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Gender Differences in the Risk of Metabolic Syndrome Among Chronic Arsenic-Exposed Individuals in Bangladesh

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Abstract

Arsenic is a ubiquitous environmental contaminant that causes cardiovascular diseases (CVDs) and diabetes. Metabolic syndrome (MeS) is a cluster of conditions associated with the future risk of CVDs and diabetes. Although CVDs are the major causes of arsenic-related mortality, the association between arsenic exposure and MeS remains elusive. Recently, we have reported that arsenic exposure increases hyperglycemia and insulin resistance with greater susceptibility in females than in males. Therefore, we explored the associations of arsenic exposure with the risk of MeS and its components focusing on gender differences. MeS was defined by the modified NCEP ATP III guidelines. A total of 569 adults were recruited from high- and low-arsenic-exposure areas in Bangladesh. Arsenic concentrations in drinking water, hair, and nails were determined as exposure markers. Among 569 subjects, 156 were found to have MeS. Levels of arsenic and the components of MeS were significantly higher in MeS group than those in non-MeS group. Prevalence and odds ratios (ORs) of MeS were increased with increasing exposure to arsenic showing more precise dose-dependent association in women than in men. Except hypertriglyceridemia, the changes in ORs for other components of MeS such as hyperglycemia, hypo-high-density lipoprotein-cholesterolemia, hyper-systolic blood pressure, and abdominal obesity with arsenic exposure were more pronounced in women than in men. Thus, the higher risk of arsenic-related MeS in women than in men suggests a greater susceptibility of women to CVDs that warrant more future investigations on the gender-based distinct pathophysiologic mechanisms of arsenic-related CVDs and diabetes.

Keywords Arsenic · Metabolic syndrome · CVDs · Diabetes · Hyperglycemia · Blood pressure

Introduction

Toxicity caused by environmental exposure to arsenic is a serious concern worldwide as arsenic is ubiquitously present in the environment, including groundwater, foods, and vegetables. Globally at least 140 million people have been estimated to be exposed to arsenic mainly via drinking water that exceeds the standard arsenic concentration in the drinking water (10 µg/L) set by World Health Organization (WHO 2018). Cancer is the most common cause of chronic arsenic-exposure-related mortality, but accumulating evidence has demonstrated that arsenic exposure increases the mortality from cardiovascular diseases (CVDs) (Rahman et al. 2019; Chen et al. 2011; Hall et al. 2017; Yuan et al. 2007; Moon et al. 2012).

Recently, epidemiological studies have demonstrated that environmental pollutants such as ambient air pollutants

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(Yang et al. 2018) or lead (Zheutlin et al. 2018) have the potential to increase the risk of hypertension. Endocrine-disrupting chemicals have also been shown to enhance the risk of diabetes mellitus (DM) in humans (Lind and Lind 2018; Rancière et al. 2019). Compared with other environmental pollutants, arsenic is a unique pollutant linked to both hypertension and DM risks, suggesting that arsenic-induced vascular dysfunctions and metabolic disorders may be acting as common underlying mechanisms for these diseases. We have previously reported that the blood markers of atherosclerosis, dyslipidemia, hyperglycemia, insulin resistance, and vascular endothelial dysfunctions were increased in the population exposed to moderate-to-high levels of arsenic in Bangladesh and suggested the involvement of multiple metabolic disorders in developing CVDs and DM by arsenic exposure (Karim et al. 2013; Rahman et al. 2015; Hasibuzzaman et al. 2017; Paul et al. 2019; Mondal et al. 2020).

Metabolic syndrome (MeS) is a cluster of risk factors including hypertension, hyperglycemia, and dyslipidemia accompanying abdominal obesity. Over the past decades, the number of people with MeS has drastically increased in both developed and developing countries, resulting in increased mortality from CVDs and DM-related complications (Mottillo et al. 2010; Malik et al. 2004; Katzmarzyk et al. 2005; Thorn et al. 2009). The diagnosis of MeS with its components is currently used worldwide for predicting the future risks for developing CVDs and DM (Ford 2005; Haffner 2006).

Since the high prevalence of DM and hypertension have been reported in arsenic-contaminated areas, several studies have investigated whether exposure to arsenic is associated with MeS also in general populations. A cross-sectional study conducted in Taiwan showed a significant association of hair arsenic concentrations with the risk of MeS (Wang et al. 2007). In the US, a population-based cross-sectional study showed a weak but significant association of arsenic-exposure levels as assessed by urinary arsenic concentrations with the risk of MeS (Bulka et al. 2019). In contrast, a prospective study conducted on the participants from the Strong Heart Family Study in the US failed to find the associations of urinary arsenic levels with the individual components or overall risks of MeS except for fasting plasma glucose concentration (Spratlen et al. 2018). However, this study found associations of arsenic metabolism, particularly lower percentage of momomethylarsonic acid (MMA) and higher percentage of dimethylarsinic acid (DMA) with the higher risk of MeS. These results were similar to the other studies conducted in arsenic-endemic areas in Iran and Taiwan (Kazemifar et al. 2020; Chen et al. 2012). Trivalent methylated arsenicals (MMA^{III} and DMA^{III}) have been recognized as the most toxic metabolites. MMA% and DMA% may reflect the levels of trivalent intermediates, MMA^{III} and DMA^{III}, respectively. Both MMA and DMA are associated

with arsenic-related diseases but may be with different sensitivities based on their concentrations. Epidemiological studies suggest that higher MMA% is associated with arsenic-related skin lesions and malignant diseases and, while DMA% is associated with the risk of MeS (Kile et al. 2011; Ahsan et al. 2007; Kuo et al. 2017; Spratlen et al. 2018; Pace et al. 2018). Most of the previous studies have focused more on the roles of arsenic methylation capacity than arsenic-exposure level itself (Bulka et al. 2019; Spratlen et al. 2018; Chen et al. 2012; Kazemifar et al. 2020). A study conducted in Korea failed to find an association between total urinary arsenic levels and the risk of MeS (Rhee et al. 2013). These inconsistent results may have been caused by the dose and duration of arsenic exposure. Another limitation is that most of the previous studies used urinary arsenic concentrations as an exposure marker, which mainly reflects recent exposure to arsenic (Bulka et al. 2019; Watanabe et al. 2001).

In Bangladesh, where many people are exposed to moderate-to-high levels of arsenic via drinking water, several studies, including ours, have shown increases in the prevalence of hypertension and DM in arsenic-endemic areas (Hossain et al. 2012; Paul et al. 2019; Chen et al. 2011; Rahman et al. 1999). However, no systematic study has been conducted yet regarding whether exposure to moderate-to-high levels of arsenic increases the risk of MeS in Bangladesh.

Our previous studies have shown that the effects of arsenic exposure on hyperglycemia and the development of insulin resistance are more evident in women than in men (Paul et al. 2019; Mondal et al. 2020). Gender is an important factor that influences the susceptibility to arsenic-related diseases (Vahter et al. 2007), although inconsistent results have been reported regarding which gender is more susceptible to arsenic-induced skin lesions and cancers (Ahsan et al. 2006; Rahman et al. 2006; Smith et al. 1998; Yang et al. 2005). D'Ippoliti et al. (2015) reported that arsenic-exposed women have a greater risk for diabetes, which is similar to our findings (Paul et al. 2019; Mondal et al. 2020). However, the same study showed that men have a greater risk for myocardial infarction and peripheral arterial diseases (D'Ippoliti et al. 2015). A cohort study conducted in Bangladesh reported a higher mortality rate from stroke in women than in men (Rahman et al. 2014). Because the MeS and its components are associated with both CVDs and DM, inconsistent results of the gender differences in arsenic-related risks of CVDs and DM prompted us to investigate whether the risk of MeS in our study population in Bangladesh is increased by arsenic exposure and whether there are gender differences in the risks of MeS and individual components of MeS. For this purpose, we determined arsenic concentrations in subjects' drinking water, hair, and nails and investigated the dose-dependent changes of the risk of MeS with arsenic exposure.

Materials and Methods

Ethical Permission

Institute of Biological Sciences (IBSc) (no. 661/320/IAME-BBC/IBSc), University of Rajshahi approved this study.

Study Areas

This study was conducted in the same areas where we carried out our previous studies (Siddique et al. 2020; Paul et al. 2019). The information about high- and low-arsenic-exposure areas was obtained from a survey report (BGS and DPHE 2001). High-exposure areas included Marua in the Jessore District, Dutpatila, Jajri, Vultie, and Kestopur in the Chuadanga District, Kazirpara in the Rajshahi District, and Khemirdia in the Kushtia District. Chowkoli, a village from a northern district (Naogaon) was selected as a low-exposure area.

Study Subjects

We visited each family in the high- and low-exposure areas and requested adult individuals (18–60 years of age), who had been living in their respective areas for at least five years, to attend the survey. In response to our request, 431 individuals from 279 families and 146 individuals from 86 families in the high- and low-exposure areas, respectively, were enrolled in the study. Six individuals (hepatic disease = 2, stroke = 1, renal disease = 1, pregnancy = 1, and hepatitis B = 1) and two individuals (hepatic disease = 1 and renal disease = 1) from high- and low-exposure areas, respectively, were excluded from the study participants based on the exclusion criteria. Exclusion criteria included history of drug addiction, hepatotoxic or anti-hypertensive drug use, malaria or leishmaniasis, or a history of hepatic, renal, or severe cardiac disease, hepatitis B infection, the recent history of surgical operation, and pregnant and lactating mothers. Finally, the total numbers of study subjects were 425 and 144 from high- and low-exposure areas, respectively. We obtained written permission for providing samples from all study subjects. All sorts of confidentialities and rights of the subjects were strictly maintained.

Questionnaire and Interview

Every individual was interviewed by the trained members of our research team. Interviews were conducted by a structured questionnaire as described previously (Karim et al. 2013; Huda et al. 2014; Hasibuzzaman et al. 2017). The information obtained through the questionnaire was the source of water for drinking and household uses, water consumption history, smoking habits, income, education, occupation, and marital status.

Collection of Water and Measurement of Arsenic Concentrations

Collection of well water samples were conducted as described previously (Siddique et al. 2020). The water samples were immediately acidified by nitric acid and shipped to Laboratory of Molecular Nutrition and Toxicology, Tokushima Bunri University, Japan, to measure arsenic. The total arsenic concentrations in the samples were measured in duplicate by inductively coupled plasma mass spectrometer (ICP-MS) (Agilent 7700x, Japan). The precision of the measurement of water arsenic was verified by determining the arsenic concentration of a certified reference material (CRM) "River water" (National Metrology Institute of Japan [NMIJ] CRM 7202-a No. 347, National Institute of Advanced Industrial Science and Technology, Japan). Average (mean ± SD) arsenic concentration in the triplicate CRM samples was 1.161 ± 0.082 mg/L, which was close to the certified value (1.18 mg/L).

Collection of Hair and Nails and Measurement of Exposure Levels

Hair and toenail samples were collected as described previously (Ali et al. 2010; Schmitt et al. 2005) and shipped to Laboratory of Molecular Nutrition and Toxicology, Tokushima Bunri University, Japan. To remove potential external contamination, hair and nail samples were washed twice in 1% Triton X-100 and then three times in Milli-Q water. Samples were placed in Teflon vials with 1.0 mL concentrated nitric acid and then digested in a High-Performance Microwave Digestion System (MILESTONE ETHOS One, Shelton, CT, USA) at 180 °C for 10 min. The digested samples were transferred into test tubes and made up to 10 mL volume with Milli-Q water for subsequent ICP-MS analysis. The average value of arsenic in duplicate samples was used for final analysis. The precision of the measurements of arsenic concentrations in hair and nail samples was verified by determining arsenic concentration in "human hair" (GBW09101, Shanghai Institute of Nuclear Research Academia Sinica, China) as a CRM. The average value (mean ± SD) of arsenic in "human hair" determined in triplicate was 0.61 ± 0.12 μg/g (certified value, 0.59 μg/g).

Blood Collection and Measurements of Serum Levels of Fasting Blood Glucose, Triglycerides, and High-Density Lipoprotein Cholesterol

Fasting blood samples (3 mL) were collected from each subject, and the serum was separated as we described previously

(Islam et al. 2015). Serum levels of fasting blood glucose (FBG), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were determined by using commercially available kits (Glucose liquicolor; Biosystems, Triglycerides; Biosystems and HDL cholesterol direct; Biosystems, respectively) through a biochemical analyzer (Humalyzer 3000, Human GmbH, Germany). The team members who measured the blood biochemistry markers were blinded to the arsenic-exposure levels of the subjects during the measurement.

Measurements of Blood Pressure and Waist Circumference

The subject's systolic (SBP) and diastolic (DBP) blood pressure were measured according to the protocol recommended by WHO. For the measurement of waist circumference (WC), the subjects were requested to keep a posture standing with both arms relaxed at each side. The WC was measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest (hip bone) using a stretch-resistant tape. The mean value of two measurements was used for analysis (WHO 2011).

Identification of MeS

The diagnosis of MeS was based on the modified criteria of National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III). The subjects fulfilling three or more diagnostic criteria including hyperglycemia (FBG levels: ≥ 100 mg/dL), hypertriglyceridemia (TG level: ≥ 150 mg/dL), hypo-HDL-cholesterolemia (HDL-C: < 40 mg/dL for men and < 50 mg/dL for women), hypertension (SBP ≥ 130 mmHg, DBP ≥ 85 mmHg), and increased WC (modified Asian criteria was used for a cutoff of WC: ≥ 90 cm for man, ≥ 80 cm for woman) were regarded as MeS (Alberti et al. 2009; Grundy et al. 2005; Tan et al. 2004).

Statistical Analyses

Differences in the categorical variables (gender, occupation, education, and smoking habit) and continuous variables (age, BMI, income, arsenic-exposure metrics, FBG, TG, HDL-C, WC, DBP, and SBP) between the MeS and non-MeS groups were examined by chi-square test and t test, respectively. The subjects were divided into low-, moderate-, and high-arsenic groups based on the water, hair, and nail arsenic concentrations. Equal numbers of subjects were allocated to each group using frequency tests. We performed the chi-square test to check the prevalence of MeS cases between men and women among the three groups of arsenic-exposure markers. The Q–Q plot was used to verify the normality of the data distribution, and log-transformed values for arsenic concentrations were used to improve the estimation quality. Binomial logistic regression and generalized linear regression analysis were conducted to assess the associations of arsenic-exposure markers with MeS and its components, respectively. Binomial logistic regression analysis was conducted to assess the associations of the categorized arsenic-exposure levels (low, moderate, and high) with the risks of MeS and its components. Odds ratios (ORs) were calculated using the low group as a referent. All the regression models were adjusted with age, gender, BMI, and smoking as they are potential confounders of MeS (Sun et al. 2012; Slagter et al. 2017; Razzouk and Muntner 2009) with one exception in the associations of arsenic-exposure markers with the MeS and its components in which analyses were also performed excluding BMI. Statistical significance of p value was defined as $p < 0.05$. All the statistical analyses were carried out with the help of a statistical package for the social sciences (SPSS) software (version 21.0; SPSS, Chicago, IL).

Results

Characteristics of the Study Subjects with and Without MeS

Table 1 shows the characteristics of the study subjects with MeS and without MeS (non-MeS) groups. Out of 569 subjects, 156 (27.4%) subjects were diagnosed as MeS fulfilling at least three criteria for MeS by the NCEP ATP III guidelines. The prevalence of MeS in women (37.6%, n = 108) was significantly higher than in men (17%, n = 48). The average age and BMI of the subjects in MeS group were significantly higher than those of the subjects in non-MeS group. There were no significant differences in socioeconomic parameters (occupation, education, and income) between the MeS and non-MeS groups. We did not find any women who were smoker. The average arsenic concentration in drinking water in the MeS group was more than twofold of the non-MeS group. Hair and nail arsenic concentrations in the MeS group were also significantly higher than those in the non-MeS group.

The levels of the Individual Components of MeS in the MeS and Non-MeS Groups

Table 2 shows the average levels of the individual components of MeS in the MeS and non-MeS groups. The levels of FBG, TG, SBP, DBP, and WC of the MeS group were significantly higher than those of the non-MeS group, and the HDL-C level of the MeS group was significantly lower than that of the non-MeS group.

Table 1 Characteristics of the subjects between MeS and non-MeS groups

Variables	All subjects	MeS		p-value
		Yes (MeS)	No (non-MeS)	
Study subjects [n, (%)]	569	156 (27.4)	413 (72.6)	
Gender [n, (%)]				
Women	287 (50.4)	108 (37.6)	179 (62.4)	<0.001[†]
Men	282 (49.6)	48 (17)	234 (83)	
Age (years)[a]	36.65 ± 11.48	38.47 ± 10.63	35.96 ± 11.73	0.015[*]
BMI (kg/m²)[a]	21.25 ± 3.48	22.32 ± 3.55	20.85 ± 3.38	<0.001[*]
Occupation [n, (%)]				
Women				
Housewives	271 (94.4)	105 (97.2)	166 (92.7)	0.139[†]
Students	9 (3.1)	1 (0.9)	8 (4.5)	
Workers	5 (1.7)	2 (1.9)	3 (1.7)	
[‡]Others	2 (0.7)	0 (0)	2 (1.1)	
Men				
Farmers	222 (78.7)	35 (72.9)	187 (79.9)	0.464[†]
Business	7 (2.5)	3 (6.3)	4 (1.7)	
Students	18 (6.4)	4 (8.3)	14 (6)	
Workers	7 (2.5)	0 (0)	7 (3)	
[+]Others	28 (9.9)	6 (12.5)	22 (9.4)	
Education [n, (%)]				
No formal education	302 (53.1)	91 (58.3)	211 (51.1)	0.185[†]
Primary	186 (32.7)	46 (29.5)	140 (33.9)	
Secondary	54 (9.5)	12 (7.7)	42 (10.2)	
Higher	27 (4.7)	7 (4.5)	20 (4.8)	
Income/month (US$)[a]	25.14 ± 7.9	25.39 ± 7.85	25.05 ± 7.92	0.648[*]
Smoking [n, (%)]				
Women[b]				
No	287 (100)	108 (37.6)	179 (62.4)	
Men				
Yes	121 (42.9)	17 (35.4)	104 (44.4)	0.251[†]
No	161 (57.1)	31 (64.6)	130 (55.6)	
Drinking water As (µg/L)[a]	117.83 ± 156.88	188.91 ± 198.5	90.98 ± 128.33	<0.001[*]
Hair As (µg/g)[a]	3.61 ± 6.13	5.51 ± 7.69	2.89 ± 5.25	<0.001[*]
Nail As (µg/g)[a]	6.64 ± 7.36	9.80 ± 9.49	5.44 ± 5.96	<0.001[*]

n number of study subjects, *As* arsenic, *BMI* body mass index. Results were presented as [a]Mean ± SD. [b]No woman was found to be a smoker. BMI was calculated as body weight (kg) divided by body height squared (m²).[*]*p* and [†]*p* values were from the independent sample t test and chi-square test, respectively. [+]Others included doctor, carpenter, driver, tailors, rickshaw puller, security guard, and retired worker. [‡]Other included doctor, carpenter, and tailor

Associations of Arsenic Exposure with MeS and Its Components

The associations between arsenic-exposure levels and MeS were analyzed by binominal logistic regression analyses (Table 3). Arsenic concentrations in the water, hair, and nails showed significant associations with MeS. Among the possible confounding factors examined, gender, BMI, and age showed significant associations with MeS, the β coefficient of gender being the highest. The associations of arsenic concentrations in the water, hair, and nails with the values of each component of MeS were analyzed by linear regression analyses. As shown in Table 3, each of the arsenic-exposure markers showed significant associations with all components of the MeS. The β coefficients values indicated stronger associations of arsenic exposure with FBG, TG, and HDL-C than with SBP, DBP, or WC. Among the confounding factors examined, gender showed significant associations with FBG and WC, and BMI showed weak but significant associations with TG, SBP, and DBP. Since BMI is a well-known risk factor for MeS, we excluded the BMI from the regression model

Table 2 Comparisons of the levels of the components of MeS between MeS and non-MeS groups

Variables	All	MeS		p value
		Yes (MeS)	No (non-MeS)	
Components of MeS				
Study number	569	156	413	
FBG (mg/dL)	95.09 ± 27.43	117.88 ± 33.12	86.49 ± 18.8	< 0.001
TG (mg/dL)	106.76 ± 38.23	124.25 ± 43.54	100.16 ± 33.81	< 0.001
HDL-C (mg/dL)	40.42 ± 13.36	34.15 ± 7.34	42.79 ± 14.32	< 0.001
SBP (mmHg)	118.8 ± 19.16	131.06 ± 26.08	114.18 ± 13.11	< 0.001
DBP (mmHg)	76.16 ± 11.34	83.08 ± 12.65	73.54 ± 9.6	< 0.001
WC (cm)	83.65 ± 6.62	88.77 ± 6.76	81.72 ± 5.43	< 0.001

Results were presented as Mean ± SD. *FBG* fasting blood glucose, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *WC* waist circumferences. *p* values were from independent sample t test

Table 3 Associations of arsenic-exposure markers with MeS and its components through regression analysis

Parameters	MeS[a] Exp β (95% CI)	FBG level[b] β (95% CI)	TG level[b] β (95% CI)	HDL-C level[b] β (95% CI)	SBP[b] β (95% CI)	DBP[b] β (95% CI)	WC[b] β (95% CI)
Water As (µg/L)	1.669 (1.386, 2.01)*	0.042 (0.035, 0.048)*	0.032 (0.021, 0.043)*	− 0.04 (− 0.048, − 0.031)*	0.01 (0.005, 0.014)*	0.009 (0.005, 0.013)*	0.008 (0.006, 0.01)*
Gender	2.592 (1.594, 4.213)*	0.035 (0.016, 0.054)*					0.012 (0.006, 0.019)*
BMI	1.107 (1.045, 1.172)*		0.008 (0.004, 0.011)*		0.005 (0.003, 0.006)*	0.004 (0.002, 0.005)*	
Age	1.027 (1.009, 1.046)‡						
Hair As (µg/g)	2.589 (1.831, 3.662)*	0.071 (0.058, 0.084)*	0.051 (0.031, 0.072)*	− 0.065 (− 0.081, − 0.048)*	0.018 (0.01, 0.026)*	0.016 (0.008, 0.025)*	0.014 (0.01, 0.018)*
Gender	2.646 (1.617, 4.329)*	0.032 (0.013, 0.052)*					0.012 (0.006, 0.018)*
BMI	1.1 (1.04, 1.163)*		0.007 (0.004, 0.011)*		0.005 (0.003, 0.006)*	0.004 (0.002, 0.005)*	
Age	1.029 (1.01, 1.047)‡						
Nail As (µg/g)	2.822 (1.911, 4.166)*	0.079 (0.064, 0.094)*	0.057 (0.033, 0.081)*	− 0.079 (− 0.097, − 0.06)*	0.017 (0.008, 0.026)*	0.017 (0.008, 0.027)*	0.015 (0.011, 0.02)*
Gender	2.463 (1.519, 3.994)*	0.032 (0.012, 0.051)‡					0.012 (0.006, 0.018)*
BMI	1.114 (1.052, 1.18)*		0.008 (0.004, 0.012)*		0.005 (0.003, 0.006)*	0.004 (0.002, 0.005)*	
Age	1.029 (1.011, 1.048)‡						

Adjusted for gender (men used as a referent), BMI, age, and smoking habit (non-smoker used as a referent)

[a,b]Data derived from binary logistic regression and linear regression analysis, respectively. Log_{10}-transformed values were used

Significant values, [†]$p < 0.05$, [‡]$p < 0.01$ and [*]$p < 0.001$

(Table S1). After excluding the BMI from the model, all the associations were similar as those were found in Table 3 with an exception between the gender and SBP. Gender was found to be significantly associated with SBP after excluding the BMI from the model (Table S1).

Associations of Arsenic Exposure with the Risks of MeS and Its Components

The prevalence of MeS was higher in women than in men (Table 1), and the regression analyses showed significant

associations of both arsenic exposure and gender with MeS (Table 3). Therefore, we compared the prevalence of MeS among low-, moderate- and high-arsenic-exposure groups separately in men and women. As shown in Table 4, percentages of MeS in women were significantly increased with increasing exposure to arsenic across the all exposure markers, while in men, the percentages were increased with the increasing concentrations of arsenic across water and nail exposure markers. The percentages of MeS were significantly higher in the groups with moderate and high concentrations of arsenic across the all exposure markers in women than those of men. The differences in prevalence of MeS between men and women were not caused by the differences in arsenic-exposure levels between men and women because the average arsenic levels in water, hair, and nails between men and women were 123.16 ± 163.78 vs. 112.58 ± 149.87 ($p = 0.422$), 3.63 ± 5.94 vs. 3.60 ± 6.31 ($p = 0.958$), and 6.39 ± 6.63 vs. 6.89 ± 8.01 ($p = 0.417$), respectively, showing no significant gender differences.

We further analyzed the risk for MeS in the low-, moderate-, and high-exposure groups of men and women separately by binominal regression analyses adjusting for age, BMI, and smoking (Fig. 1, S1 and S2). In women, the ORs for MeS were approx. threefold (OR 2.67, 95% CI 1.36–5.3, $p < 0.01$) and sixfold (OR 6.33, 95% CI 3.3–12.14, $p < 0.001$) higher in the groups with moderate and high concentrations of water arsenic, respectively, than the group with low concentration of arsenic. Furthermore, ORs for MeS were also increased in the groups with moderate and high concentrations of hair and nail arsenic compared to the respective groups with low concentrations of hair and nail arsenic in a

similar manner as observed in water arsenic-based tertiles in women. On the other hand, in men, the groups with high concentrations of water and nail arsenic showed approx. threefold increase in ORs compared to their respective groups with low-arsenic concentrations.

We also examined the risks for individual component of MeS with arsenic-exposure markers based on the diagnostic criteria of each component. The ORs for hyperglycemia, hypertriglyceridemia, hypo-HDL-cholesterolemia, hypertension, and abdominal obesity in the groups with moderate and high concentrations of arsenic with regard to the groups with low concentrations were analyzed separately in men and women. As shown in Figs. 1, S1, and S2, women showed significant and dose-dependent increases in the ORs for hyperglycemia and significant and dose-dependent decreases in hypo-HDL-cholesterolemia in both groups with moderate and high concentrations of arsenic across all exposure markers. Men also showed significant changes in the ORs for hyperglycemia and hypo-HDL-cholesterolemia, but only in the groups with high concentrations of arsenic across all three exposure markers. The ORs for hypertriglyceridemia showed an opposite pattern of risk between men and women. The groups with high concentrations of arsenic across all exposure markers in men, but not in women, showed a significant increase in the OR for hypertriglyceridemia (Figs. 1, S1, and S2). In case of high blood pressure, only ORs for hyper-SBP were found to be significantly increased in the groups with high concentrations of water and hair arsenic compared to the respective groups with low concentrations in women. OR of hyper-SBP was also found to be marginally significant ($p = 0.062$) in the group with high concentration

Table 4 Comparisons of the prevalence of MeS in low-, moderate- and high-arsenic-exposure groups of all and gender-stratified subjects

Variables	Range	n	Prevalence of MeS (%)			p-value[‡]
			All	Women	Men	
Water As (µg/L)						
Low	0.03–10.91	196	16.8	20.5	11.9	0.11
Moderate	10.92–127	183	23.5	38.5	12.4	<0.001
High	127.01–1006.7	190	42.1	56.7	26.9	<0.001
p-value[†]			<0.001	<0.001	0.007	
Hair As (µg/g)						
Low	0.02–0.85	190	18.9	23.8	12.9	0.057
Moderate	0.84–2.99	189	24.3	33.7	16	0.005
High	3–62.02	190	38.9	57	21.6	<0.001
p-value[†]			<0.001	<0.001	0.117	
Nail As (µg/g)						
Low	0.05–2	191	18.8	22.9	13.4	0.805
Moderate	2.01–6.81	188	22.3	37.5	11.1	0.001
High	6.82–47.83	190	41.1	54.1	18.5	<0.001
p-value[†]			<0.001	<0.001	0.013	

p values were from chi-square test. [†]p values of intra-group differences in all, men and women. [‡]p values of inter-group differences between men and women
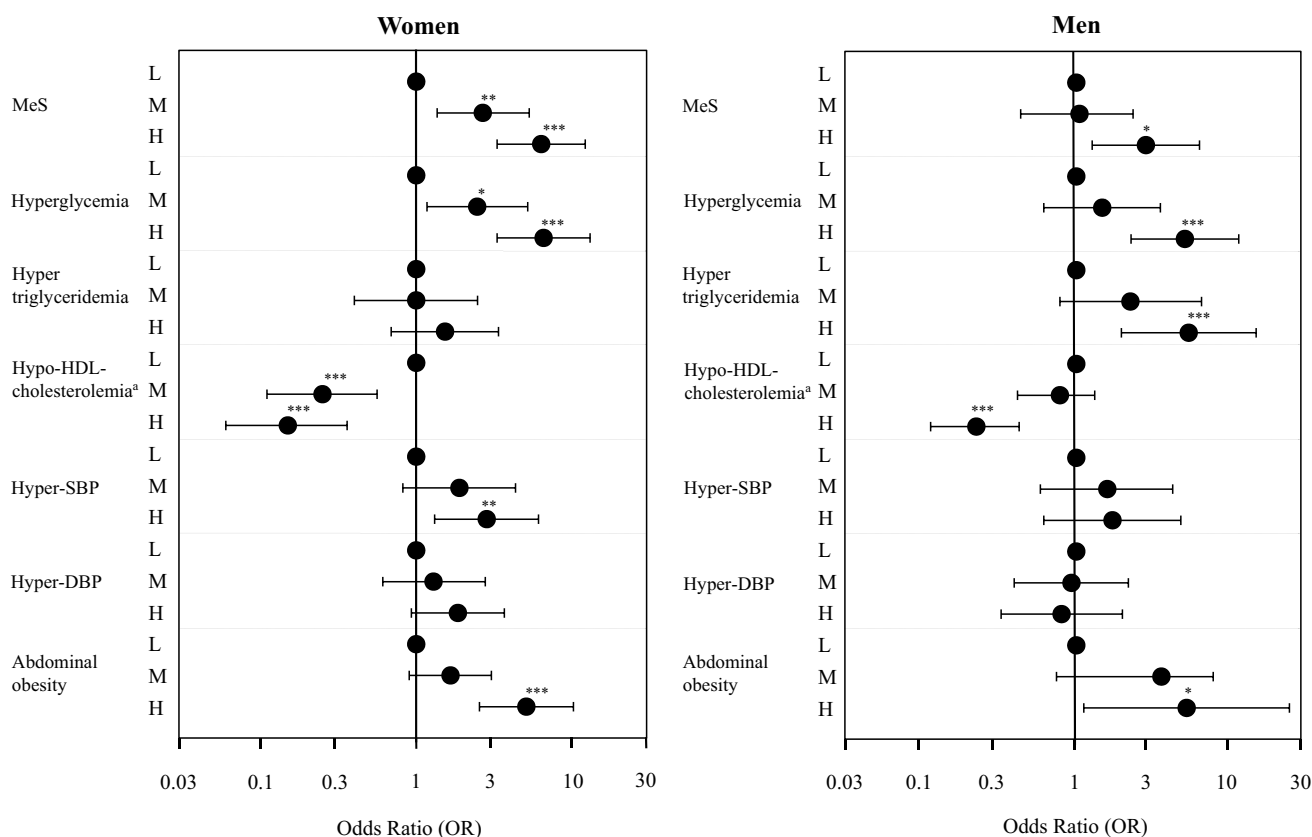
Fig. 1 Associations of water As with the risk of MeS and its components. Abbreviation; L, M, H: low, moderate, and high groups of water As, respectively. Associations of water As with the risk of MeS, hyperglycemia, hypertriglyceridemia, hypo-HDL-cholesterolemia, hyper-SBP, hyper-DBP, and abdominal obesity in women and men are shown. ORs adjusted by age and BMI for women; age, BMI, and smoking (non-smoker used as referent) for men. As levels in water: low (0.03–10.91 µg/L), moderate (10.92–127 µg/L), and high (127.01–1006.7 µg/L). Log_{10} transformed values of OR were used. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. In all cases, low group was used as referent. [a]In case of hypo-HDL-cholesterolemia, the lowering of the ORs were evaluated

of nail arsenic compared to the group with low concentration of arsenic. However, no significant increases in ORs were observed in hyper-SBP in the groups with moderate and high concentrations of arsenic in men across any of the exposure markers. ORs for abdominal obesity as assessed by WC were increased with increasing exposure to arsenic in women across the all exposure markers; however, significant changes were found only in the groups with high concentrations of arsenic compared to the respective groups with low concentrations of all exposure markers. OR for abdominal obesity was significantly higher only in the group with high concentration of water arsenic than the group with low water concentration in men.

Discussion

This study aimed to investigate the association between arsenic exposure and the risk of MeS among the subjects recruited from high- and low-arsenic-exposure areas in Bangladesh. We found that the study subjects with MeS had significantly higher levels of arsenic exposure as assessed by the drinking water, hair, and nail arsenic concentrations than the subjects without MeS (non-MeS) (Table 1). When men and women were analyzed inclusively, the overall prevalence of MeS was increased with increasing exposure to arsenic (Table 4); however, in regression analysis, gender showed a significant confounding effect on the associations between arsenic-exposure metrics and the risk of MeS (Table 3). In gender-stratified analyses, women showed the increased prevalence of MeS (Table 4) with increasing concentrations of arsenic across all three exposure markers. The risk of MeS was also significantly higher in moderate- and high-exposure groups compared to the respective low- exposure groups across all exposure markers in a dose-dependent manner (Figs. 1, S1, and S2). On the other hand, in men, the prevalence of MeS were increased with increasing concentration of hair and nail arsenic and the risk of MeS were found to be higher only in the high-exposure groups across the water and nail exposure markers. Differences in prevalence and risk of

MeS between men and women (Figs. 1, S1, and S2) explicitly indicate that women had greater risk of MeS than men.

We also examined the associations of arsenic exposure with individual components of MeS in men and women. Women with moderate and high-arsenic-exposure levels showed dose-dependent changes in the ORs for hyperglycemia and hypo-HDL-cholesterolemia (Fig. 1, S1, and S2). In contrast, only men with the high-arsenic-exposure levels showed significant changes in the ORs for those components. These results suggest the higher susceptibility of women to the risk of arsenic-related hyperglycemia and hypo-HDL-cholesterolemia. Arsenic exposure increased the risk of hypertriglyceridemia only in men; however, the reason for arsenic-exposure-related male-specific hypertriglyceridemia remains unclear. Women with high levels of water and hair arsenic showed significantly higher ORs for hyper-SBP than the group with low levels of water and hair arsenic (Figs. 1 and S1) while arsenic exposure in men did not show any significant increases in ORs for hyper-SBP. This result was consistent with our previous study in which we found that SBP levels and percentages of hypertensive patients were higher in arsenic-exposed women than those in men (Hossain et al. 2017). Moreover, arsenic exposure showed more precise dose–response relationship with the risk of abdominal obesity in women than men (Figs. 1, S1, and S2), suggesting that arsenic exposure increases the abdominal obesity in both sexes, however, and the effects of arsenic on abdominal fat deposition is more pronounced in women than men.

In addition to arsenic exposure and gender, BMI and age also showed significant associations with MeS in regression analysis (Table 3). The increased risk of MeS with aging has been well documented in the previous studies (Sanisoglu et al. 2006; Park et al. 2003; Razzouk and Muntner 2009). Consistent with the other studies, BMI also showed significant associations with TG, SBP, and DBP levels (Kazemifar et al. 2020; Meigs et al. 2006). When we excluded BMI from the regression model (Table S1), the gender was found to be significantly associated with SBP. These could be potentially due to the fact that distribution of BMI differs across the males and females. Average BMI of the female subjects was significantly different from the male subjects (20.47 ± 3 for men and 22.02 ± 3.75 for women, $p < 0.001$).

The increased risk of MeS ultimately causes the increased risk of CVDs and DM (Ford 2005; Haffner 2006). The presence of MeS was highly predictive of new-onset diabetes (Grundy et al. 2005). Although we did not perform mediation analysis, the associations of arsenic exposure with the MeS particularly, its components such as waist circumference (a obesity marker) and circulating lipid parameters suggest that changes of the components of MeS with increasing exposure to arsenic are causally linked to the insulin resistance leading to DM since obesity and dyslipidemia are the most important causal factors for insulin resistance (Patel and Abate 2013). The increased risk of MeS accompanying hyperglycemia in the arsenic-exposed women may lead to the development of DM with a greater possibility than men. In our previous study, we have reported that chronic arsenic exposure resulted in the impaired glucose tolerance and increased insulin resistance to a greater extent in women than men in the same study area in Bangladesh (Paul et al. 2019; Mondal et al. 2020), which support the results of this study. Since both abdominal obesity and hypo-HDL-cholesterolemia are the major risk of CVDs (Després and Lemieux 2006; Rader and Hovingh 2014), the higher abdominal obesity and lower level of HDL-C in women observed in our study suggest that women in arsenic-endemic areas are more susceptible to the risk of developing CVDs than man. This notion is supported by the finding of a prospective cohort study conducted in Bangladesh showing a significantly higher mortality rate from stroke in arsenic-exposed women than in men (Rahman et al. 2014). Moreover, a recent experimental study using an ex vivo ischemia/reperfusion injury model showed that the heart of female mice exposed to low concentrations of arsenic showed higher susceptibility to ischemia/reperfusion stress than male mice (Veenema et al. 2019). In spite of the above reports, many epidemiological studies did not find any gender differences in arsenic-induced CVDs (Cheng et al. 2010; Yuan et al. 2007; Afridi et al. 2010; Meliker et al. 2007; Lewis et al. 1999; Engel and smith 1994; Wu et al. 1989). Therefore, more future studies are required to compare the mortality rate from CVDs between arsenic-exposed men and women who are with the risk of MeS.

Several studies have examined the associations of arsenic exposure with the risk of MeS in Taiwan (Wang et al. 2007; Chen et al. 2012), Korea (Rhee et al. 2013), Iran (Kazemifar et al. 2020), China (Xu et al. 2021), Poland (Rotter et al. 2015), and the US (Pace et al. 2018; Spratlen et al. 2018; Bulka et al. 2019). Most of the previous studies have been conducted on the general population exposed to low level of arsenic (ranges of water arsenic of Wang's and Pace's studies were 0.02–16 µg/L, ≤ 10 µg/L, respectively); however, two studies were conducted in the high-exposure areas in Taiwan (range of water arsenic: 700–900 µg/L) (Chen et al. 2012) and Iran (ranges of water arsenic concentrations: 257–342 µg/L) (Kazemifar et al. 2020). Chen et al. (2012) found that the lower percent of monomethylarsonic acid (%MMA) in the urine, an indicator of the primary methylation ability of arsenic, but not the total urinary arsenic, was associated with the risk of MeS among the residents living in Southwestern Taiwan where arsenic pollution of groundwater occurred decades ago. Kazemifar et al. (2020) also found that the lower %MMA but not percentage of inorganic arsenic in the urine was significantly associated with the increased risk of MeS in the arsenic-exposure area in

Iran. Except two (Wang et al. 2007 and Bulka et al. 2019), other studies (Pace et al. 2018; Spratlen et al. 2018; Rotter et al. 2015; Rhee et al. 2013) conducted on general populations failed to find the associations between arsenic-exposure markers and MeS. Wang et al. (2007) found an association between subjects' hair arsenic levels and the risk of MeS and its components in the general population recruited in industrial areas in Taiwan. Bulka et al. (2019) found a significant association between the urinary arsenic concentrations and the risk of MeS among the general population in the US. However, none of these studies recognized gender differences in the arsenic-associated risk of MeS.

Our study differs from the above-mentioned studies in several points. First, we used both environmental (water arsenic) and individual exposure marker (hair and nail arsenic) to assess the arsenic-exposure levels of the subjects. Most of the previous studies (Spratlen et al. 2018; Bulka et al. 2019; Kazemifar et al. 2020; Chen et al. 2012) used urinary arsenic concentrations as an exposure marker, which reflect temporary or recent exposure to arsenic (Bulka et al. 2019; Watanabe et al. 2001). Hair and nail arsenic concentrations used in our study reflect exposure levels for several months to years (Harkey 1993; Fleckman 1985). Perhaps, because of using of recent exposure marker, the results of the previous studies were inconsistent. Additionally, urinary arsenic concentrations are generally adjusted by the urinary creatinine levels that may mislead the association of arsenic exposure and health outcomes such as obesity (Bulka et al. 2017). Second, the ranges drinking water, hair, and nail arsenic concentrations of our study subjects were 0.03–1006.7 µg/L, 0.02–62.02 µg/g, and 0.05–47.83 µg/g, respectively. These wide variations of arsenic-exposure levels have enabled us to detect more pronounced and dose-dependent effects of arsenic on MeS. Third, the age limit of our subjects was 18–60 years and the average age was only 37 years (Table 1). A majority (approx. 58%) of the subjects were under 40 years of age. The increased risk of MeS observed in our study, thus, suggests that chronic exposure to arsenic may increase the rate of morbidity and mortality from CVDs and DM among relatively young people in arsenic-endemic areas.

The mechanism of the gender difference in the susceptibility to the arsenic-related metabolic disorders remains unclear. The endocrine-disrupting activity of arsenic may be a possible factor involved in the increased susceptibility of the arsenic-exposed women to hyperglycemia. Experimental studies have shown that arsenic disrupts estrogen signaling (Chatterjee and Chatterji 2010; Watson and Yager 2007; Davey et al. 2007). Treatment of female rats with arsenic for 28 days resulted in decreased circulating levels of gonadotropins and estradiol (Chatterjee and Chatterji 2010). Exposure of ovariectomized female mice to arsenic resulted in alterations in glucose metabolism, such as increased blood glucose, decreased insulin, and glucose intolerance, compared with sham-operated female mice, suggesting that estrogen deficiency enhances arsenic-induced disturbances in glucose metabolism (Huang et al. 2015). Despite of the fact, more epidemiological and experimental studies are required to provide further evidence in sex-based distinct mechanisms of CVDs.

There were several limitations of the study that must be addressed. First, the results were limited by cross-sectional study design that couldn't explain the cause-effects relationship between arsenic exposure and MeS. Second, we did not measure the nutritional status of the study participants. The study participants recruited from the rural areas of Bangladesh had socioeconomic and ethnic homogeneity. However, the influence of nutritional factors, such as iron/folate deficiency-related anemia, could not be ignored. Third, we only examined the subjects' arsenic-exposure levels. Other metals such as lead (Rhee et al. 2013) could modify the observed associations of arsenic with MeS. Fourth, all the subjects recruited in our study were mainly from the low socioeconomic group. It may limit the reproducibility of the results with other populations. Fifth, we used drinking water arsenic concentration as an external exposure marker. Not only drinking water, but also consumption of contaminated food, particularly rice has been recognized as one of the important routes of arsenic exposure (Meharg and Rahman 2003; Williams et al. 2006; Meharg et al. 2014). Although in our study, we considered hair and nail arsenic as internal exposure markers, which represent prolonged arsenic exposure at individual levels irrespective of the sources or routes of exposure, future studies are required to examine the contribution of rice arsenic to develop arsenic-related diseases. Despite these limitations, this study for the first time showed the gender-differentiated risk of cardiometabolic disorders caused by chronic arsenic exposure among relatively young people. Gender difference in cardiometabolic disorders is a widespread concern because based on the gender, the strategies for treatment, diagnosis, and prevention should be different (Gerdts and Regitz-Zagrosek 2019). The results of our study are important for policy implications. The study was conducted recruiting subjects from high- and low-exposures areas in Bangladesh. Compared to the low-exposure areas, the prevalence of MeS were much higher in the high-exposure areas that may cause higher rate of morbidity and mortality from cardiovascular diseases—the major causes of death worldwide. Thus, the results of this study warrant immediate attention from policymakers and health professionals in Bangladesh to formulate and undertake effective arsenic-mitigation action.

Conclusion

This study showed that increasing exposure to arsenic increased the prevalence of MeS. Gender was found to be significant modifier in the association between arsenic exposure and MeS. In gender-specific analysis, the prevalence of arsenic-exposure-related MeS were significantly higher in women than those in men. Arsenic exposure in women also showed more precise nature of dose–response relationship with the risk of MeS than in men. Except the risk of hypertriglycerdemia, the risk of other components of MeS such as hyperglycemia and hypo-HDL-cholesterolemia, high blood pressure, and abdominal obesity were more pronounced in arsenic-exposed women than those in men. Taken together our results suggest that women living in arsenic-endemic areas have greater risks for developing CVDs and DM than men. Future studies on the underlying pathophysiologic mechanisms of these diseases concerning gender difference are warranted.

Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval Institute of Biological Sciences (IBSc) (no. 661/320/IAMEBBC/IBSc), University of Rajshahi approved this study.

Consent to participate Written consent from each human subject was taken prior to his/her participation in this study.

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