International Journal of Hygiene and Environmental Health 237 (2021) 113834

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Associations between rice consumption, arsenic metabolism, and insulin resistance in adults without diabetes

Xiang Li [a], Xin Wang [a], Sung Kyun Park [a,b,*]

[a] Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, MI, USA
[b] Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, MI, USA

ARTICLE INFO

Keywords:
iArsenic
Arsenic metabolism
Insulin resistance
Rice consumption

ABSTRACT

Rice consumption is an important source of arsenic exposure. Little has known about the impact of rice consumption on arsenic metabolism, which is related to insulin resistance. In this study, we examined the associations between rice consumption and arsenic metabolism, and between arsenic metabolism and insulin resistance in non-diabetic U.S adults who participated in the National Health and Nutrition Examination Survey (NHANES) 2003–2016. Rice consumer was defined as ≥0.25 cups of cooked rice/day. HOMA2-IR was calculated using HOMA2 Calculator software based on participant's fasting glucose and insulin values. Urinary arsenic concentrations below limits of detection were imputed first, and then arsenic metabolism (the proportions of inorganic arsenic (iAs), monomethylarsonate (MMA), and dimethylarsinate (DMA) to their sum) were calculated (expressed as iAs%, MMA%, and DMA%). Using the leave-one-out approach, rice consumers compared with non-consumers had a 1.71% (95% CI: 1.12%, 2.29%) higher DMA% and lower MMA% when iAs% fixed; a 1.55% (95% CI: 0.45%, 2.66%) higher DMA% and lower iAs% when MMA% fixed; and a 1.62% (95% CI: 0.95%, 2.28%) higher iAs% and lower MMA% when DMA% fixed, in multivariable adjustment models. With every 10% decrease in MMA%, the geometric mean ratio of HOMA2-IR was 1.06 (95% CI: 1.03,1.08) and 1.05 (95% CI: 1.02, 1.09) when DMA% and iAs% was fixed, respectively; however, the associations were attenuated after adjusting for body mass index. In stratified analysis, we found that lower MMA% was associated with higher HOMA2-IR in participants with obesity: a 10% increase in iAs% with a 10% decrease in MMA% was associated with higher HOMA2-IR with the geometric mean ratio of 1.05 (95% CI: 1.01, 1.09). Our findings suggest that rice consumption may contribute to lower MMA% that was further associated with higher insulin resistance, especially in individuals with obesity. Future prospective studies are needed to confirm our results in different populations.

1. Introduction

Inorganic arsenic is common in ground water and certain foods (e.g. rice, grains), and it is a toxicant that has been related to several acute, subacute, and chronic diseases (Nurchi et al., 2020; Wang et al., 2020; Xue et al., 2010). After absorption in human bodies, inorganic arsenic is methylated to form monomethylarsonate (MMA) (~10–20%) and dimethylarsinate (DMA) (~60–70%), which are excreted in urine together with unmethylated inorganic arsenic (~10–30%) (Thomas et al., 2007; Vahter, 2000). Inter-individual differences in methylation capacity are responsible for various arsenic metabolic profiles, which may be further linked to the differences in risks of arsenic-induced diseases. For example, a relatively higher proportion of MMA (MMA%) and a lower proportion of DMA (DMA%) in urine have been associated with cardiovascular disease (Chen et al., 2013; Huang et al., 2007, 2008) and several cancers (Chen et al., 2003; Huang et al., 2008; Steinmaus et al., 2006, 2010; Yu et al., 2000). On the contrary, a decreased urinary MMA % has been linked to higher body mass index (BMI) (Gribble et al., 2013), type 2 diabetes mellitus (Kuo et al., 2015; Mendez et al., 2016; Navas-Acien et al., 2008; Nizam et al., 2013), insulin resistance (Grau-Perez et al., 2017), and metabolic syndrome (MetS) (Chen et al., 2012). These findings highlight the possibility that methylated arsenic compounds may exert unique toxic effects and an evaluation of the arsenic metabolisms in addition to arsenic exposures is critical to better understand arsenic toxicity and associated health risks.

Several studies have examined the association between arsenic and insulin resistance, though the results are mixed. For example, a small cross-sectional study of non-diabetic Amish adults reported a positive

* Corresponding author. Department of Epidemiology, University of Michigan, M5541 SPH II, 1415 Washington Heights, Ann Arbor, MI, 48109-2029, USA.
E-mail address: sungkyun@umich.edu (S.K. Park).

https://doi.org/10.1016/j.ijheh.2021.113834
Received 13 April 2021; Received in revised form 28 July 2021; Accepted 24 August 2021
Available online 3 September 2021

association between urinary total arsenic and insulin resistance (Park et al., 2016). In a prospective cohort study of American Indian adults, lower MMA% due to an increase in either inorganic arsenic% (iAs) or DMA% was associated with greater insulin resistance (Grau-Perez et al., 2017). In contrast, other studies found no significant associations between arsenic and insulin resistance (Wang et al., 2020). Other lab evidence pointed out that arsenite (As III), the more toxic oxidation state of inorganic arsenic, and/or its methylated trivalent metabolites cause insulin resistance in adipocytes by inhibiting insulin signaling and insulin-activated glucose uptake. This inorganic arsenic species can also interfere with the formation of insulin-sensitive adipocytes and myotubes by inhibiting adipogenic and myogenic differentiation (Salazard et al., 2004; Trouba et al., 2000; Walton et al., 2004; Yen et al., 2010).

Rice consumption is one of the major sources of inorganic arsenic in the U.S., especially in populations exposed to relatively low arsenic in drinking water (Kurzius-Spencer et al., 2014). Rice consumption as a contributor to higher arsenic exposure has been established in several U. S. adult populations (Wang et al., 2020; Wei et al., 2014). The high dietary glycemic index and glycemic load after eating rice may lead to excess postprandial variations in blood glucose and insulin concentrations, leading to insulin resistance has been found in previous studies, primarily carried out in Asian populations (Zuñiga et al., 2014). However, whether arsenic exposure and its metabolisms involve in the relationship between rice consumption and insulin resistance are largely unknown.

In this study, we examined rice as a source of arsenic exposure and evaluated the association of arsenic metabolism calculated using urinary concentrations of arsenic species with insulin resistance in non-diabetic U.S. adults using data from the National Health and Nutrition Examination Survey (NHANES). Specifically, we examined (1) the associations between rice consumption and arsenic metabolism biomarkers, and (2) the associations between arsenic metabolism biomarkers and insulin resistance.

2. Methods

2.1. Study population

Participants included were from 7 subsequent cycles of NHANES from 2003 to 2004 to 2015–2016, which used a complex, multi-stage, probability sampling design, to obtain a representative sample of the civilian, noninstitutionalized U.S. population. All NHANES protocols were approved by the National Center for Health Statistics (NCHS) Ethics Review Board, and all participants gave written informed consent (Zipf et al., 2013).

The participants included 5469 adults aged 20 years and older (age threshold was set in accordance with NHANES questionnaires and questionnaire strategies for adults and to meet our goal of evaluating arsenic and insulin resistance in adults) who had their arsenic data and fasting glucose and insulin data. While the NHANES does not distinguish type 1 from type 2 diabetes, an estimated of 90%–95% persons are with type 2 diabetes (Menke et al., 2015). The overall term "Diabetes" is used through the present study. We excluded 928 participants with prevalent diabetes (defined as fasting glucose $\geq$ 126 mg/dL, self-reported use of insulin or oral medications for diabetes, or self-reported physician diagnosis of diabetes), and 811 participants who had missing information on rice consumption and other key covariates, leaving a final analytical sample of 3730 participants. An overview of our sampling procedures is illustrated in Fig. 1.

2.2. Fasting glucose, insulin and HOMA2-IR

Participants who had glucose and insulin levels measured in a morning examination were asked to fast overnight. Fasting serum glucose level was determined using the enzyme hexokinase method (Roche Diagnostics, Indianapolis, IN) (Selvin et al., 2014). Serum insulin was measured using a two-site immunoenzymometric assay (TOSOH Bioscience Inc., South San Francisco, CA) (Park et al., 2016). HOMA2-IR (homeostasis model assessment for insulin resistance) was used as the indicator of insulin resistance and calculated from fasting glucose and insulin levels with the computed solved model, using the University of Oxford Diabetes Trails Unit HOMA Calculator software (Diabetes Trials Unit & University of Oxford, 2019). A higher HOMA2-IR indicates greater insulin resistance.

2.3. Arsenic measurements and urine creatinine

Urinary concentrations of total arsenic and arsenic species including arsenous acid (AsIII), arsenic acid (AsV), MMA, DMA, and arsenobetaine were measured using high performance liquid chromatography coupled to Multi-Element Inductively Coupled Plasma-Mass Spectrometry (National Health and Nutrition Examination Survey, 2020). The detection rates of arsenic concentrations are summarized in Table S2. Given the low detection rates of AsIII and AsV, iAs was calculated using the following formula: iAs = Total arsenic − MMA − DMA − arsenobetaine. Concentrations of total arsenic, MMA, DMA, and arsenobetaine below the LODs were imputed using multiple imputation by chained equation (Azur et al., 2011). Details of multiple imputation

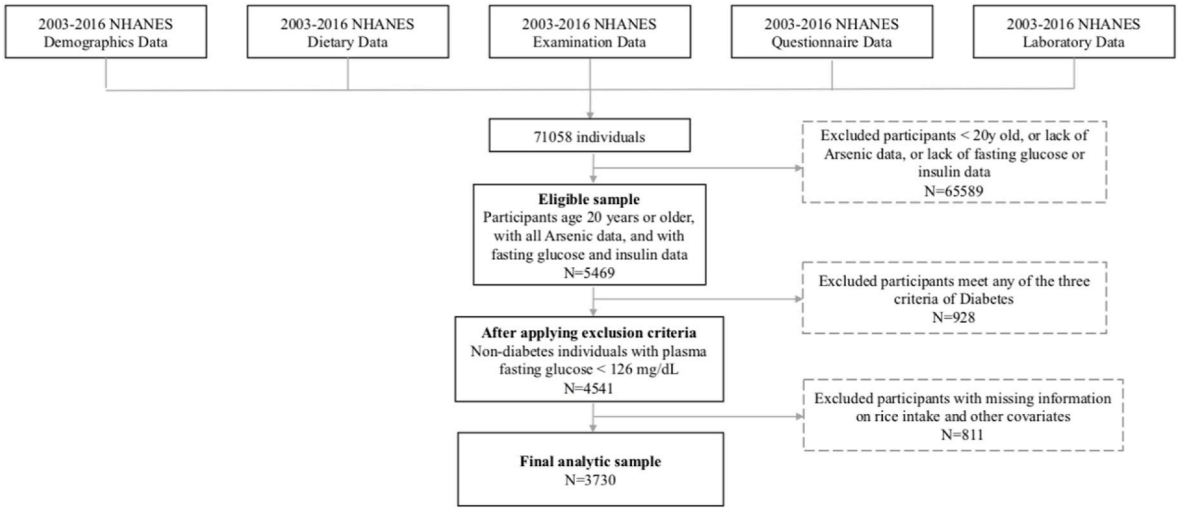

Fig. 1. Schematic diagram of analytic sample.

are described in supplementary methods. Urinary creatinine adjusted concentrations of total arsenic and its metabolites were calculated to account for urine dilution. Based on the urinary creatinine adjusted forms, the percentage of iAs, MMA, and DMA were calculated for the present study by using the individual concentration divided by the sum of arsenic (ΣAs = iAs + MMA + DMA).

2.4. Rice consumption

Information on rice consumption was collected through an interviewer-administered questionnaire that included a validated 24-hr dietary recall instrument on two nonconsecutive survey days (Alanna J et al., 2008). Dietary intake of each food item including rice as component, for example, "Spanish rice", was measured by recorded "as consumed" or not. This food intake was then converted to the amount of rice consumed by linking with the Food Commodity Intake Database (FCID) created by the U.S. Environmental Protection Agency (U.S. EPA) and U.S. Department of Agriculture (USDA) (Gilbert-Diamond et al., 2011; A. E. Nigra et al., 2017), which provides information on individual food ingredients of each food item recorded. For example, FCID food commodities in 100g of "Spanish rice" included 15.57g of white rice. The most recent FCID (FCID 2005–2010) includes all food items collected in NHANES 1999–2010 survey cycles but not those added to the survey after 2011. We considered food items in the current FCID that most closely represent those after 2011. There are eight categories of rice in the FCID codes, including white, brown, flour, bran, and their baby food types. We omitted baby food types since we focused on the adult population.

We computed the sum of rice consumption included all types of rice consumed because urinary inorganic arsenic concentrations were not different between people who primarily consumed white rice versus those who ate brown rice evidenced in a previous NHANES study (Wu et al., 2015). We defined "rice consumer" in consistence with previous studies where individuals reported at least 14.1g dry weight per day (0.25 cup of cooked rice) (Davis et al., 2012; Fulgoni et al., 2010).

2.5. Other covariates

Information on age, sex, race/ethnicity, education, poverty income ratio (PIR), smoking status, alcohol drinking was collected using self-administered questionnaires. We categorized age groups as 20–39, 40–59, 60–69, and 70 years and older. Race/ethnicity was classified as "Mexican American", "Other Hispanic", "Non-Hispanic White", "Non-Hispanic Black", and "Others". Education was categorized as "<high school", "Some high school", and "High school or more". PIR was classified as "<1" or "≥1" where a value below 1 indicates that the family is living below the poverty threshold. Smoking status was categorized into "never smoker", "former smoker", and "current smoker". Alcohol drinking was calculated using the response to questions of whether had at least 12 drinks of any type of alcoholic beverage in entire life, the frequency of drinking in the past 12 months, and the average alcohol drinks per day in the past 12 months, then, was categorized into tertiles. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters and was further categorized into "underweight (BMI<18.5)", "normal weight (18.5 ≤BMI< 25)", "overweight (25 ≤BMI< 30)" and "obese (BMI≥ 30). Physical activity was measured as metabolic equivalent (MET) scores and categorized into tertiles. Dietary fish consumption and blood mercury as indicators of fish consumption were included because fish consumption is a well-known source of DMA (DeCastro et al., 2014). Total energy intake-adjusted fish consumption was calculated using all types of fish consumption in the past 24 h and categorized into tertiles. Additionally, individuals reported any fish consumption were defined as "fish consumer" in the present study. Blood mercury concentration was measured using inductively coupled-plasma dynamic reaction cell-mass spectrometry and categorized into tertiles.

2.6. Statistical analysis

Distributions of HOMA2-IR and urinary arsenic concentrations were compared by participant characteristics using Wilcoxon Rank Sum Test or Kruskal-Wallis Test. Urinary arsenic concentrations and HOMA2-IR were log-transformed to normalize the distributions for subsequent statistical analyses. Pairwise Spearman correlation coefficients were calculated between urinary arsenic concentrations, arsenic metabolism biomarkers, rice consumption, and presented via a correlation-matrix plot.

Linear regression models were used to compare arsenic metabolism (iAs%, MMA%, and DMA%) between rice consumers and non-consumers. Rather than having one arsenic metabolism biomarker in the model at a time, we followed "leave-one-out approach" by (Kuo et al., 2015), that helps addressing the difficult interpretation of the traditional "conventional approach" given that arsenic metabolism markers are proportions of their sum and therefore, a change in one metabolism marker yields changes in one or two of the other metabolism markers. By entering two arsenic metabolism biomarkers in the same model (variable of interest as outcome and the other as covariate), we were able to obtain the impact of rice consumption on the mean changes of arsenic metabolism of interest, when fixing the second biomarker constant, meaning that the third biomarker we left out of the model changed the same amount in the opposite direction. Two sequentially adjusted models were fitted. Model 1 included age, sex, race/ethnicity, smoking status, alcohol drinking, education level, PIR, physical activity (tertiles), fish consumption, blood mercury (tertiles), and the sum of arsenic (ΣAs, log-transformed). Model 2 additionally adjusted for BMI because BMI as a measure of adiposity is a risk factor for insulin resistance and can be affected by arsenic exposure (Gomez-Rubio et al., 2011; Grashow et al., 2014; Tseng et al., 2000). We also examined individual arsenic concentrations (iAs, MMA, and DMA) as the outcomes. Geometric mean ratios (GMR) of individual arsenic concentrations was compared given the outcome was log-transformed in the linear regression models.

Arsenic exposure was evaluated based on the urinary concentration of total arsenic or the sum of inorganic arsenic (iAs+DMA+MMA). We first evaluated the insulin resistance effect of urinary total arsenic and the sum of inorganic arsenic in separate models. Then the "leave-one-out approach" was used to examine the associations between HOMA2-IR and arsenic metabolism. By entering two arsenic metabolism biomarkers in the same model (variable of interest as the predictor and the other as the covariate), we were able to evaluate the association between one specific arsenic biomarker of interest on HOMA2-IR when fixing the second biomarker constant, meaning that the third biomarker we left out of the model changed the same amount in the opposite direction. GMRs (and 95% CIs) of HOMA2-IR for a 10% increase in each arsenic biomarker was computed with adjustment for the same covariates above.

Additionally, we examined the possible effect modifications by obesity on the association between arsenic and HOMA2-IR by stratifying the study population into BMI< 30 and BMI≥ 30.

Finally, we conducted additional sensitivity analyses to evaluate the robustness of primary analyses. First, because rice consumption is also considered to increase the risk of insulin resistance through high glycemic index and glycemic load after meals (Villegas et al., 2007), we therefore further adjusted rice consumption in the association of arsenic metabolism and insulin resistance with the existing covariates. Second, to examine any different effect by consuming different types of rice, we categorized rice consumption in the present study into subtypes – white, brown, or both. Then we evaluated the difference of urinary arsenic concentrations by rice consumption category using white rice as the reference level. Last, rice category was included as a potential effect modifier into the association between arsenic metabolism and insulin resistance.

The NHANES applied a complex sampling method that makes it

Table 1
Urinary arsenic concentrations, HOMA2-IR by sociodemographic variables (Median (IQR)).

Variables	No (%)	iAs (μg/g creatinine)	MMA (μg/g creatinine)	DMA (μg/g creatinine)	HOMA2-IR
All	3730 (100.00)	0.63 (2.50)	1.21 (0.74)	3.98 (3.82)	1.02 (1.00)
Urine creatinine calibrated	3730 (100.00)	0.54 (1.89)	0.93 (0.97)	4.05 (4.01)	–
Age group (y)					
20–39	1487 (39.87)	0.54 (1.87)	0.84 (0.87)	3.76 (3.58)	1.01 (1.04)
40–59	1197 (32.09)	0.55 (1.83)	0.96 (0.97)	4.17 (4.34)	1.02 (1.00)
60–69	502 (13.46)	0.56 (2.22)	1.07 (1.11)	4.65 (4.98)	1.16 (1.02)
≥70	544 (14.58)	0.50 (2.12)	1.04 (1.02)	4.17 (3.88)	0.95 (0.84)
P-value		0.9931	<.0001	<.0001	0.0009
Sex					
Male	1854 (49.71)	0.63 (1.89)	0.84 (0.77)	3.61 (3.46)	1.04 (1.03)
Female	1876 (50.29)	0.43 (1.90)	1.05 (1.16)	4.57 (4.47)	1.01 (0.98)
P-value		0.0353	<.0001	<.0001	0.5019
Race/Ethnicity					
Mexican American	600 (16.09)	0.55 (1.79)	1.03 (0.98)	4.24 (3.48)	1.19 (1.00)
Other Hispanic	327 (8.77)	0.73 (2.20)	1.11 (1.08)	5.13 (4.37)	1.16 (1.03)
Non-Hispanic White	1810 (48.53)	0.40 (1.71)	0.97 (1.01)	3.95 (3.79)	0.93 (0.96)
Non-Hispanic Black	706 (18.93)	0.74 (1.97)	0.68 (0.60)	3.07 (2.84)	1.09 (1.08)
Others	287 (7.69)	0.91 (4.07)	1.18 (1.38)	7.55 (8.48)	0.98 (0.94)
P-value		<.0001	<.0001	<.0001	<.0001
Body Mass Index (BMI, kg/m^2)					
Under weight	71 (1.90)	0.52 (2.64)	1.24 (1.94)	4.74 (4.43)	0.51 (0.47)
Normal weight	1157 (31.02)	0.61 (2.11)	1.06 (1.17)	4.58 (3.42)	0.66 (0.51)
Over weight	1324 (35.50)	0.55 (1.95)	0.96 (0.90)	4.11 (3.94)	1.02 (0.78)
Obese	1178 (31.58)	0.48 (1.63)	0.78 (0.82)	3.59 (3.89)	1.67 (1.35)
P-value		0.1042	<.0001	<.0001	<.0001
Education level					
Less than high school	343 (9.20)	0.52 (1.83)	1.15 (1.00)	4.39 (4.13)	1.10 (0.99)
Some high school	527 (14.13)	0.78 (2.01)	0.88 (0.87)	3.91 (3.75)	1.01 (1.16)
High school or more	2860 (76.68)	0.51 (1.89)	0.91 (0.97)	4.03 (4.02)	1.01 (0.98)
P-value		0.0879	<.0001	0.0353	0.2451
Smoking status					
Never	2035 (54.56)	0.51 (1.95)	0.94 (0.99)	4.16 (4.22)	1.05 (0.96)
Former	915 (24.53)	0.64 (2.03)	1.00 (1.03)	4.15 (3.83)	1.05 (1.03)
Current	780 (20.91)	0.51 (1.73)	0.83 (0.86)	3.60 (3.47)	0.92 (1.09)
P-value		0.7276	0.0004	<.0001	<.0001
Alcohol drinking tertiles (drinks/d)					
T1 (= 0)	1353 (36.27)	0.42 (1.74)	0.92 (0.99)	4.00 (4.13)	1.09 (1.08)
T2 (0–0.14)	888 (23.81)	0.40 (1.60)	0.91 (1.08)	3.96 (4.02)	1.11 (1.03)
T3 (>0.14)	1489 (39.92)	0.77 (2.14)	0.95 (0.89)	4.14 (3.86)	0.93 (0.90)
P-value		<.0001	0.4874	0.3131	<.0001
Physical activity (MET) Z score tertiles*					
T1	1201 (32.20)	0.56 (1.92)	0.92 (0.97)	3.97 (4.00)	1.08 (1.00)
T2	1295 (34.72)	0.55 (1.96)	0.98 (0.98)	4.35 (4.15)	1.03 (1.02)
T3	1234 (33.08)	0.51 (1.83)	0.90 (0.94)	3.85 (3.77)	0.95 (0.96)
P-value		0.8575	0.1024	0.0015	<.0001
Poverty income ratio (PIR)					
<1	712 (19.09)	0.39 (1.46)	0.97 (1.03)	3.72 (3.70)	1.02 (1.03)
≥1	3018 (80.91)	0.59 (1.97)	0.92 (0.96)	4.13 (4.08)	1.02 (1.00)
P-value		<.0001	0.7132	0.0092	0.2189
Blood mercury tertiles ($\mu mol/L$)					
T1 (<2.90)	1224 (32.82)	0.15 (1.01)	0.83 (0.89)	3.33 (2.96)	1.09 (1.05)
T2 (2.90–6.50)	1264 (33.89)	0.53 (1.69)	0.88 (0.91)	3.93 (3.33)	1.04 (0.99)
T3 (>6.50)	1242 (33.30)	1.31 (3.92)	1.10 (1.11)	5.32 (5.75)	0.93 (0.97)
P-value		<.0001	<.0001	<.0001	<.0001
Rice consumed over 24-h					
Non-consumer (<14.1g)	2651 (71.07)	0.38 (1.58)	0.89 (0.99)	3.67 (3.64)	1.04 (1.00)
Rice consumer (≥14.1 g)	1079 (28.93)	1.13 (2.74)	1.03 (0.92)	5.04 (4.62)	0.97 (0.99)
P-value		<.0001	<.0001	<.0001	0.0020
Fish consumed over 24-h					
No	2972 (79.68)	0.37 (1.40)	0.89 (0.93)	3.69 (3.38)	1.03 (1.00)
Yes	758 (20.32)	2.15 (5.97)	1.14 (1.25)	6.11 (6.81)	0.98 (1.01)
P-value		<.0001	<.0001	<.0001	0.0836

Medians (IQRs) of arsenic species across covariates were urine creatinine-corrected.
P-values obtained from Wilcoxon Rank Sum Test if comparing two groups, and obtained from Kruskal-Wallis Test if comparing more than two groups.
*, Z scores were calculated as $(X - \mu)/\sigma$

possible to derive national estimates from survey data. However, arsenic biomarkers and HOMA2-IR (derived from fasting glucose and insulin) were measured in two separate subsamples that only partially overlapped. For this reason, we did not use sampling weights in all of analyses per recommendation of NHANES (Trasande et al., 2013; Peng et al. 2015). All data analyses were performed using the imputed arsenic data. Multiple imputations and correlation matrix plot in this study were performed with R software (version 3.6.3). All other analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC).

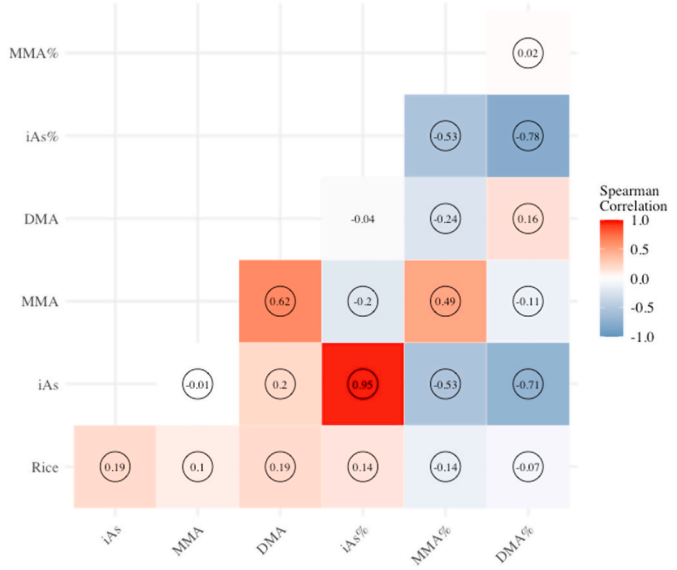

Fig. 2. Spearman correlation matrix of arsenic concentrations, arsenic metabolites, and rice consumption ("iAs", "MMA", and "DMA" are urinary creatinine calibrated and log-transformed; "Rice" represents rice consumption, continuous variable). Numbers shown in matrix represent correlation coefficients; circles highlight the significance at 0.05 level.

Table 2
The mean difference (β (95%*CI*)) in As metabolism biomarkers by rice consumption (Rice consumer versus non-consumer) using the leave-one-out approach.

Outcome	Covariate (fixed)	Model 1[a] (N = 3730)		Model 2[b] (N = 3730)	
		β_1 (95% CI)	p-value	β_1 (95% CI)	p-value
iAs%	MMA%	−1.55% (−2.66%, −0.45%)	0.006	−1.54% (−2.65%, −0.43%)	0.007
	DMA%	1.62% (0.95%, 2.28%)	<.0001	1.64% (0.97%, 2.30%)	<.0001
MMA%	iAs%	−1.71% (−2.29%, −1.12%)	<.0001	−1.72% (−2.31%, −1.13%)	<.0001
	DMA%	−1.62% (−2.28%, −0.95%)	<.0001	−1.64% (−2.30%, −0.97%)	<.0001
DMA%	iAs%	1.71% (1.12%, 2.29%)	<.0001	1.72% (1.13%, 2.31%)	<.0001
	MMA%	1.55% (0.45%, 2.66%)	0.006	1.54% (0.43%, 2.65%)	0.007

[a] Model1: Adjusted for Age group (20–39, 40–49, 50–69, 70 and older), Sex (Male, Female), Race/ethnicity (Mexican America, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Others), Smoking Status (Never, Former, Current), Alcohol drinking tertiles, Education level (Less than high school, Some high school, High school or more), Physical activity Z score tertiles, PIR (PIR<1 vs. PIR> = 1), Fish consumption (Yes vs. No), Blood mercury tertiles.

[b] Model2: Further adjusted for BMI (Underweight, Normal weight, Overweight, Obese).

3. Results

The median (IQR) age was 45.0 (29.0) years. The median (IQR) HOMA2-IR was 1.02 (1.00). Median (IQR) concentrations of ΣAs, iAs, MMA, and DMA in urine were 5.96 (6.44) μg/L, 0.63 (2.50) μg/L, 1.21 (0.74) μg/L, and 3.98 (3.82) μg/L, and corresponding creatinine-corrected concentrations were 6.23 (6.32) μg/g, 0.54 (1.89) μg/g, 0.93 (0.97) μg/g, and 4.05 (4.01) μg/g, respectively. The median (IQR) rice consumption over 24 h was 0.01 (18.69) g and 28.9% of the participants consumed at least 14.1g rice over the past 24 h (i.e., rice consumers).

Table 3
The geometric mean ratio (GMR) of HOMA2-IR associated with per doubling increase in total arsenic or sum of inorganic arsenic (iAs + DMA + MMA).

Per doubling increase	GMR of HOMA2-IR[a] (95% CI)	p-value
Total Arsenic[b]		
Model 1[c]	0.97 (0.95, 0.99)	0.0005
Model 2[d]	0.99 (0.97, 1.00)	0.1235
Sum of Inorganic Arsenic[b]		
Model 1[c]	0.94 (0.92, 0.97)	<.0001
Model 2[d]	0.99 (0.97, 1.01)	0.1447

[a] HOMA2-IR is log-transformed.

[b] Total arsenic and Sum of Inorgainc Arsenic are urine creatinine corrected, and logged to the base 2.

[c] Model1: Adjusted for Age group (20–39, 40–49, 50–69, 70 and older), Sex (Male, Female), Race/ethnicity (Mexican America, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Others), Smoking Status (Never, Former, Current), Alcohol drinking tertiles, Education level (Less than high school, Some high school, High school or more), Physical activity tertiles, PIR (PIR<1 vs. PIR> = 1), Fish consumption (Yes vs. No), Blood mercury tertiles.

[d] Model 2: Further adjusted for BMI (Underweight, Normal weight, Overweight, Obese).

Arsenic concentrations (iAs, MMA, and DMA), and HOMA2-IR by characteristics were presented in Table 1. Rice consumers and fish consumers had higher level of arsenic concentration (iAs, MMA and DMA) but lower level of HOMA2-IR. Participants with older age, female, "Others" race/ethnicity, and lower BMI showed higher concentrations of MMA and DMA. Males, individuals in the highest alcohol drinking tertile, and those had PIR≥ 1 showed higher concentration of iAs. HOMA2-IR were different by age and race/ethnicity and were higher in participants who had higher BMI and less physical activity.

Rice consumption was positively correlated with arsenic concentrations (iAs, MMA, and DMA), with the correlation coefficients 0.19, 0.10, and 0.19, respectively (Fig. 2). Rice consumption was positively correlated with iAs% ($\rho = 0.14$), but negatively correlated with MMA% ($\rho = -0.14$) and DMA% ($\rho = -0.07$). Within arsenic concentration-metabolism pairs, iAs showed strong correlations with iAs% ($\rho = 0.95$), and negatively correlated with either MMA% ($\rho = -0.53$) or DMA% ($\rho = -0.71$). MMA also had moderate correlation with MMA% ($\rho = 0.49$). DMA was positively correlated with DMA% and negatively correlated with MMA%.

Using the "leave-one-out" approach, compared with non-consumers, rice consumers had a 1.71% (95% CI: 1.12%, 2.29%) and a 1.55% (95% CI: 0.45%, 2.66%) higher DMA% when fixing iAs% and MMA%, respectively, after adjusting for age, sex, race/ethnicity, education, PIR, smoking, alcohol drinking, physical activity, fish consumption, blood mercury concentration, and log-transformed sum of arsenic (Table 2). In contrast, rice consumers were observed to have a 1.71% (95% CI: −2.29%, −1.12%) and a 1.62% (95% CI: −2.28%, −0.95%) lower MMA %s, when fixing iAs% and DMA% respectively, adjusting for the same covariates. The rice consumers also had a lower iAs% when MMA% was fixed but a higher iAs% when DMA% was fixed. Robust findings were observed after further adjustment for BMI (Table 2, Model 2). Similar associations were observed between rice consumption and urinary concentrations of iAs, MMA, and DMA (Table S3).

Arsenic exposure, assessed as total arsenic or sum of inorganic arsenic in urine, was not associated with insulin resistance (measured as HOMA2-IR) in the fully-adjusted model (Table 3, Model 2).

For every 10% increase in MMA%, the GMR of HOMA2-IR was 0.95 (95% CI: 0.92, 0.97) and 0.95 (95% CI: 0.92, 0.98) when fixing DMA% and iAs% respectively, after adjusting for age, sex, race/ethnicity, education, PIR, smoking, alcohol drinking, physical activity, fish consumption, blood mercury concentration, and log-transformed sum of

Table 4
Geometric Mean Ratios (GMR) (95% CIs) of HOMA2-IR by Arsenic Metabolism Biomarkers using the leave-one-out approach.

As metabolism biomarker			Model 1 (N = 3730)		Model 2 (N = 3730)	
10% increase	10% decrease	Covariate (fixed)	GMR (95% CI)	p-value	GMR (95% CI)	p-value
iAs%	MMA%	DMA%	1.06 (1.03,1.08)	<.0001	1.02 (1.00,1.04)	0.12
	DMA%	MMA%	1.00 (0.99,1.02)	0.77	1.00 (0.98,1.01)	0.75
MMA%	iAs%	DMA%	0.95 (0.92,0.97)	<.0001	0.98 (0.96,1.00)	0.12
	DMA%	iAs%	0.95 (0.92,0.98)	0.0003	0.98 (0.96,1.01)	0.12
DMA%	iAs%	MMA%	1.00 (0.98,1.01)	0.77	1.00 (0.99,1.02)	0.75
	MMA%	iAs%	1.05 (1.02,1.09)	0.0003	1.02 (0.99,1.04)	0.12

[a] Model1: Adjusted for Age group (20–39, 40–49, 50–69, 70 and older), Sex (Male, Female), Race/ethnicity (Mexican America, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Others), Smoking Status (Never, Former, Current), Alcohol drinking tertiles, Education level (Less than high school, Some high school, High school or more), Physical activity tertiles, PIR (PIR<1 vs. PIR> = 1), Fish consumer (Yes vs. No), Blood mercury tertiles, and log-transformed sum of arsenic (sum of iAs, MMA and DMA, μg/g creatinine).
[b] Model 2: Further adjusted for BMI (Underweight, Normal weight, Overweight, Obese).

Table 5
Geometric Mean Ratios (GMR) (95% CIs) of HOMA2-IR by Arsenic Metabolism Biomarkers using the leave-one-out approach by obesity.

As metabolism biomarker			Non-obese[a] (N = 2552)		Obese (N = 1178)	
10% increase	10% decrease	Covariate (fixed)	GMR[b] (95% CI)	p-value	GMR (95% CI)	p-value
iAs%	MMA%	DMA%	1.02 (0.99,1.05)	0.21	1.05 (1.01,1.09)	0.02
	DMA%	MMA%	0.99 (0.98,1.01)	0.52	1.01 (0.99,1.03)	0.40
MMA%	iAs%	DMA%	0.98 (0.95,1.01)	0.21	0.96 (0.92,0.99)	0.02
	DMA%	iAs%	0.98 (0.95,1.01)	0.14	0.96 (0.92,1.01)	0.09
DMA%	iAs%	MMA%	1.01 (0.99,1.02)	0.52	0.99 (0.97,1.01)	0.40
	MMA%	iAs%	1.02 (0.99,1.05)	0.14	1.04 (0.99,1.08)	0.09

[a] Obese was defined as *BMI* ≥ 30.
[b] All models were adjusted for Age group (20–39, 40–49, 50–69, 70 and older), Sex (Male, Female), Race/ethnicity (Mexican America, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Others), Smoking Status (Never, Former, Current), Alcohol drinking tertiles, Education level (Less than high school, Some high school, High school or more), Physical activity tertiles, PIR (PIR<1 vs. PIR> = 1), Fish consumer (Yes vs. No), Blood mercury tertiles, and log-transformed sum of arsenic (sum of iAs, MMA and DMA, μg/g creatinine).

arsenic (Table 4, Model 1). Inverse associations were observed between MMA% and HOMA2-IR when either iAs% or DMA% were fixed. However, no significant associations between arsenic metabolism and HOMA2-IR were observed after further adjustment for BMI (Table 4, Model 2).

Table 5 showed that MMA% was inversely associated with HOMA2-IR and iAs% was positively associated with HOMA2-IR only in participants with obesity. After multiple adjustments, a 10% increase in iAs% with a 10% decrease in MMA% was associated with 1.05 (95% CI: 1.01, 1.09) geometric GMR of HOMA2-IR. The GMR of HOMA2-IR was 0.96 (95% CI: 0.92,0.99) for a 10% increase in MMA% increases with a 10% decrease in iAs% decreases.

In sensitivity analyses further adjusting for rice consumption in the association of arsenic metabolism and insulin resistance, the results showed that the GMRs, 95%CIs, and the significance remain robust (Table S5). Additionally, we did not observe differences in arsenic concentration when comparing either brown rice consumption only, or both white and brown consumption to white consumption only (Table S6, Table S7). Consuming different types of rice did not modify the associations between arsenic metabolism and insulin resistance in our data (Table S8).

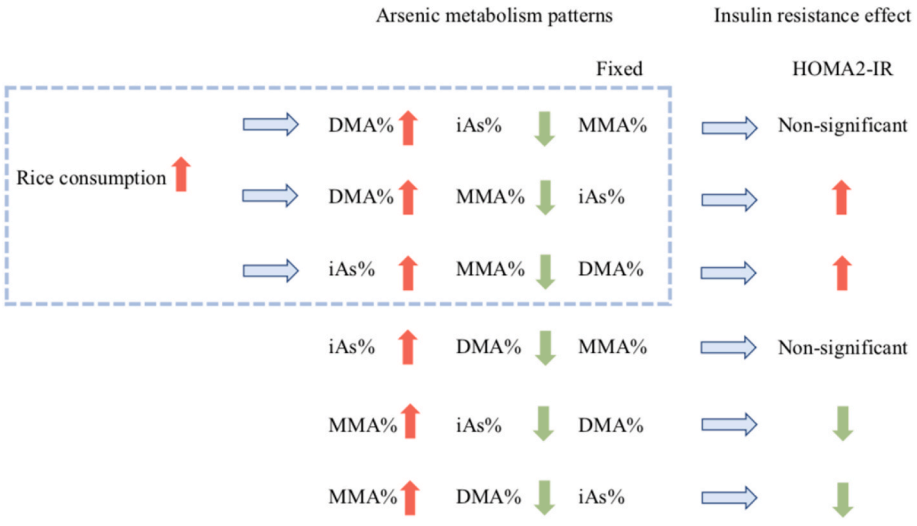

Fig. 3. Summary of the associations between rice consumption, arsenic metabolisms, and insulin resistance. Three scenarios of arsenic metabolism effects resulted from rice consumption that observed in present study are highlighted in the dashed box.

4. Discussion

In this sample of non-diabetes U.S. adults, we found rice consumption was associated with higher DMA% and lower MMA%. Lower MMA %, due to either higher iAs% or higher DMA%, was further associated with higher HOMA2-IR level after adjustment for sociodemographic factors, lifestyle factors, and fish consumption (Fig. 3). However, the associations attenuated after additional adjustment for BMI. In stratified analyses by obesity, lower MMA% due to higher iAs% was associated with higher HOMA2-IR only in participants with obesity.

The arsenic metabolism pattern, in particular lower MMA% with either higher iAs% or DMA%, was found to be associated with insulin resistance. Our findings were consistent with a previous study conducted in adults from American Indian communities (Grau-Perez et al., 2017), where lower MMA% was associated with greater insulin resistance and risk of diabetes. The biological plausibility for arsenic metabolism in the pathogenesis of insulin resistance is supported by evidence from laboratory studies (Douillet et al., 2017). MMA is a middle stage product of methylation, and high MMA% was considered insufficiency of methylation to DMA. Due to a relatively shorter half-life and rapid excretion through urine than iAs, higher DMA% is considered a more efficient arsenic metabolism profile and protective against arsenic toxicity (Spratlen et al., 2018). In contrast, the full methylation of MMA to DMA, possibly its toxic trivalent form (DMA^{III}), was also found to enhance the diabetic effects of iAs exposure (Del Razo et al., 2011) by inhibitory effects on adipogenesis (Hou et al., 2013). Impairment of triglyceride storage in white adipose tissue also results in reduced insulin sensitivity (Vigouroux et al., 2011).

Our study detected associations between arsenic metabolism and insulin resistance in participants with obesity. Additionally, Table S3 reflected the distributions of arsenic metabolites changed across BMI levels. Specifically, higher mean of iAs% and DMA% but lower MMA% as BMI increased though the trend of significance only observed in MMA %. Previous studies have provided similar findings that lower MMA% and higher DMA% were observed in people with higher BMI compared to those with lower (Gribble et al., 2013; Hall et al., 2009; Pace et al., 2018; Tseng, 2009). Alternatively, the observed association may be related to arsenic induce dysfunction of adipocytes and dysregulation of differentiation (Klei et al., 2013; Salazard et al., 2004), which further associated with insulin resistance (Hou et al., 2013). More investigations into the potential role of obesity in the association between arsenic and insulin resistance are needed in future studies.

The present study found that rice consumption was associated with higher DMA% and lower MMA%. Evidence from both Asian populations (Bahadoran et al., 2014; Zuñiga et al., 2014) and Western populations (Cascio et al., 2011; Gilbert-Diamond et al., 2011; Wei et al., 2014) supports that rice consumption is a major source of inorganic arsenic exposure. The effect of rice consumption on arsenic metabolism identified in the present study was relatively small compared to the wide inter-individual variability in arsenic metabolism (Table S2). Further investigation in populations with a broader range in rice consumption is needed to determine the extent of rice consumption affecting arsenic metabolism where nutrition conditions (i.e. protein (LeCroy and Stevens, 2017), etc.) should also be accounted for.

Important strength of this study includes the use of multiple imputations enabled a less biased calculation of arsenic metabolism biomarkers comparing to the conventional method of replacing values with the LOD divided by the square root of two (A. Nigra et al., 2019). Our study also has several limitations. First, misclassification in self-reported dietary assessments would most likely nondifferential and therefore biased the associations toward null. Second, we were unable to disentangle urinary DMA concentrations from different sources, considering urinary DMA concentrations reflect the DMA methylated from iAs and those uptaken directly from rice (Molin et al., 2014; Signes-Pastor et al., 2016). Information on DMA from different sources would improve the assessment of the association between rice consumption and arsenic metabolism in future studies. Third, the cross-sectional nature of NHANES data precludes the ability to determine chronicity of rice consumption, arsenic exposure, and persistence of insulin resistance. Urinary inorganic arsenic and its metabolites have elimination half-lives of approximately 2–4 days (Centers for Disease Control and Prevention, Biomonitoring Summary), which may not reflect long-term exposure. Therefore reverse causation could be an explanation for our results since participants with insulin resistance may have adapted lifestyle changes, including diet (Torjesen et al., 1997). Fourth, despite of extensive adjustment for confounding factors, residual confounding due to unmeasured dietary factors and environmental competing risk factors, such as use of water (Rahman and Hasegawa, 2011) or heavy metal contamination (Wang et al., 2020) cannot be completely ruled out. Lastly, while we found associations between rice consumption and arsenic metabolism, arsenic metabolism and insulin resistance in the present study, we did not observe the association between rice consumption and insulin resistance in the fully adjusted model, which is one of the premises for a mediation analysis. This can be addressed in future studies where insulin resistance results from rice consumption is well-established with less reverse causality.

5. Conclusion

In conclusion, the present study provides evidence of the association between rice consumption and arsenic metabolism. In particular, the rice consumption was positively associated with DMA%, while inversely associated with MMA%. Lower MMA% due to either higher iAs% or higher DMA% were further associated with insulin resistance in participants with obesity. Future prospective cohort studies are needed to confirm our findings in different populations with a wider range of rice consumption and arsenic exposures.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2021.113834.

References

Alanna J, M., Donna G, R., DJavid J, B., Murayi, T., JC, C., WV, R., DR, P., RS, S., KJ, K., LA, I., RC, S., LE, C., 2008. The US Department of Agriculture Automated Multiple-Pass Method reduces bias in the collection of energy intakes. Am. J. Clin. Nutr. 88 (2), 324–332. https://doi.org/10.1093/ajcn/88.2.324.

Azur, M.J., Stuart, E.A., Frangakis, C., Leaf, P.J., 2011. Multiple imputation by chained equations: what is it and how does it work? Int. J. Methods Psychiatr. Res. 20 (1), 40–49. https://doi.org/10.1002/mpr.329.

Bahadoran, Z., Mirmiran, P., Delshad, H., Azizi, F., 2014. White rice consumption is a risk factor for metabolic syndrome in Tehrani adults: a prospective approach in Tehran lipid and glucose study. Arch. Iran. Med. 17 (6), 435–440.

Cascio, C., Raab, A., Jenkins, R.O., Feldmann, J., Meharg, A.A., Haris, P.I., 2011. The impact of a rice based diet on urinary arsenic. J. Environ. Monit. 13 (2), 257–265. https://doi.org/10.1039/c0em00482k.

Centers for Disease Control and Prevention. (n.d.). Biomonitoring Summary . Retrieved July 27, 2021, from https://www.cdc.gov/biomonitoring/Arsenic_BiomonitoringSummary.html.

Chen, Y.C., Su, H.J.J., Guo, Y.L.L., Hsueh, Y.M., Smith, T.J., Ryan, L.M., Lee, M.S., Christiani, D.C., 2003. Arsenic methylation and bladder cancer risk in Taiwan. Cancer Causes Control 14 (4), 303–310.

Chen, J.W., Wang, S.L., Wang, Y.H., Sun, C.W., Huang, Y.L., Chen, C.J., Li, W.F., 2012. Arsenic methylation, GSTO1 polymorphisms, and metabolic syndrome in an arseniasis endemic area of southwestern Taiwan. Chemosphere 88 (4), 432–438. https://doi.org/10.1016/j.chemosphere.2012.02.059.

Chen, Y., Wu, F., Liu, M., Parvez, F., Slavkovich, V., Eunus, M., Ahmed, A., Argos, M., Islam, T., Rakibuz-Zaman, M., Hasan, R., Sarwar, G., Levy, D., Graziano, J., Ahsan, H., 2013. A prospective study of arsenic exposure, arsenic methylation capacity, and risk of cardiovascular disease in Bangladesh. Environmental Health Perspectives. https://doi.org/10.1289/ehp.1205797.

Davis, M.A., Mackenzie, T.A., Cottingham, K.L., Gilbert-Diamond, D., Punshon, T., Karagas, M.R., 2012. Rice consumption and urinary arsenic concentrations in U.S.

children. Environmental Health Perspectives. https://doi.org/10.1289/ehp.1205014.
DeCastro, B.R., Caldwell, K.L., Jones, R.L., Blount, B.C., Pan, Y., Ward, C., Mortensen, M. E., 2014. Dietary Sources of Methylated Arsenic Species in Urine of the United States Population, NHANES 2003-2010. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0108098.
Del Razo, L.M., García-Vargas, G.G., Valenzuela, O.L., Castellanos, E., Sánchez-Peña, L. C., Currier, J.M., Drobná, Z., Loomis, D., Stýblo, M., 2011. Exposure to arsenic in drinking water is associated with increased prevalence of diabetes: a cross-sectional study in the Zimapán and Lagunera regions in Mexico. Environmental Health: A Global Access Science Source 10, 73. https://doi.org/10.1186/1476-069X-10-73.
Diabetes Trials Unit, & University of Oxford, 2019. HOMA2 Calculator : overview. https://www.dtu.ox.ac.uk/homacalculator/.
Douillet, C., Huang, M.C., Saunders, R.J., Dover, E.N., Zhang, C., Stýblo, M., 2017. Knockout of arsenic (+3 oxidation state) methyltransferase is associated with adverse metabolic phenotype in mice: the role of sex and arsenic exposure. Arch. Toxicol. 91 (7), 2617–2627. https://doi.org/10.1007/s00204-016-1890-9.
Fulgoni, V.L., Fulgoni, S.A., Upton, J.L., Moon, M., 2010. Diet quality and markers for human health in rice eaters versus non-rice eaters: an analysis of the US National Health and Nutrition Examination Survey, 1999-2004. Nutr. Today 45, 262–272. https://doi.org/10.1097/NT.0b013e3181fd4f29.
Gilbert-Diamond, D., Cottingham, K.L., Gruber, J.F., Punshon, T., Sayarath, V., Gandolfi, A.J., Baker, E.R., Jackson, B.P., Folt, C.L., Karagas, M.R., 2011. Rice consumption contributes to arsenic exposure in US women. In: Proceedings of the National Academy of Sciences of the United States of America. https://doi.org/10.1073/pnas.1109127108.
Gomez-Rubio, P., Roberge, J., Arendell, L., Harris, R.B., O'Rourke, M.K., Chen, Z., Cantu-Soto, E., Meza-Montenegro, M.M., Billheimer, D., Lu, Z., Klimecki, W.T., 2011. Association between body mass index and arsenic methylation efficiency in adult women from southwest U.S. and northwest Mexico. Toxicol. Appl. Pharmacol. 252 (2), 176–182. https://doi.org/10.1016/j.taap.2011.02.007.
Grashow, R., Zhang, J., Fang, S.C., Weisskopf, M.G., Christiani, D.C., Kile, M.L., Cavallari, J.M., 2014. Inverse association between toenail arsenic and body mass index in a population of welders. Environ. Res. 131, 131–133. https://doi.org/10.1016/j.envres.2014.03.010.
Grau-Perez, M., Kuo, C.C., Gribble, M.O., Balakrishnan, P., Jones Spratlen, M., Vaidya, D., Francesconi, K.A., Goessler, W., Guallar, E., Silbergeld, E.K., Umans, J.G., Best, L.G., Lee, E.T., Howard, B.V., Cole, S.A., Navas-Acien, A., 2017. Association of low-moderate arsenic exposure and arsenic metabolism with incident diabetes and insulin resistance in the strong heart family study. Environmental Health Perspectives 125 (12), 127004. https://doi.org/10.1289/EHP2566.
Gribble, M.O., Crainiceanu, C.M., Howard, B.V., Umans, J.G., Francesconi, K.A., Goessler, W., Zhang, Y., Silbergeld, E.K., Guallar, E., Navas-Acien, A., 2013. Body composition and arsenic metabolism: a cross-sectional analysis in the Strong Heart Study. Environmental Health: A Global Access Science Source 12, 107. https://doi.org/10.1186/1476-069X-12-107.
Hall, M.N., Liu, X., Slavkovich, V., Ilievski, V., Pilsner, J.R., Alam, S., Factor-Litvak, P., Graziano, J.H., Gamble, M.V., 2009. Folate, cobalamin, cysteine, homocysteine, and Arsenic metabolism among children in Bangladesh. Environmental Health Perspectives 117 (5), 825–831. https://doi.org/10.1289/ehp.0800164.
Hou, Y., Xue, P., Woods, C.G., Wang, X., Fu, J., Yarborough, K., Qu, W., Zhang, Q., Andersen, M.E., Pi, J., 2013. Association between arsenic suppression of adipogenesis and induction of CHOP10 via the endoplasmic reticulum stress response. Environmental Health Perspectives 121 (2), 237–243. https://doi.org/10.1289/EHP.1205731.
Huang, Y.K., Huang, Y.L., Hsueh, Y.M., Yang, M.H., Wu, M.M., Chen, S.Y., Hsu, L.I., Chen, C.J., 2008. Arsenic Exposure, Urinary Arsenic Speciation, and the Incidence of Urothelial Carcinoma: A Twelve-Year Follow-Up Study. Cancer Causes and Control. https://doi.org/10.1007/s10552-008-9146-5.
Huang, Y.K., Tseng, C.H., Huang, Y.L., Yang, M.H., Chen, C.J., Hsueh, Y.M., 2007. Arsenic methylation capability and hypertension risk in subjects living in arseniasis-hyperendemic areas in southwestern Taiwan. Toxicol. Appl. Pharmacol. 218 (2), 135–142. https://doi.org/10.1016/j.taap.2006.10.022.
Klei, L.R., Garciafigueroa, D.Y., Barchowsky, A., 2013. Arsenic activates endothelin-1 Gi protein–coupled Receptor signaling to Inhibit Stem cell differentiation in adipogenesis. Toxicol. Sci. 131 (2), 512. https://doi.org/10.1093/TOXSCI/KFS323.
Kuo, C.C., Howard, B.V., Umans, J.G., Gribble, M.O., Best, L.G., Francesconi, K.A., Goessler, W., Lee, E., Guallar, E., Navas-Acien, A., 2015. Arsenic exposure, arsenic metabolism, and incident diabetes in the strong heart study. Diabetes Care 38 (4), 620–627. https://doi.org/10.2337/dc14-1641.
Kurzius-Spencer, M., Burgess, J.L., Harris, R.B., Hartz, V., Roberge, J., Huang, S., Hsu, C. H., O'Rourke, M.K., 2014. Contribution of diet to aggregate arsenic exposures - an analysis across populations. J. Expo. Sci. Environ. Epidemiol. 24, 156–162. https://doi.org/10.1038/jes.2013.37.
LeCroy, M.N., Stevens, J., 2017. Dietary intake and habits of South Asian immigrants living in Western countries. Nutr. Rev. 75, 391–404. https://doi.org/10.1093/nutrit/nux023.
Mendez, M.A., González-Horta, C., Sánchez-Ramírez, B., Ballinas-Casarrubias, L., Cerón, R.H., Morales, D.V., Baeza Terrazas, F.A., Ishida, M.C., Gutiérrez-Torres, D.S., Saunders, R.J., Drobná, Z., Fry, R.C., Buse, J.B., Loomis, D., García-Vargas, G.G., Del Razo, L.M., Stýblo, M., 2016. Chronic exposure to arsenic and markers of cardiometabolic risk: a cross-sectional study in Chihuahua, Mexico. Environmental Health Perspectives. https://doi.org/10.1289/ehp.1408742.
Menke, A., Casagrande, S., Geiss, L., Cowie, C.C., 2015. Prevalence of and trends in diabetes among adults in the United States, 1988-2012 Original investigation. J. Am. Med. Assoc. 314 (10), 1021–1029. https://doi.org/10.1001/jama.2015.10029.
Molin, M., Ulven, S.M., Dahl, L., Goessler, W., Fliegel, D., Holck, M., Sloth, J.J., Oshaug, A., Alexander, J., Meltzer, H.M., Ydersbond, T.A., 2014. Urinary excretion of arsenicals following daily intake of various seafoods during a two weeks intervention. Food Chem. Toxicol. 66, 76–88. https://doi.org/10.1016/j.fct.2014.01.030.
National Health and Nutrition Examination Survey, 2020. NHANES 2013-2014 laboratory methods. https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/labmethods.aspx?BeginYear=2013.
Navas-Acien, A., Silbergeld, E.K., Pastor-Barriuso, R., Guallar, E., 2008. Arsenic exposure and prevalence of type 2 diabetes in US adults. JAMA - Journal of the American Medical Association 300 (7), 814–822. https://doi.org/10.1001/jama.300.7.814.
Nigra, A.E., Nachman, K.E., Love, D.C., Grau-Perez, M., Navas-Acien, A., 2017. Poultry consumption and arsenic exposure in the U.S. population. Environmental Health Perspectives. https://doi.org/10.1289/EHP351.
Nigra, A., Y, L., A, D., Ana, N.-A., Q, C., 2019. Bayesian-imputation of urinary arsenic species below the detection limit in NHANES 2003-2016. Environmental Epidemiology 3, 289. https://doi.org/10.1097/01.ee9.0000609116.29388.a4.
Nizam, S., Kato, M., Yatsuya, H., Khalequzzaman, M., Ohnuma, S., Naito, H., Nakajima, T., 2013. Differences in urinary arsenic metabolites between diabetic and non-diabetic subjects in Bangladesh. Int. J. Environ. Res. Publ. Health 10 (3), 1006–1019. https://doi.org/10.3390/ijerph10031006.
Nurchi, V.M., Djordjevic, A.B., Crisponi, G., Alexander, J., Bjørklund, G., Aaseth, J., 2020. Arsenic toxicity: molecular targets and therapeutic agents. Biomolecules 10 (2), 235. https://doi.org/10.3390/biom10020235.
Pace, C., Smith-Gagen, J., Angermann, J., 2018. Arsenic methylation capacity and metabolic syndrome in the 2013–2014 U.S. National health and nutrition examination survey (NHANES). Int. J. Environ. Res. Publ. Health 15 (1), 168. https://doi.org/10.3390/ijerph15010168.
Park, S.K., Peng, Q., Bielak, L.F., Silver, K.D., Peyser, P.A., Mitchell, B.D., 2016. Arsenic exposure is associated with diminished insulin sensitivity in non-diabetic Amish adults. Diabetes Metabol. Res. Rev. 32 (6), 565–571. https://doi.org/10.1002/dmrr.2769.
Peng, Q., Harlow, S.D., Park, S.K., 2015. Urinary arsenic and insulin resistance in US adolescents. Int. J. Hyg Environ. Health 218 (4), 407–413. https://doi.org/10.1016/j.ijheh.2015.03.006.
Rahman, M. Azizur, Hasegawa, H., 2011. High levels of inorganic arsenic in rice in areas where arsenic-contaminated water is used for irrigation and cooking. Sci. Total Environ. 409 (22), 4645–4655. https://doi.org/10.1016/J.SCITOTENV.2011.07.068.
Salazard, B., Bellon, L., Jean, S., Maraninchi, M., El-Yazidi, C., Orsière, T., Margotat, A., Botta, A., Bergé-Lefranc, J.L., 2004. Low-level arsenite activates the transcription of genes involved in adipose differentiation. Cell Biol. Toxicol. 20 (6), 375–385. https://doi.org/10.1007/s10565-004-1471-1.
Selvin, E., Parrinello, C.M., Sacks, D.B., Coresh, J., 2014. Trends in prevalence and control of diabetes in the United States, 1988-1994 and 1999-2010. Ann. Intern. Med. 160 (8), 517–525. https://doi.org/10.7326/M13-2411.
Signes-Pastor, A.J., Carey, M., Carbonell-Barrachina, A.A., Moreno-Jiménez, E., Green, A.J., Meharg, A.A., 2016. Geographical variation in inorganic arsenic in paddy field samples and commercial rice from the Iberian Peninsula. Food Chem. 202, 356–363. https://doi.org/10.1016/j.foodchem.2016.01.117.
Spratlen, M.J., Grau-Perez, M., Umans, J.G., Yracheta, J., Best, L.G., Francesconi, K., Goessler, W., Balakrishnan, P., Cole, S.A., Gamble, M.V., Howard, B.V., Navas-Acien, A., 2018. Arsenic, One Carbon Metabolism and Diabetes-Related Outcomes in the Strong Heart Family Study. Environment International. https://doi.org/10.1016/j.envint.2018.09.048.
Steinmaus, C., Bates, M.N., Yuan, Y., Kalman, D., Atallah, R., Rey, O.A., Biggs, M.L., Hopenhayn, C., Moore, L.E., Hoang, B.K., Smith, A.H., 2006. Arsenic methylation and bladder cancer risk in case-control studies in Argentina and the United States. J. Occup. Environ. Med. 48 (5), 478–488. https://doi.org/10.1097/01.jom.0000200982.28276.70.
Steinmaus, C., Yuan, Y., Kalman, D., Rey, O.A., Skibola, C.F., Dauphine, D., Basu, A., Porter, K.E., Hubbard, A., Bates, M.N., Smith, M.T., Smith, A.H., 2010. Individual differences in arsenic metabolism and lung cancer in a case-control study in Cordoba, Argentina. Toxicol. Appl. Pharmacol. 247 (2), 138–145. https://doi.org/10.1016/j.taap.2010.06.006.
Thomas, D.J., Li, J., Waters, S.B., Xing, W., Adair, B.M., Drobna, Z., Devesa, V., Styblo, M., 2007. Arsenic (+3 oxidation state) methyltransferase and the methylation of arsenicals. Experimental Biology and Medicine. https://doi.org/10.3181/00379727-207-2320003.
Torjesen, P.A., Birkeland, K.I., Anderssen, S.A., Hjermann, I., Holme, I., Urdal, P., 1997. Lifestyle changes may reverse development of the insulin resistance syndrome: the Oslo Diet and Exercise Study: a randomized trial. Diabetes Care 20 (1), 26–31. https://doi.org/10.2337/diacare.20.1.26.
Trasande, L., Spanier, A.J., Sathyanarayana, S., Attina, T.M., Blustein, J., 2013. Urinary phthalates and increased insulin resistance in adolescents. Pediatrics 132 (3), e646–e655. https://doi.org/10.1542/peds.2012-4022.
Trouba, K.J., Wauson, E.M., Vorce, R.L., 2000. Sodium arsenite inhibits terminal differentiation of murine C3H 10T1/2 preadipocytes. Toxicol. Appl. Pharmacol. 168 (1), 25–35. https://doi.org/10.1006/taap.2000.9012.
Tseng, C.H., 2009. A review on environmental factors regulating arsenic methylation in humans. Toxicol. Appl. Pharmacol. 235 (3), 338–350. https://doi.org/10.1016/j.taap.2008.12.016.
Tseng, C.H., Tai, T.Y., Chong, C.K., Tseng, C.P., Lai, M.S., Lin, B.J., Chiou, H.Y., Hsueh, Y. M., Hsu, K.H., Chen, C.J., 2000. Long-term arsenic exporure and incidence of non-insulin-dependent diabetes mellitus: a cohort study in arseniasis-hyperendemic

villages in Taiwan. Environmental Health Perspectives 108 (9), 847–851. https://doi.org/10.1289/ehp.00108847.

Vahter, M., 2000. Genetic polymorphism in the biotransformation of inorganic arsenic and its role in toxicity. Toxicol. Lett. 112-113, 209–217. https://doi.org/10.1016/s0378-4274(99)00271-4.

Vigouroux, Corinne, Caron-Debarle, Martine, Le Dour, Caroline, Magré, Jocelyne, Capeau, Jacqueline, 2011. Molecular mechanisms of human lipodystrophies: from adipocyte lipid droplet to oxidative stress and lipotoxicity. Int. J. Biochem. Cell Biol. 43 (6), 862–876. https://doi.org/10.1016/J.BIOCEL.2011.03.002.

Villegas, Raquel, Liu, Simin, Gao, Yu-Tang, Yang, Gong, Li, Honglan, Zheng, Wei, Xhu, Xiao Ou, 2007. Prospective study of dietary carbohydrates, glycemic index, glycemic load, and incidence of type 2 diabetes mellitus in middle-aged Chinese women. Arch. Intern. Med. 167 (21), 2310–2316. https://doi.org/10.1001/ARCHINTE.167.21.2310.

Walton, F.S., Harmon, A.W., Paul, D.S., Drobná, Z., Patel, Y.M., Styblo, M., 2004. Inhibition of insulin-dependent glucose uptake by trivalent arsenicals: possible mechanism of arsenic-induced diabetes. Toxicol. Appl. Pharmacol. 198 (3), 424–433. https://doi.org/10.1016/j.taap.2003.10.026.

Wang, X., Karvonen-Gutierrez, C.A., Herman, W.H., Mukherjee, B., Harlow, S.D., Park, S. K., 2020a. Urinary metals and incident diabetes in midlife women: study of Women's Health across the Nation (SWAN). BMJ Open Diabetes Research & Care. https://doi.org/10.1136/bmjdrc-2020-001233.

Wang, X., Mukherjee, B., Karvonen-Gutierrez, C.A., Herman, W.H., Batterman, S., Harlow, S.D., Park, S.K., 2020b. Urinary metal mixtures and longitudinal changes in glucose homeostasis: the Study of Women's Health across the Nation (SWAN). Environ. Int. 145, 106109. https://doi.org/10.1016/J.ENVINT.2020.106109.

Wei, Y., Zhu, J., Nguyen, A., 2014. Rice consumption and urinary concentrations of arsenic in US adults. Int. J. Environ. Health Res. 24 (5), 459–470. https://doi.org/10.1080/09603123.2013.857393.

Wu, H., Grandjean, P., Hu, F.B., Sun, Q., 2015. Consumption of white rice and brown rice and urinary inorganic arsenic concentration. Epidemiology 26 (6), e65–e67. https://doi.org/10.1097/EDE.0000000000000369.

Xue, J., Zartarian, V., Wang, S.W., Liu, S.V., Georgopoulos, P., 2010. Probabilistic modeling of dietary arsenic exposure and dose and evaluation with 2003-2004 NHANES data. Environmental Health Perspectives 118 (3), 345–350. https://doi.org/10.1289/ehp.0901205.

Yen, Y.P., Tsai, K.S., Chen, Y.W., Huang, C.F., Yang, R. Sen, Liu, S.H., 2010. Arsenic inhibits myogenic differentiation and muscle regeneration. Environmental Health Perspectives 118 (7), 949–956. https://doi.org/10.1289/ehp.0901525.

Yu, R.C., Hsu, K.H., Chen, C.J., Froines, J.R., 2000. Arsenic Methylation Capacity and Skin Cancer. Cancer Epidemiology Biomarkers and Prevention.

Zipf, G., Chiappa, M., Porter, K.S., Lewis, B.G., Ostchega, Y., Dostal, J., 2013. National Health and Nutrition Examination Survey: Plan and Operations, 1999-2010. *Vital And Health Statistics, Series 1: Programs And Collection Procedures*.

Zuñiga, Y.L.M., Rebello, S.A., Oi, P.L., Zheng, H., Lee, J., Tai, E.S., Van Dam, R.M., 2014. Rice and noodle consumption is associated with insulin resistance and hyperglycaemia in an Asian population. Br. J. Nutr. 111 (6), 1118–1128. https://doi.org/10.1017/S0007114513003486.