabolic transformation. Both are undetectable in the arsine generation assay. Thus arsenobetain and arsenocholin were not measured by the HG-AAS method (Buchet et al., 1981).

2.5. Serum biochemical examination

Total cholesterol and triglyceride serum levels were determined by autoanalyzer (Hitachi 737, USA) with reagents obtained from Boehringer Mannheim Diagnostics. High density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and insulin were also assessed. An enzymatic assay for serum homocysteine was described by Chan et al. (2005). Close correlation (r > 0.9) was observed between the results by the enzymatic method and a reference HPLC procedure (Chan et al., 2005). HOMA-IR values were calculated using the formula: fasting insulin (μU/mL) × fasting glucose (mg/dL)/405 (Katz et al., 2000).

2.6. Statistical analysis

The sum of urinary inorganic and methylated arsenic (TotalAs) concentrations (μg/g creatinine) was defined as the total sum of iAs^{III}, iAs^V, MMA^V, and DMA^V, and was normalized by urine creatinine. The inorganic arsenic percentages (iAs%), MMA^V%, and DMA^V% were calculated by dividing the concentration of each species [(iAs^{III} + iAs^V), MMA^V and DMA^V] by the TotalAs concentrations. The Student's *t*-test was used to compare differences in the variables of age, biochemical indices, and urinary arsenic profiles between elementary school and junior high school students. The χ^2 test was used to test for differences in categorical variables between elementary school and junior high school students. Analysis of variance and Scheffé's test were used to compare differences in variables of BMI, BMI Z score, birth weight, body fat, biochemical indices, and urinary arsenic profiles for lower than normal weight, normal weight, and overweight/obese groups. Simple linear regression analysis was used to examine associations between the TotalAs concentrations and $\log_{10}$ HOMA-IR levels, and between BMI Z score and $\log_{10}$ HOMA-IR levels, respectively. Multiple linear regression models were used to estimate multivariate adjusted regression coefficients and 95% confidence intervals (CIs). The cut-off point for the TotalAs (≤19.535 μg/L) for joint effect analysis was the median distribution for all participants. Participants who were lower than normal weight and overweight/obese were pooled together and classified as abnormal weight. The combined TotalAs and normal weight/abnormal weight were stratified into four exposure groups as follows: TotalAs ≤ 19.535 μg/L and normal weight; TotalAs ≤ 19.535 μg/L and abnormal weight; TotalAs > 19.535 μg/L and normal weight; TotalAs > 19.535 μg/L and abnormal weight. The TotalAs ≤ 19.535 μg/L and normal weight was used as a reference group. The linear regression model was used to calculate the regression coefficients and 95% confidence intervals that were used to evaluate the relationships between HOMA-IR levels and the four exposure groups using three dummy variables. The significance tests for linear trends among regression coefficients across

exposure strata were calculated by categorizing exposure variables and treatment scored variables as being continuous.

3. Results

Elementary school students' parents had higher educational levels and had fewer paternal smokers than junior high school students (Table 1). Among elementary school students, lipid profile and glutamate oxaloacetate transaminase (GOT) were significantly higher and serum insulin, blood glucose, HOMA-IR, and homocysteine were significantly lower than in junior high school students (Table 2). The distribution of overweight/obesity, normal weight and lower than normal weight was significantly different between elementary school students and junior high school students. The TotalAs concentrations (μg/g creatinine) and DMA% were significantly higher, and iAs% was significantly lower in elementary school students compared to junior high school students. It seems that arsenic methylation capability of elementary school students was more efficient than that of junior high school students (Table 2).

HDL of lower than normal weight participants were significantly higher than those of normal weight and overweight/obese subjects. In contrast, body fat of lower than normal weight subjects was significantly lower than normal weight and overweight/obese subjects. Glutamic-Pyruvate Transaminase (GPT), triglyceride, serum insulin and HOMA-IR of lower than normal weight and normal weight subjects were significantly lower than those of overweight/obese subjects. The TotalAs concentrations and also iAs%, MMA^V%, and DMA^V% did not differ across the strata (Table 3).

A linear regression analysis showed that $\log_{10}$ HOMA-IR levels were significantly related to both BMI Z score increments and the TotalAs concentrations adjusted for age and gender (Fig. 1), with the regression coefficients being 0.058 ($p < 0.001$) and 0.001 ($p < 0.027$), respectively. Lipid profiles, glucose levels, insulin levels, and liver function were all related to the categories of lower than normal weight, normal weight, and overweight/obesity. Stepwise multiple linear regression models were used to analyze the relationships between age, gender, BMI Z score, the TotalAs concentrations, lipid profiles, liver function indices, paternal educational level, maternal educational level, paternal cigarette smoking status, and HOMA-IR levels (Table 4). We found that for all students in the summary model, HOMA-IR levels were significantly increased with increases in BMI Z score, triglycerides, GPT, and the TotalAs concentrations (μg/L). Furthermore, when analyzing these variables in the summary model, we found similar results for elementary school and junior high school students, and except for the body fat% variable, also found similar results across the lower than normal weight, normal weight, and overweight/obese strata. HOMA-IR levels were significantly related to triglycerides in overweight/obese and lower than normal weight students, and also to the TotalAs concentrations (μg/L) in all three groups of students (lower than normal, normal, and overweight/obese). Because both BMI and the TotalAs concentrations affected HOMA-IR values, further analyses were conducted to evaluate the joint effects of the two risk factors on HOMA-IR (Fig. 2). When using normal weight and the TotalAs concentrations (≤19.54 μg/L) as the reference group, the regression coefficients and 95% confident intervals (CI) of HOMA-IR values for normal weight and the TotalAs concentrations > 19.54 μg/L, abnormal weight and the TotalAs concentrations ≤ 19.54 μg/L, and abnormal weight and the TotalAs concentrations > 19.54 μg/L were 0.366 (−0.631–1.326), 1.605 (0.674–2.536), and 2.146 (1.192–3.100), respectively. These results suggest that higher BMI values tended to interact with higher TotalAs concentrations in modifying the HOMA-IR levels.

4. Discussion

The present study showed that elementary school students had significantly higher TotalAs concentrations (μg/g creatinine) and DMA percentages but significantly lower inorganic arsenic percentages than junior high school students. Our results also suggest that elementary school students had a more efficient arsenic methylation capacity than junior high school students. However, the TotalAs concentrations (μg/L) was not different between elementary school students and junior high school students, and this may be due to

Table 1
Sociodemographic characteristics of elementary school students and junior high school students.

Variables	Elementary school students (N = 303) No. (%)	Junior high school students (N = 319) No. (%)	p value
Age (Mean ± SE)	8.82 ± 0.09	12.69 ± 0.03	<0.0001[a]
Gender			
Male	161 (53.14)	174 (54.55)	0.724[b]
Female	142 (46.86)	145 (45.45)	
Paternal educational level			0.0005[b]
Junior high school or below	23 (7.96)	46 (15.28)	
High school	105 (36.33)	131 (43.52)	
University or above	161 (55.71)	124 (41.20)	
Maternal educational level			<0.0001[b]
Junior high school or below	15 (5.17)	47 (15.11)	
High school	138 (47.59)	152 (48.87)	
University or above	137 (47.24)	112 (36.02)	
Paternal cigarette smoking status			0.0021[b]
Non-smoker	137 (47.24)	105 (34.43)	
Former smoker	28 (9.66)	50 (16.39)	
Current smoker	125 (43.10)	150 (49.18)	
Maternal cigarette smoking status			0.362[b]
Non-smoker	267 (92.07)	274 (88.67)	
Former smoker	4 (1.38)	7 (2.27)	
Current smoker	19 (6.55)	28 (9.06)	

[a] *t* test.
[b] χ^2 test.
Information on paternal educational level was not available for 14 elementary school students and 18 junior high school students.
Information on maternal educational level was not available for 13 elementary school students and eight junior high school students.
Information on paternal cigarette smoking status was not available for 13 elementary school students and 14 junior high school students.
Information on maternal cigarette smoking status was not available for 13 elementary school students and 10 junior high school students.

Table 2
Birth weight, body fat, biochemical indices, TotalAs concentrations, and percentage of arsenic species for elementary school students and junior high school students.

Variables	Elementary school students (N = 303) Mean ± SE	Junior high school students (N = 319) Mean ± SE	p value
Birth weight (g)	2910.4 ± 60.17	2770.4 ± 60.17	0.096
Body fat (%)	26.39 ± 0.56	21.88 ± 0.46	<0.0001
BMI (kg/m^2)	20.07 ± 0.25	20.57 ± 0.24	0.1531
BMI Z-score	−0.06 ± 0.06	0.06 ± 0.06	0.1531
BMI group			
Lower than normal weight	31 (10.23)	52 (16.30)	<0.0001
Normal weight	109 (35.97)	168 (52.66)	
Overweight/obese	163 (53.80)	99 (31.03)	
Insulin (μIU/mL)	11.91 ± 1.07	16.81 ± 0.76	0.0002
Blood glucose	88.98 ± 1.10	91.76 ± 0.41	0.019
HOMA-IR	2.80 ± 0.32	3.92 ± 0.21	0.0032
Cholesterol (mg/dL)	173.9 ± 1.72	160.1 ± 1.54	<0.0001
Triglyceride (mg/dL)	71.73 ± 2.20	75.53 ± 2.22	0.2252
HDL (mg/dL)	59.40 ± 0.71	55.82 ± 0.71	0.0004
LDL (mg/dL)	100.20 ± 1.47	90.03 ± 1.30	<0.0001
Homocysteine (μmole/L)	8.24 ± 0.13	9.67 ± 0.15	<0.0001
GOT (IU/L)	25.53 ± 0.53	21.07 ± 0.45	<0.0001
GPT (IU/L)	18.81 ± 1.15	16.20 ± 0.98	0.085
TotalAs concentrations (μg/g creatinine)	29.64 ± 1.72	23.55 ± 1.34	0.005
TotalAs concentrations (μg/L)	24.54 ± 1.22	25.92 ± 1.23	0.4252
Urine creatinine (mg/L)	93.52 ± 2.70	128.30 ± 3.57	<0.0001
iAs%	5.06 ± 0.50	7.57 ± 0.31	<0.0001
MMA^V%	5.00 ± 0.33	5.30 ± 0.28	0.4910
DMA^V%	90.52 ± 0.58	87.50 ± 0.44	<0.0001

The Student's *t*-test was used to compare differences in the variables of age, biochemical indices, and urinary arsenic profiles between elementary school and junior high school students.
HOMA-IR, homeostasis model assessment of insulin resistance, HOMA-IR = Fasting insulin (μU/mL) × Fasting glucose (mg/dL)/405; HDL, high density lipoprotein-cholesterol; LDL, low density lipoprotein-cholesterol; MMA^V, monomethylarsonic acid; DMA^V, dimethylarsinic acid; iAs%, inorganic arsenic (iAs^{III} + iAs^V)/TotalAs × 100; MMA^V%, MMA^V/TotalAs × 100; DMA^V%, DMA^V/TotalAs × 100.

the dilution of water consumption (urine creatinine of the former was lower than those of the latter). In addition, data from both elementary school and junior high school students showed that HOMA-IR values were significantly increased with corresponding increases in GPT and the TotalAs concentrations (μg/L).

High MMA^V%, and low DMA^V% in the urine have been used to identify an inefficient methylation capacity in human subjects, and many epidemiological studies have shown that it is associated with arsenic-related disease including bladder cancer and cardiovascular disease (Huang et al., 2009; Pu et al., 2007). Interindividual

Table 3
Birth weight, body fat, biochemical indices, TotalAs concentrations, and percentage of arsenic species stratified by normal weight, overweight/obese, and lower than normal weight.

Variables	Lower than normal weight (N = 83)	Normal weight (N = 277)	Overweight/obese (N = 262)	p value	p value[#]
Age	11.16 ± 0.26[a]	11.12 ± 0.13[b]	10.35 ± 0.14	<0.0001	
BMI (kg/m^2)	14.88 ± 0.16[a,c]	18.26 ± 0.11[b]	24.23 ± 0.21	<0.0001	
BMI Z-score	−1.26 ± 0.04[a,c]	−0.48 ± 0.02[b]	0.90 ± 0.05	<0.0001	
Body fat (%)	14.35 ± 0.63[a,c]	19.83 ± 0.30[b]	31.66 ± 0.45	<0.0001	<0.0001
Cholesterol (mg/dL)	169.87 ± 3.00	164.86 ± 1.71	167.72 ± 1.94	0.308	0.8084
Triglyceride (mg/dL)	64.40 ± 3.90[a]	66.77 ± 1.73[b]	84.27 ± 2.90	<0.0001	<0.0001
HDL (mg/dL)	63.41 ± 1.33[a,c]	59.27 ± 0.71[b]	53.76 ± 0.78	<0.0001	<0.0001
LDL (mg/dL)	94.25 ± 2.37	91.78 ± 1.38[b]	98.57 ± 1.70	0.0064	0.0229
GOT (IU/L)	23.05 ± 0.64	22.02 ± 0.36[b]	24.59 ± 0.74	0.0038	0.0492
GPT (IU/L)	12.96 ± 1.08[a]	13.04 ± 0.35[b]	23.76 ± 1.67	<0.0001	<0.0001
Homocysteine (μmole/L)	8.69 ± 0.22	9.05 ± 0.15	9.35 ± 0.21	0.143	0.020
Birth weight (kg)	2.67 ± 0.11[a]	2.82 ± 0.06	2.91 ± 0.07	0.148	0.164
Urine creatinine (mg/L)	107.83 ± 6.90	117.15 ± 3.81	106.94 ± 3.23	0.110	0.807
Blood glucose	90.34 ± 1.24	89.61 ± 0.53	91.33 ± 1.20	0.383	0.048
Insulin (μIU/mL)	10.19 ± 1.64[a]	11.75 ± 0.72[b]	18.79 ± 1.22	<0.0001	<0.0001
HOMA-IR	2.34 ± 0.41[a]	2.77 ± 0.25[b]	4.39 ± 0.33	<0.0001	<0.0001
TotalAs concentrations (μg/L)	27.06 ± 2.41	26.82 ± 1.43	23.01 ± 1.16	0.090	0.306
TotalAs concentrations (μg/g creatinine)	30.85 ± 3.25	27.35 ± 1.83	24.27 ± 1.38	0.124	0.187
iAs%	7.15 ± 0.68	6.12 ± 0.26	6.33 ± 0.60	0.537	0.345
MMA^V%	4.35 ± 0.39	5.43 ± 0.29	5.11 ± 0.38	0.266	0.899
DMA^V%	88.85 ± 0.85	88.82 ± 0.42	89.17 ± 0.70	0.899	0.527

Analysis of variance and Scheffé's test were used to compare differences in variables of BMI, birth weight, body fat, biochemical indices, and urinary arsenic profiles for lower than normal weight, normal weight, and overweight/obese groups.
HOMA-IR, homeostasis model assessment of insulin resistance, HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mg/dL)/405; MMA^V, monomethylarsonic acid; DMA^V, dimethylarsinic acid; iAs%, inorganic arsenic (iAs^{III} + iAs^V)/TotalAs × 100; MMA^V%, MMA^V/TotalAs × 100; DMA^V%, DMA^V/TotalAs × 100.
[a] Lower than normal weight vs. overweight and obese; [b] normal weight vs. overweight and obese; [c] lower than normal weight vs. normal weight.[#] p value for the relationship between variables and BMI adjusted for age, sex, paternal and maternal educational level, and paternal cigarette smoking status.

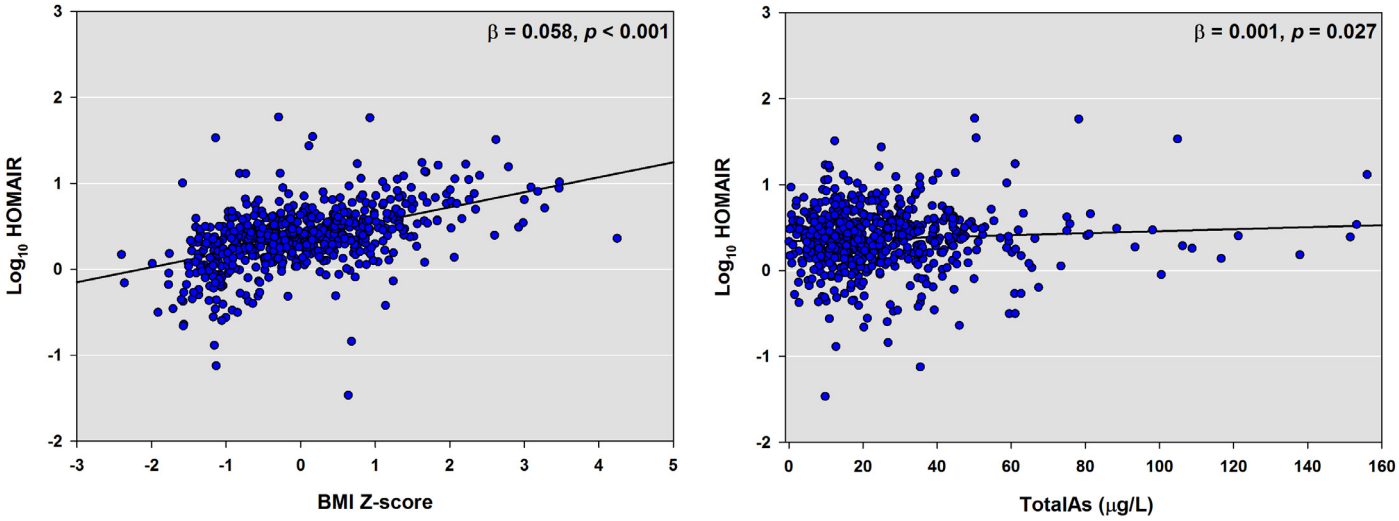

Fig. 1. Associations between the TotalAs concentrations and $\log_{10}$ HOMA-IR, and between BMI Z score and $\log_{10}$ HOMA-IR as determined using simple linear regression adjusted age and gender.

variation in arsenic metabolism has been suggested as one of the possible explanations for the individual susceptibility to arsenic-induced human diseases (Tseng, 2007). Children are thought to have a different response from adults for both arsenic exposure and metabolism (Tseng, 2009). A study found that children had lower MMA^{V}% and higher DMA^{V}% than adults when exposed to the same level of inorganic arsenic from drinking water in Inner Mongolia (Sun et al., 2007). It has also been reported that children had more efficient arsenic methylation capacity than adults (Chowdhury et al., 2003). These findings imply that arsenic methylation capacity is higher in children than in adults same as the present study showing that elementary school students had a better arsenic methylation capacity than junior high school students. All of the children and adolescents in this study lived in Taipei City and New Taipei City. They drank tap water provided by the Taipei Water Department of the Taipei City Government, which has arsenic levels less than the standard 10 μg/L. However, recent studies reported that arsenic-containing groundwater used for irrigation markedly increases the arsenic content of various parts of rice plants grown in Taiwan (Hsu et al., 2012). In addition, arsenic or arsenic species have been detected in seafood (Liang et al., 2013), in edible oils (Chu and Jiang, 2011) and in cereals (Tsai and Jiang, 2011) in Taiwan. Therefore, except for drinking water, the exact source of arsenic exposure for children and adolescents in this study is unknown.

Several environmental (Tseng, 2009) and genetic factors (Chung et al., 2009) have been proposed to modulate the arsenic methylation pathway. Our previous study pointed out that the individuals with the arsenic (+3 oxidation state) methyltransferase (AS3MT) 12390 (rs3740393) GC genotype had lower MMA^{V}% and higher DMA^{V}% than GG genotype in adults (Chung et al., 2009), suggesting that carrier of this GC genotype may have a higher capacity to convert MMA^{V} to DMA^{V}. Another study also revealed that AS3MT genetic variation may play an important role in modulating DNA damage especially among children (Sampayo-Reyes et al., 2010), suggesting that this functional AS3MT Met287Thr change possibly related to MMA^{V} production is particularly low, as occurs during

Table 4
Multiple linear regression analyses using HOMA-IR as dependent variable.

Variables	All students (N = 622) β (95% CI)	Elementary school students (N = 303) β (95% CI)	Junior high school students (N = 319) β (95% CI)
Age (year)	0.290 (0.051–0.373)*	0.188 (–0.204–0.580)	–0.507 (–1.266–0.253)
BMI Z-score	0.568 (0.123–1.012)*	1.088 (0.168–2.007)*	0.545 (0.045–1.046)*
Cholesterol (mg/dL)	–0.011 (–0.014–0.010)	0.007 (–0.013–0.027)	–0.013 (–0.027–0.001)
Triglyceride (mg/dL)	0.019 (0.012–0.031)***	0.016 (–0.001–0.032)+	0.025 (0.015–0.035)***
GPT (IU/L)	0.064 (0.080–0.142)***	0.159 (0.105–0.214)***	0.059 (0.025–0.093)***
GOT (IU/L)	–0.036 (–0.114–0.015)	–0.108 (–0.223–0.007)+	–0.009 (–0.078–0.060)
TotalAs concentrations (μg/L)	0.024 (0.017–0.047)***	0.044 (0.017–0.071)**	0.017 (0.001–0.034)*
Variables	**Lower than normal weight (N = 83) β (95% CI)**	**Normal weight (N = 277) β (95% CI)**	**Overweight and obesity (N = 262) β (95% CI)**
Age (year)	0.302 (–0.102–0.705)	0.120 (–0.184–0.423)	0.026 (–0.270–0.322)
Cholesterol (mg/dL)	–0.025 (–0.051–0.001)*	0.017 (–0.001–0.035)	–0.016 (–0.035–0.004)
Triglyceride (mg/dL)	0.073 (0.053–0.093)***	0.009 (–0.010–0.027)	0.022 (0.009–0.034)***
GPT (IU/L)	0.027 (–0.051–0.105)	0.033 (–0.064–0.129)	0.117 (0.075–0.160)***
GOT (IU/L)	–0.008 (–0.164–0.148)	–0.084 (–0.185–0.018)	–0.041 (–0.138–0.056)
TotalAs concentrations (μg/L)	0.037 (0.008–0.067)*	0.025 (0.005–0.046)*	0.029 (–0.002–0.059)+

β, regression coefficient; 95% CI, 95% confidence interval.
Stepwise multiple linear regression models were used to analyze the relationships between age, gender, BMI, the TotalAs concentrations, lipid profiles, liver function indices, paternal educational level, maternal educational level, paternal cigarette smoking status, and HOMA-IR levels.
$^{+}0.05 < p < 0.10$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

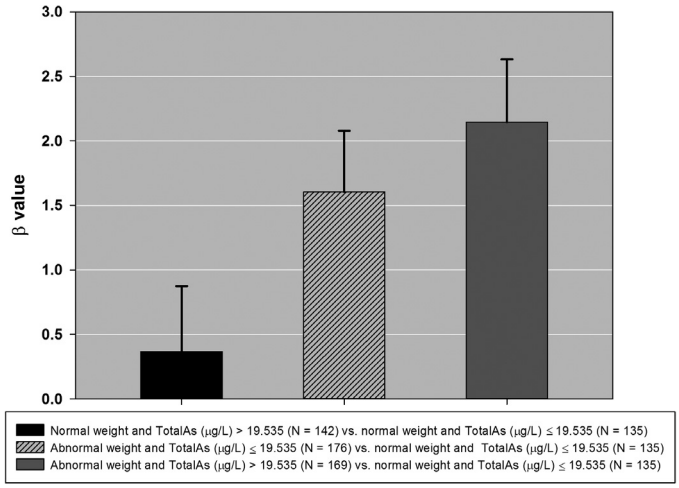

Fig. 2. Joint effect of body mass index (BMI) and the TotalAs concentrations on HOMA-IR as determined by multiple linear regression analysis.

childhood. This different methylation rate may protect children from hazardous arsenicals during a particularly sensitive life stage.

In 2005, Steinmaus et al. found that subjects in the lower quartile for dietary protein, iron and niacin had higher MMA^V% and lower DMA^V% than those in the higher quartile (Steinmaus et al., 2005). Another study reported that folic acid supplementation resulted in a decline in total blood arsenic (Gamble et al., 2007). It suggests that the methylation and elimination of arsenic are influenced by nutrients involved in one-carbon metabolism, especially folate (Hall and Gamble, 2012). On the other hand, a positive correlation between the percentage of protein intake and the HOMA-IR value and a negative correlation between the percentage of sucrose in the diet and the HOMA-IR value were reported (Ostrowska et al., 2013), implying that the HOMA-IR value is also influenced by nutrients.

In this study, it was also found that higher BMI were related to a higher HOMA-IR value, higher serum insulin levels, and higher blood glucose. This finding is similar to previous studies that observed a positive relationship between BMI and HOMA-IR (Sobiczewski et al., 2013). BMI is a measure of total body fat, but provides no indication of body fat distribution and does not distinguish well between lean and fat mass in children from a general population (Bennett et al., 2012). However, in clinical and public health settings, BMI is the most widely used measure to evaluate obesity status and predict cardiovascular risks in children. In addition, obesity, adiposity, lower cardiorespiratory fitness and physical activity are key factors influencing insulin resistance in children (Ghouri et al., 2013; Gill and Malkova, 2006; Mueller et al., 2013). Insulin is secreted by the pancreatic islet β-cells; stimulated glucose uptake by peripheral tissues is a crucial process responsible for the regulation of blood glucose levels. Insulin insufficiency causes deleterious effects on glucose homeostasis and is involved in the pathophysiological processes of diabetes (Consoli et al., 1990). Therefore, identifying children at high risk of insulin resistance is important for primary prevention of cardiometabolic diseases later in life (Pereira and Ludwig, 2003).

The present study found that HOMA-IR values were significantly increased in relation to the TotalAs concentrations (μg/L). A recent study also showed that urinary arsenic levels were significantly and inversely associated with the insulin secretion index, homeostatic model assessment 2 β-cell function (HOMA2%B) (Rhee et al., 2013). This finding indicates that arsenic exposure may be related to β-cell dysfunction, increasing the risk of diabetes in Korean adults (Rhee et al., 2013). Based on previous studies conducted in animal models, arsenic exposure inhibits insulin-dependent glucose uptake, impairs insulin secretion by repressing beta cell insulin signaling and transcription, and also increases the risk of diabetes by modifying the expression of genes related to insulin resistance (Diaz-Villasenor et al., 2006; Walton et al., 2004). Results of a study conducted in animals showed that exposure to low levels of inorganic arsenic induced insulin resistance in male rats (Palacios et al., 2012). In addition, low concentrations of arsenite, methylarsonate (MMA^{III}), and dimethylarsenate (DMA^{III}) inhibited glucose-stimulated insulin secretion in pancreatic islet cells (Douillet et al., 2013), which may be the key mechanism for inorganic arsenic-induced diabetes. Taken together, high TotalAs concentrations may induce HOMA-IR value increases, and result in impaired glucose homeostasis in children and adolescents in Taiwan; however, this hypothesis requires further investigation. Additionally, there are a number of studies that have found no association between arsenic and HOMA-IR levels in adults (Del Razo et al., 2011; Gribble et al., 2012).

Our present study found that the joint effect of abnormal weight and a high TotalAs concentration was significantly associated with high HOMA-IR values. This finding provided advanced evidence that chronic inorganic arsenic exposure acts synergistically with high-fat diet-induced obesity in producing insulin resistance in C57BL/6 mice (Del Razo et al., 2011). It suggests that arsenic can inhibit glucose-stimulated insulin expression or secretion by cultured β-cells. Thus, both insulin resistance and impaired β-cell function determined the diabetic phenotype produced by the joint effect of arsenic exposure and obesity. However, whether arsenic exposure or obesity may interfere with the glucagon-like peptide-1 secretion related to insulin resistance (Fernandez-Garcia et al., 2013) needs further investigation.

This study has some limitations that need to be taken into consideration when interpreting these results. First, a single-spot evaluation of urinary arsenic species and blood biochemical indices may be limited. In addition, the methylation of arsenic and HOMA-IR may be influenced by nutrients for which information was unavailable in this study. However, the evaluations done in this study can be considered reliable if participants did not change their lifestyle and maintained their homeostatic metabolism. A limitation of this study is that we did not collect information on diet, and did not measure arsenobetaine in the urine. Although rice and seafood are likely to be important sources of arsenic exposure, the arsenic species found in urine reflect an integrated exposure resulting from both dietary and environmental exposures (Fangstrom et al., 2009). Urinary DMA levels can be easily influenced by certain arsenicals found in seafood, including arsenosugars and arsenolipids (Choi et al., 2010). However, the DMA^V percentages in all participants in this study were not extremely high, suggesting a lack of effect from seafood consumption. Furthermore, because this study employed a cross-sectional design, it could not determine the causality of the observed associations. We cannot exclude the possibility that the association between high TotalAs concentrations and high HOMA-IR values might be the result rather than the cause of an increase in HOMA-IR values. In spite of these limitations, this study represents the first attempt to address the effect of change in urinary arsenic profiles on HOMA-IR after adjustments for lipid profiles, lifestyle and anthropometric measurements.

In conclusion, elementary school students showed a more efficient arsenic methylation capacity as compared to junior high school students, and higher BMI levels were associated with higher HOMA-IR values. Additionally, higher TotalAs concentrations were associated with higher HOMA-IR values after multivariate adjustment. Furthermore, higher BMI levels and higher TotalAs concentrations significantly increased HOMA-IR values with a trend relationship. This is the first study to show a relationship between the TotalAs concentrations and HOMA-IR levels in children and adolescents with low arsenic exposure in Taiwan.

Conflict of interest

The authors declare that there are no conflicts of interest.

Transparency document

The Transparency document associated with this article can be found in the online version.

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