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RESEARCH ARTICLE

Urinary speciated arsenic and depression among US adults

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Abstract

Arsenic is a naturally occurring chemical in the environment. The International Agency for Research on Cancer (IARC) declared arsenic a class 1 human carcinogen. The inorganic form of arsenic is considered toxic to the human population; arsenic is a neurotoxin and can cause memory dysfunction. Very few studies have investigated the association between exposure to arsenic and depression in humans. The purpose of this study was to assess the association between urinary speciated arsenic and depression among adults in the USA using the 2015–2016 National Health and Nutrition Examination Survey (NHANES) III dataset. Depression was measured using the nine-item Patient Health Questionnaire (PHQ-9). We computed a total depression score from the PHQ-9 and categorized individuals with a score ≥ 10 as depressed. The exposure included six different speciated arsenic concentrations dichotomized as at or above the limit of detection and below the limit of detection. We conducted a crude and multivariate logistic regression analysis using complex survey procedures to assess the association between speciated arsenic concentrations and depression. The sample included 1619 adults, of whom approximately half were females (51.69%) and married (53.29%). Seven percent of the sample had depression. Urinary arsenous acid was significantly associated with depression. In the adjusted model, arsenous acid was associated with depression with an odds ratio of 1.76 (95% CI 1.05–2.96, $p = 0.035$). No other forms of arsenic were significantly associated with depression. In this study, urinary arsenous acid was significantly associated with depression. Future research in humans is required to confirm or refute this finding.

Keywords Arsenic · Urinary speciated arsenic · Depression · Arsenous acid · NHANES III · Chemical

Introduction

Arsenic contamination is a major threat to human health worldwide; the most common exposure is through contaminated food and water. Approximately 200 million people are affected by arsenic-contaminated water globally (Shakoor et al. 2017; IARC 2012). Exposure to arsenic can cause health effects such as reproductive toxicity, neurological effects, peripheral vascular diseases, and skin pigmentation. In addition, arsenic is a known carcinogen and can cause bladder, skin, liver, and lung cancer. Many epidemiological studies have established an association between human exposure to arsenic and different types of cancers (Shankpal et al. 2012).

In humans, contact with arsenic can occur through exposure to organic and inorganic forms of the chemical element. Arsenic is primarily in the inorganic form and then converts to organic arsenic through a biological process. Organic arsenic is less toxic than inorganic arsenic and can be found in aquatic animals and plants such as fish, shellfish, and seaweed (Caldwell et al. 2009). Examples of organic arsenic include arsenobetaine, arsenocholine, and arsenosugars. The most toxic form of arsenic is the trivalent form, which can be detected in human urine (Cohen et al. 2006; Vahter 2002).

Arsenic has been linked to depression and depressive-like behaviors in mouse studies. Studies have suggested this link is due to the carcinogenic potential of arsenic, while others have suggested that arsenic affects brain development and neural function. Mice exposed to high levels of arsenic in the perinatal period had elevated serum corticosterone and elevated dorsal

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hippocampal serotonin $5HT_{1A}$ receptor binding and showed signs of increased learned helplessness. These changes reflect a change in the hypothalamic-pituitary-adrenal axis, which could predispose mice to depression (Martinez et al. 2008).

Few studies have assessed the association between arsenic exposure and depression in humans. Depressive disorders are chronic conditions that severely disable individuals and place a burden on human health worldwide (Opie et al. 2017). According to the World Health Organization, approximately 350 million people suffer from depression worldwide; death and disability due to depression ranked ninth globally. Depression is more prevalent than diseases such as stroke, heart disease, and HIV and is often undiagnosed and untreated worldwide (Smith 2014).

Knowledge gap

The role of arsenic in mental health, such as depression, is unclear. Very few studies have been conducted on arsenic exposure and the risk of depression in the human population. The purpose of this study is to assess the association between urinary speciated arsenic and depression among adults in the USA using the 2015–2016 National Health and Nutrition Examination Survey (NHANES) III dataset.

Methods

Study design

NHANES III is a long-standing study conducted by the National Center for Health Statistics (NCHS) throughout the USA. It combines interviews and physical examinations to determine the health and nutritional status of adults and children (CDC/National Center for Health Statistics 2017). Health examinations are conducted at mobile examination centers (MECs) (CDC/National Center for Health Statistics 2018). Data from NHANES III 2015–2016 "Speciated Arsenic-Urine-Special Sample (UASS_I)" was used in conjunction with NHANES III, 2015–2016 "Mental Health-Depression Screener (DPQ_I)" to analyze a potential relationship between arsenic and depression. Demographic data collected during interviews was reported in the NHANES 2015–2016 "Demographic Variables and Sample Weights (DEMO_I)" Report (CDC 2017b). Due to truncation in the NHANES data, persons aged 80 years or older were classified as a single age group. NHANES was approved by the Research Ethics Review Board of the National Center for Health Statistics. As this is a public-use dataset, this study was exempt from additional review by an institutional review board.

Study population

The study population was selected from the NHANES III 2015–2016 dataset. The NHANES population includes non-institutionalized civilian residents of the USA. Urinary speciated arsenic samples were collected in participants 18 years and older (CDC 2018). The depression screening was also given at the MEC to participants 12 years and older; however, only responses from participants 18 and older were included in the NHANES data file (CDC 2017a). Our data analyses were limited to adults ≥ 20 years of age, with non-missing information for the variables of interest.

Urinary arsenic assessment

The analytes in the speciated arsenic dataset with variable names ending in "LC" were utilized. The concentration of speciated arsenic in urine was determined using inductively coupled plasma dynamic reaction cell-mass spectrometry (ICP-DRC-MS) (CDC 2018). The Urine Arsenic Speciation NHANES 2015–2016 "Laboratory Procedure Manual" can be referred to for a detailed description of the laboratory methods used in the NHANES data (Jones and Pirkle 2016). Urinary arsenic acids were conceptualized as six different arsenic compounds. These variables were dichotomized based on their lower limit of detection (LLOD, in μg/L): "0" indicated that the result was at or above the limit of detection and "1" meant that the result was below the limit of detection. The speciated arsenic was analyzed and the corresponding LLOD were as follows: urinary arsenous acid (0.12 μg/L), urinary arsenic acid (0.79 μg/L), urinary arsenobetaine (1.16 μg/L), urinary arsenocholine (0.11 μg/L), urinary dimethylarsinic acid (1.91 μg/L), and urinary monomethylarsonic acid (0.2 μg/L) (CDC 2018).

Depression assessment

Depression was measured using the Patient Health Questionnaire (PHQ-9), a nine-item screening tool that evaluates the frequency of depression symptoms. Each question is scored based on the frequency of the symptom over the previous 2 weeks. Scores included 0: "not at all," 1: "several days," 2: "more than half the days," or 3: "nearly every day." Responses to each item were summed with 27 being the highest total possible score. This method has high sensitivity and specificity of 88% to detect cases of major depression (Kroenke et al. 2001). A score of ≥ 10 was defined as depression.

Covariates

Covariates included socio-demographic factors such as gender, age category (20 to < 40, 40 to < 65, ≥ 65 years), race/ethnicity

(non-Hispanic white, non-Hispanic black, Mexican-American, other/multiracial), the ratio of family income to federal poverty level, education (< high school diploma, high school diploma or equivalent, some college, college graduate), and marital status. The poverty-to-income ratio (PIR) was calculated as the annual household income divided by the poverty threshold determined annually by the US Department of Health and Human Services. This variable was categorized as follows: < 130, 130–350, > 350% (Bailey et al. 2017).

Statistical analyses

All analyses were weighted using survey design procedures, accounting for the effects of sampling design stratification and clustering procedures. Descriptive statistics were performed to assess the distribution of participants' demographic and socioeconomic status by depression status. Unadjusted logistic regression was used to compute odds ratios (ORs) and 95% confidence intervals (95% CI) for the association between urinary arsenic and depression. Controlling for potential confounders, multivariate logistic regression was used to compute adjusted odds ratios (ORs) and 95% CI for the exposure-disease relationship of interest. Separate models were run for each independent variable. Confounders controlled for in the analyses were variables that were significantly associated with depression in the bivariate analyses. These included the ratio of family income to federal poverty level, education, and marital status. All analyses were conducted using SAS® (version 9.4, Cary, NC).

Results

The study sample was made up of 1619 participants, of whom about half were female (51.69%) and married (53.29%) (Table 1). Approximately 65.32% of participants were non-Hispanic white, 44.23% were aged 40 to < 65 years, and 31.97% were college graduates. Seven percent of the sample had depression. Depressed individuals were more likely to have less than high school education, more likely to have a low family poverty-to-income ratio, and less likely to be married or living with a partner (Table 1).

The proportion of participants with speciated arsenic acid levels at or above the detection limit was as follows: monomethylarsonic acid (53.01%), dimethylarsinic acid

Table 1 Selected demographic characteristics of the study sample by depression status, NHANES 2015–2016

Variable	Overall (%)	Depressed (%)	Not Depressed (%)	*p* values
Age (years)				
20 to < 40	35.32	6.61	93.39	0.935
40 to < 65	44.23	7.22	92.78	
65 and older	20.45	7.19	92.81	
Gender				
Male	48.31	6.55	93.45	0.541
Female	51.69	7.42	92.45	
Race/ethnicity				
Hispanic	15.14	6.81	93.18	0.645
Black, non-Hispanic	10.89	8.49	91.51	
White, non-Hispanic	65.32	7.05	92.95	
Other/multiracial	8.65	5.10	94.89	
Highest level of education				
Less than high school	14.69	12.87	87.13	*0.009*
High school/GED	20.31	8.19	91.81	
Some college/AA degree	33.03	6.74	93.26	
At least college degree	31.97	3.82	96.18	
Family poverty-to-income ratio				
0–< 130%	26.55	11.98	88.02	*< 0.001*
130–350%	35.07	8.15	91.85	
> 350%	38.38	2.50	97.50	
Marital status				
Married	53.29	4.81	95.19	*0.002*
Widowed/divorced/separated	17.98	10.60	89.40	
Never married	18.41	10.68	89.32	
Living with partner	10.32	5.47	94.53	
Total	1619 (100.0%)	131 (7.0%)	1488 (93.0%)	

(66.68%), arsenocholine (14.43%), arsenobetaine acid (45.41%), arsenic acid (1.91%), and arsenous acid (46.77%). Table 2 shows the unadjusted association between urinary arsenic acid and depression. Overall, most of the speciated arsenic acids showed slightly elevated odds of depression at or above the limit of detection, but they were mostly not statistically significant. Only arsenous acid was associated with significantly higher odds of depression (odds ratio and 95% confidence interval 1.69 (1.09–2.62), $p = 0.022$).

Table 3 includes the adjusted odds ratio for the association between urinary arsenic acid and depression, controlling for education, family income to federal poverty level, and marital status. Individuals who had arsenous acid at or above the limit of detection had 76% higher odds of depression than those with arsenous acid below the limit of detection (odds ratio and 95% confidence interval 1.76 (1.05–2.96), $p = 0.035$). Other significant predictors of depression in this study were family poverty-to-income ratio and educational level (results not shown). The results showed a dose-response relationship between family poverty-to-income ratio and the odds of depression. A higher level of education was also associated with significantly lower odds of depression.

Discussion

Metals and chemicals can disrupt the neurological system by altering brain function in addition to affecting the mental health system (Shiue 2015; Tyler and Allan 2014). Learning disorders, attention deficit, aggressiveness, and autism can develop due to metal exposure in humans (Kajta and Wójtowicz 2013). This study assessed the association between arsenic exposure (speciated urinary arsenic concentration) and the risk of developing depression among 1619 US residents aged ≥ 20 years. We found that arsenic exposure was associated with depression. An association between arsenic and depression was reported by Zierold et al. (2004) in a population of arsenic-contaminated well water users. However, the arsenic level was measured by well water concentration rather than urinary arsenic in the individuals. Valdés et al. (2017) established an association between arsenic and post-partum depression, though this study was restricted to women over the age of 25. Also, a recent study linked high maternal arsenic levels to lower brain-derived neurotrophic factor (BDNF), a substance that plays a role in newborn neurodevelopment and maternal depressive disorder (Zaw and Taneepanichskul 2019). In our study, urinary arsenous acid, an inorganic type of arsenic acid, showed a positive statistical association with depression.

Arsenous acid is the "hydroxide" of the arsenic ion and only occurs in aqueous solutions. It has not yet been isolated as a pure material (Jekel and Amy 2006). Arsenous acid is a type of arsenite, which is the most common form of arsenic encountered by humans in the natural environment. Arsenite, naturally from the soil, can leach into drinking water. This type of arsenic compound can be in foods, beverages, water, pharmaceuticals, and pesticide-treated crops. Inorganic arsenicals are the most prominent cause of health issues related to arsenic exposure (McQueen 2010). As expected, other factors that were associated with depression in this study were education and poverty-to-income ratio. Previous studies have shown protective effects of higher education and income level on depression (Bjelland et al. 2008).

Animal studies support the observed effect of arsenic on the risk of depression and other neurological effects such as memory and learning impairment. Chang et al. (2015) conducted a study in mice to assess subchronic arsenic exposure with anxiety- and depression-like behavior in normal mice. The study demonstrated that subchronic arsenic exposure caused anxiety-like behavior in mice and exacerbated depression-like behavior in the depressed mice population. The investigators concluded that arsenic could increase depression symptoms in the human population, which was confirmed in our study. Zhang et al. (2014) examined arsenic associated impairment of memory and learning using a mice model. The mice were exposed to arsenic through drinking water for 60 days. The study observed that the thickness of brain material changed due to arsenic exposure in mice.

Table 2 Unadjusted odds ratios (OR) and 95% confidence intervals (CI) of the association between arsenic and depression, NHANES III 2015–2016

Urinary acid	OR (95% CI)	*p* value
Monomethylarsonic acid (μg/L)	1.16 (0.71–1.90)	0.532
Dimethylarsinic acid (μg/L)	1.00 (0.60–1.68)	1.000
Arsenocholine (μg/L)	1.32 (0.69–2.55)	0.373
Arsenobetaine acid (μg/L)	1.18 (0.703 1.99)	0.502
Arsenic acid (μg/L)	0.50 (0.09–2.89)	0.411
Arsenous acid (μg/L)	*1.69 (1.09–2.62)*	*0.022*

Table 3 Adjusted* odds ratios (OR) and 95% confidence intervals (CI) of the association between arsenic and depression, NHANES III 2015–2016

Urinary Acid	OR (95% CI)	*p* value
Monomethylarsonic acid (μg/L)	1.19 (0.74–1.91)	0.454
Dimethylarsinic acid (μg/L)	1.02 (0.58–1.81)	0.934
Arsenocholine (μg/L)	1.50 (0.76–2.96)	0.220
Arsenobetaine acid (μg/L)	1.18 (0.67–2.08)	0.537
Arsenic acid (μg/L)	0.57 (0.01–3.25)	0.504
Arsenous acid (μg/L)	*1.76 (1.05–2.96)*	*0.035*

*Adjusted for marital status, educational level, and the ratio of family income to poverty

Statistical analysis established a positive association between impairment of memory and learning due to arsenic exposure in mice. Studies also established mild and moderate levels of depression and depression-like behavior in rats, mice, and in vivo cells in laboratory experiments due to arsenic exposure (Martinez et al. 2008; Savabieasfahani et al. 1998). Our study also established a positive statistical association between arsenic exposure and depression in the human population.

As previously noted, metal exposure can cause neurological deficits, including behavior change, depression, and depression-like behavior in the human population (Chang et al. 2015). The same mechanism of action might explain the relationship between arsenic and depression. We analyzed the NHANES III data to assess the relationship between arsenic exposure and the risk of depression in the US adult population. Researchers have also used the NHANES III population to examine the risk of depression due to folate, zinc, copper, selenium, iron, and manganese exposure. Those studies also used PHQ-9 scores to assess depression in the human population (Sun et al. 2018; Li et al. 2017; Nguyen et al. 2017). Their study designs were similar to ours and showed positive associations between metals/chemicals and depression. In this current study, we used the NHANES III population as a representative sample of the US population. As a measure of arsenic exposure from NHANES III laboratory data, we utilized six types of urinary speciated arsenic and assessed depression using the PHQ-9 scale. Studies on humans and the adverse effects of arsenic and depression and other neurological deficits are recommended to confirm or refute our findings.

Strengths and limitations

Our study is one of the very few studies that examined arsenic exposure and depression in the adult population using NHANES data. The population represents different demographics such as age, gender, marital status, ethnicity, and educational level of the US population. One of the limitations of this study is the cross-sectional nature, which limits causal inference. Hence, a longitudinal study design is recommended in order to establish a causal association between arsenic exposure and depression. Other limitations included the sampling method employed by NHANES. NHANES oversamples people 60 years and older, Hispanics, and African Americans to produce reliable statistics. This resulted in slightly different demographics than the composition of that in the USA. The sample only included adults ≥ 20 years; as a result, our findings are only generalizable to adults and do not reflect the effect of arsenic and depression on children in the developmental years. Data from 2015 to 2016 were utilized in this analysis as NHANES has not released the 2017–2018 and 2019–2020 datasets. As a result, we had a smaller sample size, and our findings may not be up-to-date.

Conclusion

Urinary arsenous acid may be associated with depression in the US adult population. There was no significant relationship observed between depression and the following arsenic compounds: urinary arsenic acid, urinary arsenobetaine, urinary arsenocholine, urinary dimethylarsinic acid, or urinary monomethylarsonic acid. Further studies on arsenic toxicity and depression should be considered in the future. Exposure to arsenous acid in humans, an inorganic source of arsenic found naturally in the soil, is associated with depression. Education and awareness of potential sources and the adverse effects of arsenic are critical and should be emphasized, especially in at-risk communities.

Author contributions Humairat H. Rahman created the idea and design of the study and contributed to the introduction and discussion. Korede K Yusuf conducted the data analysis and formulated the methodology. Danielle Niemann contributed to the methods and reviewed the paper. Shariar R Dipon contributed to the discussion.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

This is an analysis using secondary data. Ethical approval is not applicable.

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