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ORIGINAL ARTICLE

The association between heavy metal exposure and erectile dysfunction in the United States

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Literature regarding the impacts of heavy metal exposure on erectile dysfunction (ED) is scarce. We aimed to evaluate the correlation between 10 urinary metals and ED in a large, nationally representative adult male sample. The dataset was extracted from the National Health and Nutrition Examination Survey (NHANES) during the period of 2001–2002 and 2003–2004. Weighted proportions and multivariable logistic regression analysis adjusted for confounding variables were utilized to determine the relationship between metal exposure and ED. Weighted quantile sum (WQS) regression was utilized to evaluate the impact of a mixture of urinary metals on ED. A total of 1328 participants were included in our study. In multivariable logistic regression analysis, cobalt (Co) and antimony (Sb) were positively associated with ED (odds ratio [OR]: 1.36, 95% confidence interval [CI]: 1.10–1.73, *P* = 0.020; and OR: 1.41, 95% CI: 1.12–1.77, *P* = 0.018, respectively) after full adjustment. Men in tertile 4 for Co (OR: 1.49, 95% CI: 1.02–2.41, *P* for trend = 0.012) and Sb (OR: 1.53, 95% CI: 1.08–2.40, *P* for trend = 0.041) had significantly higher odds of ED than those in tertile 1. Furthermore, the WQS index was significantly linked with increased odds of ED after full adjustment (OR: 1.31, 95% CI: 1.04–1.72, *P* < 0.05). Our study expanded on previous literature indicating the possible role of heavy metal exposure in the etiology of ED. The evaluation of heavy metal exposure should be included in the risk assessment of ED.

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INTRODUCTION

Erectile dysfunction (ED) is one of the most common disorders that primarily affects men over the age of 40 years. The prevalence rate of ED varies from 1% to 10% in men aged <40 years,[1] and this rate increases to 52% in men who are aged 40 years or older.[2] In addition, ED prevalence is projected to be 322 million worldwide in 2025.[3] The economic burden of ED increases with the aging of the male population, and the expenditures are estimated to be 15 billion US dollars if all patients seek medical attention or take ED medication.[4] Although ED is not life-threatening, it has a detrimental impact on sexual intimacy[5] and might be a harbinger of cardiovascular disease.[6,7] The intimate association between ED and cardiovascular disease highlights many common risk factors, including a sedentary lifestyle, lack of physical exercise, hyperlipidemia, hypertension, obesity, diabetes, and smoking.[8,9] Furthermore, medications that are utilized to treat hypertension (diuretics and beta-blockers) have also been linked with ED.[10]

Heavy metals are a class of pollutants that ubiquitously exist in air, water, soil, food and cigarettes.[11] Heavy metal exposure can lead to oxidative stress, DNA damage, and lipid peroxidation.[12] Accumulating evidence demonstrates that exposure to heavy metals might increase the risks of obesity, kidney dysfunction, diabetes, neurodevelopmental disorders, cardiovascular diseases, and cancer.[13–15] However, literature regarding the relationship between heavy metal exposure and ED is scarce.[16,17] A previous study with a small sample size (34 ED patients) found that the ED group had a significantly higher blood lead (Pb) level than the control group.[16] Another study published by Musa Obadia *et al*.[17] reported that 54% of men with ED were engaged in mining-related jobs. The small explorative study (42 men) indicated the critical role of mining-related jobs in ED but failed to determine the links between specific metal exposure and ED.[17]

Given the uncertainty in the relationship between heavy metal exposure and ED, our study aimed to evaluate the correlation between several common heavy metals including barium (Ba), cadmium (Cd), cobalt (Co), cesium (Cs), molybdenum (Mo), Pb, antimony (Sb), thallium (Tl), tungsten (W), and uranium (U), as measured in urine, and the presence of ED in 1328 participants from the National Health and Nutrition Examination Survey (NHANES) during the period of 2001–2002 and 2003–2004.

PARTICIPANTS AND METHODS

Data source and study population

The NHANES is a population-based program conducted by the National Center of Health Statistics for the Centers for Disease Control and Prevention (CDC) in the USA. The surveys are utilized to evaluate

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Table 1: Baseline characteristics of the participants with or without a history of erectile dysfunction from the National Health and Nutrition Examination Survey participants during the period of 2001–2002 and 2003–2004

Characteristic	*History of erectile dysfunction*		*P*
	No	*Yes*	
Participants (*n*)	931	397	
Age (year), mean±s.d.	41.3±13.4	62.4±15.1	<0.001
Race, *n* (%)			0.058
Mexican American	80 (8.6)	29 (7.3)	
Other Hispanic	31 (3.3)	28 (7.1)	
Non-Hispanic White	688 (73.9)	295 (74.4)	
Non-Hispanic Black	98 (10.5)	35 (8.7)	
Other race	35 (3.7)	10 (2.5)	
Family income-to-poverty ratio, *n* (%)			0.036
<1.5	153 (16.4)	87 (22.0)	
1.5–3.5	290 (31.1)	139 (35.0)	
Over 3.5	448 (48.1)	153 (38.6)	
Missing	40 (4.4)	18 (4.4)	
Education level, *n* (%)			<0.001
Less than high school	130 (14.0)	109 (27.5)	
High school	289 (31.0)	89 (22.4)	
Above high school	512 (55.0)	199 (50.1)	
Marital status, *n* (%)			0.164
Married or living with a partner	656 (70.5)	301 (75.8)	
Living alone	275 (29.5)	96 (24.2)	
BMI (kg m^{-2}), *n* (%)			0.005
BMI <20	33 (3.5)	15 (3.8)	
BMI ≥20 and BMI <25	239 (25.7)	89 (22.4)	
BMI ≥25 and BMI <30	423 (45.4)	153 (38.5)	
BMI ≥30	227 (24.4)	127 (32.0)	
Missing values	9 (1.0)	13 (3.3)	
Alcohol intake, *n* (%)			0.002
Nondrinker	655 (70.3)	320 (80.6)	
Light drinker	114 (12.2)	30 (7.5)	
Heavy drinker	103 (11.1)	19 (4.8)	
Missing values	59 (6.4)	28 (7.1)	
Smoking, *n* (%)			<0.001
Nonsmoker	394 (42.3)	143 (36.0)	
Former smoker	248 (26.7)	179 (45.1)	
Current smoker	289 (31.0)	75 (18.9)	
Serum cotinine (ng ml^{-1}), mean±s.d.	78.5±142.5	44.6±104.9	<0.001
Moderate physical activity status, *n* (%)			<0.001
Yes	581 (62.4)	191 (48.1)	
No	350 (37.6)	206 (51.9)	
Vigorous physical activity status, *n* (%)			<0.001
Yes	404 (43.4)	75 (18.8)	
No	527 (56.6)	322 (81.2)	
History of cardiovascular disease, *n* (%)			<0.001
Yes	33 (3.5)	82 (20.7)	
No	898 (96.5)	315 (79.3)	
History of diabetes, *n* (%)			<0.001
Yes	29 (3.1)	90 (22.7)	
No	902 (96.9)	307 (77.3)	
History of hypertension, *n* (%)			<0.001
Yes	245 (26.3)	226 (56.9)	
No	686 (73.7)	171 (43.1)	
History of high cholesterol, *n* (%)			<0.001
Yes	317 (34.0)	206 (51.9)	
No	614 (66.0)	191 (48.1)	

The values are presented as weighted means±s.d. or unweighted counts (weighted%). s.d.: standard deviation; BMI: body mass index

Contd..

Table 1: Contd...

the health and nutritional information of adults and children. This study used deidentified publicly available data not requiring ethical review. The current study was conducted using data from the cycles of the NHANES (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx; last accessed on April 27, 2022) during the period of 2001–2002 and 2003–2004, as questionnaire data regarding ED were available only for those years.

Assessment of ED

ED was assessed with the following question from the Massachusetts Male Aging Study:[18] "Many men experience problems with sexual intercourse. How would you describe your ability to get and keep an erection adequate for satisfactory intercourse?" The response options were provided as "always or almost always able", "usually able", "sometimes able", and "never able". In our study analysis, the definition of ED was "sometimes able" or "never able" to keep an erection as validated previously.[19] Participants who answered "almost always able" or "usually able" to maintain an erection were regarded as not having ED. In this study, we excluded 27 participants who refused to answer the question, 59 participants who responded with "don't know", and 459 participants with missing data on ED.

Measurement of urinary metal levels

A total of 12 metals, including Ba, beryllium (Be), Cd, Co, Cs, Mo, Pb, platinum (Pt), Sb, Tl, W and U, were detected in the participants' urine sample by plasma-mass spectrometry. The standard laboratory procedures are available on the NHANES website. Metal concentrations lower than the limit of detection (LOD) were replaced with LOD/$\sqrt{2}$ to increase the statistical power and precision of the effect estimates.[18] We adjusted the urinary dilution by dividing each metal by the grams of creatinine per liter of urine (μg per g creatinine). All urinary metal concentrations were adjusted for $\log_2$ transformation to reduce the skewness of values.

Covariates

Based on the previous studies, potential variables confounding the relationship between metal exposure and ED were included in the multivariable models.[20,21] The covariates were age, race, body mass index (BMI), the family income-to-poverty ratio, education level, marital status, alcohol intake, smoking status, physical activity status, cardiovascular disease, diabetes, hypertension, and high cholesterol. The family income-to-poverty ratio was classified as lower than 1.5, 1.5–3.5, and over 3.5.[22] Alcohol intake was categorized as none (<1 drink per week), light (1–3 drinks per week), and heavy (4 drinks or more per week).[23] Serum cotinine was utilized as an indicator of exposure to environmental tobacco smoke. Individuals were considered as current smokers if they smoked more than 100 cigarettes in their entire life, reported smoking every day or some days at the time of the interview, and had a cotinine level ≥10 ng ml^{-1}. Men who had smoked more than 100 cigarettes in their entire life but were not smoking at the time of the interview were regarded as former smokers. Men who had smoked less than 100 cigarettes in

their entire life were considered nonsmokers. Physical activity status was determined based on the answers to the question regarding whether the individuals participated in moderate or vigorous activity during the past month. Men who reported a previous diagnosis of angina, heart attack, or coronary heart disease were considered to have cardiovascular disease. Those who had a prior diagnosis of diabetes or a fasting plasma glucose level ≥126 mg dl^{-1} were regarded as having a diabetics diagnosis. Four readings of systolic and diastolic blood pressure on 2 separate occasions were obtained from the participants. The average of these 4 measurements (≥140/90 mmHg), a prior diagnosis of high blood pressure, or the self-reported use of antihypertensive medication was considered as hypertension. The definition of hypercholesterolemia was a total cholesterol level ≥240 mg dl^{-1}, a prior diagnosis of "high cholesterol", or the self-reported use of a cholesterol-lowering medication.

Statistical analyses

Continuous variables were expressed as the mean ± standard deviation (s.d.), and categorical variables were presented as proportions. We utilized sampling weights as well as strata and primary sampling units to account for the selective bias, nonresponse, and oversampling of certain subpopulations. Student's *t*-test and Chi-square tests were utilized to evaluate the diversity of characteristics between individuals with or without a history of ED. The multivariate models included the nonadjusted Crude model, minimally adjusted Model 1 (only age, race, and BMI were adjusted), and fully adjusted Model 2 (age, race, the family income-to-poverty ratio, education level, marital status, BMI, alcohol intake, smoking status, physical activity status, cardiovascular disease, diabetes, hypertension, and high cholesterol were adjusted). The effects of a mixture of urinary metals on ED were determined with the weighted quantile sum (WQS) regression as previously described.[24] Briefly, the WQS index (ranging from 0 to 1 and summing to 1) was obtained by bootstrap sampling. The WQS regression model was also adjusted for all potential confounding variables.

We also performed additional analyses. We categorized the urinary metal levels into four clinically relevant categories as ordinal categorical variables (first to fourth, setting the first as a reference) to examine potential trends in the association. Missing values were input by the median (continuous variables) or mode (categorical variables) of existing cases of that variable. All statistical analyses were performed using the software packages R (http://www.R-project.org; The R Foundation, Vienna, Austria) and Empower (www.empowerstats.com). Two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

A total of 1328 participants were included in our study. The demographic data of the participants are demonstrated in **Table 1**. Men with ED were older and were more likely to have a lower socioeconomic status, be less educated, have a BMI higher than 30 kg m^{-2}, be a former smoker, and be lacking in exercise (all $P < 0.05$). The ED group also tended to have a history of cardiovascular disease, diabetes, hypertension, and high cholesterol (all $P < 0.001$; **Table 1**).

Table 2 presents the distributions of blood and urine metals concentrations, including the detection rate, the median, and the interquartile range. All metals values were detectable in >80% of the participants' samples, except for Be (0.94%) and Pt (0.40%), which were excluded from our analysis as more than 99% of the values were lower than the LOD (**Table 2**).

Table 3 shows the links between urinary heavy metals and ED. In the crude model, Ba, Cd, Co, Cs, Mo, Pb, and Sb were demonstrated to negatively impact erectile function. After full adjustment, Co and Sb were still positively associated with ED (odds ratio [OR]: 1.36, 95% confidence interval [CI]: 1.10–1.73, $P = 0.020$; and OR: 1.41, 95% CI: 1.12–1.77, $P = 0.018$, respectively).

Furthermore, we converted the urinary metal concentrations from continuous variables to categorical variables (tertiles), as shown in **Table 4**. The positive associations among Co, Sb, and ED remained statistically significant after variables conversion. After full adjustment, men in Co tertile 4 had a 49% increased risk of developing ED than those in the lower tertile (tertile 1; OR: 1.49, 95% CI: 1.02–2.41, P for trend = 0.012). Moreover, participants with the urinary Sb concentrations in the highest tertile had a 53% higher risk of developing ED (OR: 1.53, 95% CI: 1.08–2.40, P for trend = 0.041).

WQS regression was utilized to evaluate the impact of a mixture of urinary metals on ED. The WQS index was significantly linked with ED after full adjustment (OR: 1.31, 95% CI: 1.04–1.72, $P < 0.05$). **Figure 1** reveals that Co (53.1%), U (34.3%), Sb (9.0%), and Pb (3.6%) were contributors to the association between exposure to multiple metals and ED.

DISCUSSION

To date, this is the first epidemiological study to determine the relationship between heavy metals exposure and ED. We found that Co and Sb exposures were linked with an increased risk of ED after full adjustment for all potential confounding variables (OR: 1.36, 95% CI: 1.10–1.73, $P = 0.020$; and OR: 1.41, 95% CI: 1.12–1.77,

Table 2: Distributions of urine metals in the study population

Urinary heavy metals	*Detection rate (%)*	*Median (μg l^{-1})*	*Interquartile range (μg l^{-1})*
Barium (Ba)	92.81	1.47	0.69–2.68
Beryllium (Be)	0.94	0.09	0.08–0.09
Cadmium (Cd)	91.11	0.31	0.17–0.59
Cobalt (Co)	96.29	0.33	0.21–0.48
Cesium (Cs)	100.00	5.41	3.40–7.82
Molybdenum (Mo)	99.88	50.2	28.5–81.2
Lead (Pb)	100.00	0.90	0.50–1.50
Platinum (Pt)	0.40	0.05	0.03–0.05
Antimony (Sb)	81.76	0.12	0.07–0.17
Thallium (Tl)	99.26	0.19	0.11–0.26
Tungsten (W)	82.69	0.07	0.03–0.13
Uranium (U)	81.19	0.008	0.004–0.016

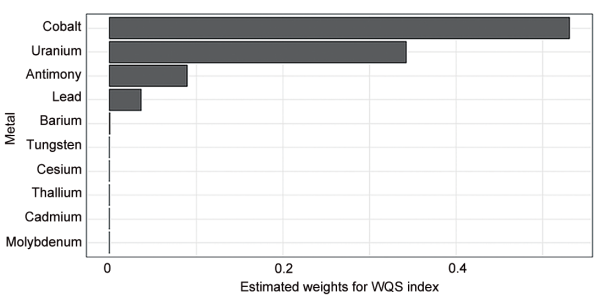

Figure 1: The WQS regression model estimated the weights of each of the ten metals associated with ED. WQS: weighted quantile sum; ED: erectile dysfunction.

Table 3: Association between urinary heavy metals (continuous variable) and erectile dysfunction among USA males from the National Health and Nutrition Examination Survey during the period of 2001–2002 and 2003–2004

Metal	*Crude model*		*Model 1*		*Model 2*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*
Barium (Ba)	1.25 (1.11–1.42)	0.001	1.10 (0.89–1.36)	0.394	1.06 (0.87–1.29)	0.674
Cadmium (Cd)	1.79 (1.53–2.07)	<0.001	1.78 (1.60–2.00)	<0.001	1.04 (0.81–1.36)	0.779
Cobalt (Co)	2.07 (1.71–2.52)	<0.001	1.38 (1.12–1.71)	0.007	1.36 (1.10–1.73)	0.020
Cesium (Cs)	1.45 (1.15–1.84)	0.005	0.96 (0.66–1.39)	0.820	1.06 (0.72–1.55)	0.825
Molybdenum (Mo)	1.46 (1.27–1.69)	0.001	1.11 (0.91–1.36)	0.314	1.09 (0.88–1.35)	0.576
Lead (Pb)	1.53 (1.33–1.76)	0.001	0.92 (0.75–1.13)	0.437	0.97 (0.77–1.21)	0.836
Antimony (Sb)	1.16 (1.02–1.35)	0.038	1.37 (1.11–1.71)	0.009	1.41 (1.12–1.77)	0.018
Thallium (Tl)	0.80 (0.62–1.04)	0.107	0.80 (0.58–1.09)	0.165	0.91 (0.65–1.28)	0.691
Tungsten (W)	1.07 (0.96–1.18)	0.223	1.13 (0.99–1.30)	0.085	1.06 (0.92–1.23)	0.550
Uranium (U)	1.07 (0.94–1.23)	0.312	1.06 (0.86–1.29)	0.607	1.02 (0.84–1.24)	0.852

Crude model: nonadjusted model; Model 1: adjusted for age, race and BMI; Model 2: adjusted for age, race, the family income-to-poverty ratio, education level, marital status, BMI, alcohol intake, smoking status, physical activity status, cardiovascular disease, diabetes, hypertension and high cholesterol. OR: odds ratio; CI: confidence interval; BMI: body mass index

Table 4: Association between urinary heavy metals (categorical variable) and erectile dysfunction among USA males from the National Health and Nutrition Examination Survey during the period of 2001–2002 and 2003–2004

Metals	*Q1, OR (95% CI)*	*Q2, OR (95% CI)*	*Q3, OR (95% CI)*	*Q4, OR (95% CI)*	*P for trend*
Barium (Ba)					
Crude model	1.00 (reference)	1.89 (1.30–2.75)	2.84 (1.97–4.09)	2.77 (1.92–3.99)	<0.001
Model 1	1.00 (reference)	1.03 (0.65–1.64)	1.27 (0.81–2.00)	1.25 (0.79–1.97)	0.226
Model 2	1.00 (reference)	1.05 (0.65–1.70)	1.14 (0.71–1.82)	1.17 (0.73–1.88)	0.472
Cadmium (Cd)					
Crude model	1.00 (reference)	2.90 (1.88–4.48)	5.10 (3.35–7.76)	7.32 (4.83–11.10)	<0.001
Model 1	1.00 (reference)	1.24 (0.73–2.11)	1.06 (0.63–1.80)	1.19 (0.70–2.03)	0.730
Model 2	1.00 (reference)	1.33 (0.76–2.30)	1.08 (0.61–1.90)	1.11 (0.60–2.05)	0.920
Cobalt (Co)					
Crude model	1.00 (reference)	1.52 (1.04–2.24)	2.51 (1.73–3.63)	4.00 (2.78–5.75)	<0.001
Model 1	1.00 (reference)	1.27 (0.79–2.02)	1.58 (0.99–2.50)	1.49 (0.94–2.36)	0.070
Model 2	1.00 (reference)	1.36 (0.83–2.22)	1.63 (1.02–2.62)	1.49 (1.02–2.41)	0.012
Cesium (Cs)					
Crude model	1.00 (reference)	1.62 (1.13–2.32)	1.94 (1.36–2.76)	2.22 (1.56–3.15)	<0.001
Model 1	1.00 (reference)	1.32 (0.82–2.11)	1.12 (0.70–1.82)	0.96 (0.60–1.55)	0.511
Model 2	1.00 (reference)	1.35 (0.83–2.21)	1.21 (0.73–2.01)	1.03 (0.62–1.70)	0.724
Molybdenum (Mo)					
Crude model	1.00 (reference)	1.29 (0.91–1.83)	1.37 (0.97–1.94)	1.91 (1.36–2.68)	<0.001
Model 1	1.00 (reference)	1.06 (0.69–1.63)	1.21 (0.79–1.87)	0.98 (0.64–1.51)	0.926
Model 2	1.00 (reference)	1.11 (0.71–1.73)	1.18 (0.75–1.85)	0.88 (0.56–1.38)	0.616
Lead (Pb)					
Crude model	1.00 (reference)	1.39 (0.96–2.04)	2.14 (1.49–3.07)	3.51 (2.46–5.01)	<0.001
Model 1	1.00 (reference)	0.69 (0.43–1.11)	0.77 (0.49–1.22)	0.96 (0.61–1.54)	0.758
Model 2	1.00 (reference)	0.84 (0.51–1.39)	0.92 (0.56–1.52)	1.17 (0.70–1.97)	0.349
Antimony (Sb)					
Crude model	1.00 (reference)	1.19 (0.84–1.69)	1.73 (1.23–2.42)	1.26 (0.89–1.79)	0.053
Model 1	1.00 (reference)	1.24 (0.81–1.91)	1.50 (0.98–2.29)	1.45 (0.94–2.22)	0.061
Model 2	1.00 (reference)	1.30 (0.83–2.04)	1.62 (1.04–2.52)	1.53 (1.08–2.40)	0.041
Thallium (Tl)					
Crude model	1.00 (reference)	0.89 (0.57–1.11)	0.69 (0.50–0.96)	0.68 (0.49–0.95)	0.017
Model 1	1.00 (reference)	0.87 (0.57–1.32)	0.73 (0.47–1.11)	0.61 (0.40–1.12)	0.130
Model 2	1.00 (reference)	1.01 (0.65–1.56)	0.82 (0.53–1.28)	0.67 (0.43–1.23)	0.460
Tungsten (W)					
Crude model	1.00 (reference)	1.13 (0.81–1.58)	1.06 (0.76–1.49)	1.07 (0.76–1.51)	0.781
Model 1	1.00 (reference)	1.24 (0.81–1.90)	1.06 (0.70–1.61)	1.28 (0.84–1.94)	0.397
Model 2	1.00 (reference)	1.14 (0.74–1.77)	0.97 (0.63–1.50)	1.11 (0.72–1.72)	0.838
Uranium (U)					
Crude model	1.00 (reference)	1.23 (0.87–1.73)	1.20 (0.85–1.69)	1.46 (1.04–2.05)	0.041
Model 1	1.00 (reference)	1.28 (0.84–1.97)	1.18 (0.76–1.82)	1.31 (0.83–2.05)	0.323
Model 2	1.00 (reference)	1.37 (0.87–2.13)	1.24 (0.79–1.95)	1.26 (0.79–2.00)	0.453

Crude model: nonadjusted model; Model 1: adjusted for age, race and BMI; Model 2: adjusted for age, race, the family income-to-poverty ratio, education level, marital status, BMI, alcohol intake, smoking status, physical activity status, cardiovascular disease, diabetes, hypertension and high cholesterol. Q1–4: tertile 1–4; OR: odds ratio; CI: confidence interval; BMI: body mass index

$P = 0.018$, respectively). This positive association remained statistically significant after conversion of the variables from continuous to categorical variables. Men in tertile 4 for Co and Sb had significantly higher risks of ED (49% and 53%, respectively) than those in tertile 1. Furthermore, the WQS index was significantly linked with ED after full adjustment (OR: 1.31, 95% CI: 1.04–1.72, $P < 0.05$).

Co is an essential trace metal that acts as the metallic constituent of vitamin B_{12} in humans. Generally, Co is mixed with other metals and utilized as trace element additives in medicine and agriculture. Occupational exposure mainly occurs via inhalation in the electroplating industry and occupations involved in the production and processing of metals. A common source of Co exposure in the general population is the ingestion of polluted food. In addition, individuals can also be exposed to Co in daily life when they come into contact with glass, paint, and ceramics.[25] In nonoccupationally exposed individuals, the concentration of Co in urine ranged from 0.35 μg l^{-2} to 0.68 μg l^{-2}.[26,27] Exposure to high Co levels can lead to asthma, dermatitis, cardiomyopathy, and cardiovascular disease.[28,29] Zhu *et al*.[29] included 3389 participants in their study and found that men in Co tertile 4 had a significantly higher risk (74%) of cardiovascular disease than those in the tertile 1 (OR: 1.74, 95% CI: 1.28–2.35). In the current study, the urinary concentrations of Co in tertile 1 and 3 were 0.21 μg l^{-1} and 0.48 μg l^{-1}, respectively (**Table 2**). Our results revealed that Co was positively associated with ED after full adjustment (OR: 1.36, 95% CI: 1.10–1.73, $P = 0.020$). This positive association remained statistically significant when we converted the Co concentration from a continuous variable to a categorical variable. The underlying mechanism of this association might be attributed to mitochondrial respiratory and oxidative stress. Chimeh *et al*.[30] reported that cell viability decreased along with inhibition of mitochondrial enzymes and the production of reactive oxygen species following Co chloride ($CoCl_2$) treatment. As the Co concentration increased, mitochondrial respiration and nonmitochondrial oxygen consumption decreased and further contributed to Co^{2+}-induced oxidative stress via induction of reactive oxygen species.[31] The increased generation of reactive oxygen species can lead to the impairment of cavernosal relaxation and penile endothelial dysfunction, which form the pathophysiology of ED.[32]

Sb is a silvery-white metal that naturally occurs as a trace element. Sb is utilized in the manufacture of batteries, solder, sheets, plastics, rubbers, and even the production of medinines.[33] Occupational exposure occurs in those who are engaged in the production of Sb, metal mining, metal refining, and coal-fired power plants. The general population can also be exposed to a low level of Sb from food, air, and drinking water.[34] Iyengar *et al*.[35] reported that the general population is exposed to measurable levels of Sb (approximately 5 μg per day) in their daily life. The reference value for Sb in urine for the general population was 0.17 μg l^{-1}.[36] Chronic exposure to Sb is associated with increased risks of pneumoconiosis, increased blood pressure, and dermatitis.[33] In our study, the urinary concentrations of Sb in tertile 1 and 3 were 0.07 μg l^{-1} and 0.17 μg l^{-1}, respectively (**Table 2**). We found that Sb exposure was linked with an increased risk of ED after full adjustment. Men in Sb tertile 4 had a 53% increased risk of developing ED than those in tertile 1. Bento *et al*.[37] reported an increase of oxidative stress in several organs of mice after treatment with meglumine antimoniate. They observed that meglumine antimoniate caused significant protein carbonylation and lipoperoxidation. Meglumine antimoniate also led to the production of reactive oxygen, which might negatively affect erection. Similarly, Wan *et al*.[38] demonstrated that Sb exposure can induce oxidative stress, which further activated autophagy and pyroptosis via reactive oxygen species pathways.

Our study had several limitations. First, the NHANES is a cross-sectional database that precludes the inference of causality. Thus, further prospective studies are needed to validate our results. Second, the diagnosis of ED was based on a self-report questionnaire, which might underestimate the actual number of ED patients. Nevertheless, the validity of the single self-report question has been previously tested with the area under the curve of 0.89.[19] Unfortunately, we were unable to assess the degree of erectile function. Third, a single measurement of urinary metal concentration might deviate from the long-term chronic exposure to metals. Finally, our analysis was conducted only based on the USA population; thus, whether the conclusion we draw applies to other populations remains to be determined. However, this is the first study to determine the association between heavy metal exposure and ED. We conducted a sensitivity analysis, and the associations remained statistically significant. The impact of a mixture of urinary metals on ED was also determined in our study.

CONCLUSIONS

In summary, our results demonstrated the possible roles of Co and Sb exposure in the pathogenesis of ED. The evaluation of heavy metal exposure should be included in the risk assessment of ED. Further studies are needed to elucidate the underlying mechanism.

AUTHOR CONTRIBUTIONS

WW and JHY proposed the conception and design. LYX, YCM, and JWC provided administrative support. LYX, LP, and XSG supplied the study materials. FXZ and YX collected and assessed the data. LYX and FQ analyzed the data. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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