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Metals in Urine and Diabetes in U.S. Adults

Our objective was to evaluate the relationship of urine metals including barium, cadmium, cobalt, cesium, molybdenum, lead, antimony, thallium, tungsten, and uranium with diabetes prevalence. Data were from a cross-sectional study of 9,447 participants of the 1999–2010 National Health and Nutrition Examination Survey, a representative sample of the U.S. civilian noninstitutionalized population. Metals were measured in a spot urine sample, and diabetes status was determined based on a previous diagnosis or an A1C ≥6.5% (48 mmol/mol). After multivariable adjustment, the odds ratios of diabetes associated with the highest quartile of metal, compared with the lowest quartile, were 0.86 (95% CI 0.66–1.12) for barium (P_{trend} = 0.13), 0.74 (0.51–1.09) for cadmium (P_{trend} = 0.35), 1.21 (0.85–1.72) for cobalt (P_{trend} = 0.59), 1.31 (0.90–1.91) for cesium (P_{trend} = 0.29), 1.76 (1.24–2.50) for molybdenum (P_{trend} = 0.01), 0.79 (0.56–1.13) for lead (P_{trend} = 0.10), 1.72 (1.27–2.33) for antimony (P_{trend} < 0.01), 0.76 (0.51–1.13) for thallium (P_{trend} = 0.13), 2.18 (1.51–3.15) for tungsten (P_{trend} < 0.01), and 1.46 (1.09–1.96) for uranium (P_{trend} = 0.02). Higher quartiles of barium, molybdenum, and antimony were associated with greater HOMA of insulin resistance after adjustment. Molybdenum, antimony, tungsten, and uranium were positively associated with diabetes, even at the relatively low levels seen in the U.S. population. Prospective studies should further evaluate metals as risk factors for diabetes.

The general population is commonly exposed to low levels of metals through food, water, and ambient air. In general population studies, lead and cadmium were associated with numerous health outcomes including increased all-cause, cardiovascular, and cancer mortality (1–6). Although exposure to other metals at high levels is also associated with adverse outcomes, relatively few studies have investigated the impact of metal exposure at the chronic low levels that occur in the general population (7,8). In addition, few studies have investigated whether environmental exposure to metals is associated with diabetes. Several population-based studies found an association between cadmium and diabetes (9,10), but this association was not consistent in all studies (11). Previous studies examining the relationship between environmental lead exposure and diabetes were also inconsistent (11–15). A previous study using data from the National Health and Nutrition Examination Survey (NHANES) found that arsenic was associated with the prevalence of diabetes (16). The association between environmental exposure to most other metals and diabetes has not been studied.

Metals without any known biological function can affect the body by substituting for essential metals, such as iron, zinc, and/or potassium (17,18). Some metals may affect health through endocrine disruption (19,20). Additionally, metals can catalyze oxidative stress reactions, and the resulting oxidative stress may decrease insulin gene promoter activity and insulin mRNA expression in islet β-cells (17). The β-cells may be particularly prone to metal-induced oxidative stress due to a high expression of metal transporters and low expression of antioxidants (17). Metals are also associated with obesity. A previous study found that some metals were positively associated (barium and thallium), some were negatively associated (cadmium, cobalt, cesium, and lead), and others were not associated (molybdenum,

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antimony, and tungsten) with BMI and waist circumference (8).

We evaluated the relationship of urine metals including barium, cadmium, cobalt, cesium, molybdenum, lead, antimony, thallium, tungsten, and uranium with the prevalence of diabetes using data from the 1999–2010 NHANES, a representative sample of the U.S. civilian noninstitutionalized population.

RESEARCH DESIGN AND METHODS

Study Population

NHANES 1999–2010 is a series of stratified, multistage probability surveys designed to be representative of the civilian, noninstitutionalized U.S. population (21). Data were collected in six phases (1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, and 2009–2010). NHANES 1999–2010 measured a panel of urine metals in a random subset of approximately one-third of participants, an analytic group capable of producing nationally representative data. Of 30,752 adults ≥20 years of age who participated in the interview and examination, 10,074 were included in the urine metals subset. We excluded 469 pregnant women and 158 participants missing urine metals data, resulting in a final sample of 9,447 participants.

The protocol for the 1999–2010 NHANES was approved by the National Center for Health Statistics of the Centers for Disease Control and Prevention research ethics board. All participants gave written informed consent.

Data Collection

Data for NHANES 1999–2010 were collected during an in-home interview and a subsequent visit to a mobile examination center (21). Standardized questionnaires were used to collect information regarding age, race/ethnicity, sex, menopause status (among women), education, household income, and smoking status during the in-home interview. Also, total calories consumed and percent of calories from saturated fat were ascertained using a 24-h recall. During the visit to the mobile examination center, waist circumference was measured. Height and weight were measured, and BMI (weight in kilograms divided by the square of height in meters) was calculated. A trained phlebotomist obtained a blood sample according to a standardized protocol, and serum C-reactive protein (CRP) was measured using latex-enhanced nephelometry, a high-sensitivity assay. Alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT) activities were measured and categorized as normal or elevated using cut points of ALT >43 units/L for men or >31 units/L for women and GGT >58 units/L for men or >35 units/L for women. These liver enzyme cut points were the 95th percentiles among persons with low risk for liver injury (negative for hepatitis C virus antibody and hepatitis B virus surface antigen, alcohol consumption ≤2 drinks/day for men and ≤1 drink/day for women, BMI <25 kg/m^2, waist circumference ≤102 cm for men and ≤88 cm for women, no provider-diagnosed diabetes, and A1C <6.5%) (22).

Participants provided a casual (or spot) urine specimen collected using materials confirmed to be uncontaminated by metals. We used in our analyses the metals measured in urine samples at the Environmental Health Sciences Laboratory of the Centers for Disease Control and Prevention and the National Center for Environmental Health by inductively coupled plasma mass spectrometry using a multielement analytic technique (22). We included barium, cadmium, cobalt, cesium, molybdenum, lead, antimony, thallium, tungsten, and uranium (uranium for 2001–2010 only). These metals were selected by the Centers for Disease Control and Prevention as part of their biomonitoring activities (they identify levels of metals likely to reflect environmental exposure). Beryllium and platinum were also measured, but most participants had levels below the limit of detection, and the metals were excluded from the analysis. Urine Standard Reference Material 2670 from the National Institute of Standards and Technology was used for external calibration. In addition, the laboratory prepared spiked pools for internal quality control. Quality-control samples incorporated bench and blind samples. The interassay coefficient of variation ranged from 1.4% to 7.2% for barium, 1.3% to 6.7% for cadmium, 1.8% to 6.0% for cobalt, 1.5% to 9.2% for cesium, 0.6% to 5.6% for molybdenum, 1.0% to 7.4% for lead, 1.3% to 6.2% for antimony, 1.2% to 8.5% for thallium, 1.1% to 5.9% for tungsten, and 4.9% to 12.7% for uranium. The limits of detection and percentage below the limit of detection are presented in the Supplementary Data (Supplementary Table 1). Participants with values below the limit of detection were assigned a value equal to the limit of detection divided by the square root of 2.

A1C was measured using a Primus Automated HPLC system (Primus Corporation, Kansas City, MO) in the 1999–2004 NHANES, and the interassay coefficient of variation was 1.0–2.0%; the respective equipment and coefficients of variation were an A1c 2.2 Plus Glycohemoglobin Analyzer (Tosoh Medics, Inc., San Francisco, CA) and 1.0–1.7% in NHANES 2005–2006 and an A1c G7 HPLC Glycohemoglobin Analyzer (Tosoh Medics, Inc.) and 0.7–1.5% in NHANES 2007–2012. Although different equipment were used over time, we did not calibrate these data, since the National Center for Health Statistics does not recommend calibrating the A1C data (21). We defined diabetes as a self-reported previous diagnosis of diabetes or an A1C ≥6.5% (48 mmol/mol). The vast majority of people with diabetes in NHANES are likely to have type 2 diabetes, since this is a general population study among adults (23).

We performed additional analyses based on the approximate half of participants (N = 4,294) randomly assigned to a morning examination including an overnight fast of 8–24 h (21). The age, race/ethnicity, and sex distributions were similar in our analytic samples and the overall adult NHANES study. They had plasma fasting glucose measured by a hexokinase method using a Roche Cobas Mira chemistry system (1999–2002), a Roche/Hitachi

911 glucose analyzer (2003–2006), or a Roche Modular P chemistry analyzer (2007–2010). Insulin was measured by an insulin radioimmunoassay using a Berthold Multi-Crystal Gamma Counter (1999–2002), an immunoenzymometric assay using a Tosoh AIA-PACK IRI (2003–2004), or a two-site enzyme immunoassay using a Beckman Coulter Biomek 2000 (2005–2008) or a Roche Elecsys 2010 (2009–2010). HOMA of insulin resistance (HOMA-IR) was calculated using the following equation (24): insulin (mU/L) * glucose (mmol/L)/22.5.

Statistical Methods

We calculated means and percentages (SEs) of participant characteristics by diabetes status. Urine metal concentrations were categorized in quartiles based on the weighted sample distribution. For each metal, we used logistic regression to estimate odds ratios and CIs for diabetes comparing each quartile with the lowest quartile. We tested for linear trends across quartiles of urine metals by including the median of each quartile as a continuous variable in logistic regression models. We included likely or suspected confounders in models based on previously published data; our covariates included variables that may be markers of healthy behaviors and other factors associated with metals that may also play a role in the development of diabetes. Initial regression models included adjustment for age, race/ethnicity, and sex, while subsequent models included further adjustment for menopausal status (among women), education, income, smoking status, pack-years smoked, alcohol consumption, waist circumference, CRP, high ALT, high GGT, daily calories consumed, percent of calories from saturated fat, and urine creatinine. Further analysis included each metal, in separate models, as a continuous log-transformed variable. For these analyses, we obtained the odds ratios associated with the difference in the log-transformed values of the 75th and 25th percentiles of the overall weighted sample distribution; the resulting odds ratios for diabetes associated with a difference in urine metal concentration equivalent to the difference between the 75th and 25th percentiles (without log-transformation) were generally comparable for all the metals.

To determine whether the metals may affect diabetes status through insulin resistance, we conducted additional analyses in a random subgroup with HOMA-IR data. Using predicted margins from a linear regression model, we calculated multivariable-adjusted geometric mean HOMA-IR by quartile of each metal among the overall population, and we repeated the analysis among participants without diabetes due to the possibility that diabetes may alter urine excretion of metals. Adjustment was identical to the diabetes models specified above.

The data were analyzed using SUDAAN (version 9.0; Research Triangle Institute, Research Triangle Park, NC) to account for the complex NHANES sampling design, including unequal probabilities of selection, oversampling, and nonresponse. The weights we used were developed specifically for the metals subsample such that the results of weighted analyses are generalizable to the U.S. non-institutional civilian population.

RESULTS

The weighted prevalence of diabetes was 9.6%. Participants with diabetes were older and more likely to be non-Hispanic black, to be postmenopausal (among women), to have less than a high school education, and to have a household income <$20,000 (each $P < 0.05$) (Supplementary Table 2). They were less likely to be current smokers and to consume alcohol and were more likely to be former smokers and to have high liver enzymes. They had higher mean waist circumference, BMI, CRP levels, and percent of calories from saturated fat, and they had lower daily calories consumed (each $P < 0.05$).

The multivariable adjusted odds ratios of diabetes associated with the highest quartile of metal, compared with the lowest quartile, were 0.86 (95% CI 0.66–1.12) for barium, 0.74 (0.51–1.09) for cadmium, 1.21 (0.85–1.72) for cobalt, 1.31 (0.90–1.91) for cesium, 1.76 (1.24–2.50) for molybdenum, 0.79 (0.56–1.13) for lead, 1.72 (1.27–2.33) for antimony, 0.76 (0.51–1.13) for thallium, 2.18 (1.51–3.15) for tungsten, and 1.46 (1.09–1.96) for uranium (Table 1).

When we modeled the metals as log-transformed continuous variables such that one unit is equivalent to the difference between the 75th and 25th percentiles of the metal distribution, the multivariable-adjusted odds ratios of diabetes were 0.94 (95% CI 0.82–1.07) for barium, 0.90 (0.75–1.10) for cadmium, 1.14 (1.00–1.30) for cobalt, 1.13 (0.97–1.32) for cesium, 1.34 (1.13–1.58) for molybdenum, 0.87 (0.75–1.02) for lead, 1.28 (1.11–1.47) for antimony, 0.91 (0.77–1.08) for thallium, 1.45 (1.21–1.73) for tungsten, and 1.26 (1.12–1.42) for uranium (Table 1). In a multivariable-adjusted model including all five metals that were significant when modeled separately (cobalt, molybdenum, antimony, tungsten, and uranium), the odds ratios of diabetes were 0.98 (95% CI 0.82–1.17) for cobalt, 1.11 (0.88–1.40) for molybdenum, 1.23 (1.04–1.45) for antimony, 1.36 (1.08–1.71) for tungsten, and 1.14 (1.01–1.29) for uranium. The variance inflation factor was <2.5 for all five metals indicating collinearity was not a concern (the variance inflation factor for the metals was as high as 3.8 in a model with all 10 metals indicating that collinearity may be a concern if all metals were included in one model).

The results were similar when we corrected for concentrations of urinary creatinine (urinary metal concentrations were divided by urinary creatinine concentration to yield micrograms of metal per gram of creatinine) instead of adjusting for it in the model (Supplementary Table 3) and when we excluded participants with chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2 or albumin ≥30 mg/L) (Supplementary Table 4). When we repeated the analysis among never smokers, the magnitudes of association were similar for molybdenum and tungsten, but results for antimony

Table 1—Odds ratios (95% CI) of diabetes associated with quartile of urinary metal and in a separate model urinary metals modeled linearly, with one unit equivalent to the difference between the 75th and 25th percentiles (metals modeled separately, N = 9,447): NHANES 1999–2010

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}	Linear model
Barium						
Age, race/ethnicity, and sex adjusted	1.00	1.02 (0.80, 1.29)	0.68 (0.55, 0.85)	0.93 (0.74, 1.17)	0.39	0.95 (0.85, 1.06)
Multivariable adjusted†	1.00	1.07 (0.80, 1.43)	0.69 (0.50, 0.94)	0.86 (0.66, 1.12)	0.13	0.94 (0.82, 1.07)
Cadmium						
Age, race/ethnicity, and sex adjusted	1.00	0.92 (0.70, 1.21)	0.90 (0.68, 1.19)	0.88 (0.64, 1.19)	0.53	0.99 (0.84, 1.17)
Multivariable adjusted†	1.00	0.80 (0.57, 1.13)	0.75 (0.54, 1.05)	0.74 (0.51, 1.09)	0.35	0.90 (0.75, 1.10)
Cobalt						
Age, race/ethnicity, and sex adjusted	1.00	1.27 (0.99, 1.63)	1.24 (1.00, 1.53)	1.06 (0.80, 1.40)	0.81	1.08 (0.96, 1.21)
Multivariable adjusted†	1.00	1.33 (0.95, 1.85)	1.26 (0.94, 1.70)	1.21 (0.85, 1.72)	0.59	1.14 (1.00, 1.30)
Cesium						
Age, race/ethnicity, and sex adjusted	1.00	1.28 (1.00, 1.65)	1.05 (0.80, 1.39)	0.95 (0.67, 1.34)	0.35	0.99 (0.86, 1.13)
Multivariable adjusted†	1.00	1.29 (0.95, 1.75)	1.16 (0.83, 1.62)	1.31 (0.90, 1.91)	0.29	1.13 (0.97, 1.32)
Molybdenum						
Age, race/ethnicity, and sex adjusted	1.00	1.49 (1.17, 1.90)	1.72 (1.32, 2.24)	1.52 (1.14, 2.03)	0.03	1.27 (1.11, 1.45)
Multivariable adjusted†	1.00	1.46 (1.09, 1.97)	1.89 (1.35, 2.66)	1.76 (1.24, 2.50)	0.01	1.34 (1.13, 1.58)
Lead						
Age, race/ethnicity, and sex adjusted	1.00	1.13 (0.86, 1.47)	0.92 (0.71, 1.20)	0.70 (0.52, 0.94)	<0.01	0.80 (0.71, 0.91)
Multivariable adjusted†	1.00	1.03 (0.74, 1.44)	0.88 (0.64, 1.21)	0.79 (0.56, 1.13)	0.10	0.87 (0.75, 1.02)
Antimony						
Age, race/ethnicity, and sex adjusted	1.00	1.27 (0.97, 1.65)	1.31 (0.98, 1.74)	1.42 (1.07, 1.89)	0.03	1.16 (1.03, 1.32)
Multivariable adjusted†	1.00	1.27 (0.92, 1.77)	1.38 (0.98, 1.94)	1.72 (1.27, 2.33)	<0.01	1.28 (1.11, 1.47)
Thallium						
Age, race/ethnicity, and sex adjusted	1.00	1.08 (0.86, 1.35)	0.92 (0.70, 1.21)	0.66 (0.48, 0.91)	<0.01	0.88 (0.75, 1.02)
Multivariable adjusted†	1.00	1.03 (0.78, 1.36)	1.01 (0.70, 1.45)	0.76 (0.51, 1.13)	0.13	0.91 (0.77, 1.08)
Tungsten						
Age, race/ethnicity, and sex adjusted	1.00	1.29 (1.01, 1.66)	1.55 (1.18, 2.04)	1.88 (1.41, 2.51)	<0.01	1.38 (1.20, 1.59)
Multivariable adjusted†	1.00	1.42 (1.06, 1.89)	1.67 (1.20, 2.34)	2.18 (1.51, 3.15)	<0.01	1.45 (1.21, 1.73)
Uranium						
Age, race/ethnicity, and sex adjusted	1.00	1.05 (0.81, 1.37)	1.24 (0.97, 1.60)	1.37 (1.03, 1.84)	0.04	1.21 (1.06, 1.38)
Multivariable adjusted†	1.00	1.18 (0.86, 1.61)	1.34 (0.99, 1.81)	1.46 (1.09, 1.96)	0.02	1.26 (1.12, 1.42)

†Multivariable adjustment included age, race/ethnicity, sex, menopausal status, education, income, smoking status, pack-years smoked, alcohol consumption, waist circumference, CRP, high ALT, high GGT, daily calories consumed, percent of calories from saturated fat, and urinary creatinine.

and uranium were partially attenuated and no longer statistically significant (Supplementary Table 5). Results were similar when we repeated the analysis among ever (current and former) smokers (Supplementary Table 6). Results stratified by 2-year time phase of NHANES show some variation over time (Supplementary Table 7), but interaction terms by time period were only significant for thallium (P = 0.03). Results were similar when we adjusted for BMI instead of waist circumference (data not shown).

After multivariable adjustment, higher quartiles of barium, molybdenum, and antimony were associated with higher levels of HOMA-IR in the overall population (each $P_{trend} < 0.05$) (Table 2). After restriction of the analysis to participants without diabetes, the association with HOMA-IR persisted for all three metals (each $P_{trend} < 0.05$). Conversely, higher quartiles of cesium were associated with lower HOMA-IR in the overall population and among participants without diabetes (both $P_{trend} < 0.05$). Cadmium, cobalt, lead, thallium, tungsten, and uranium were not associated with HOMA-IR.

DISCUSSION

Molybdenum, antimony, tungsten, and uranium were consistently positively associated with prevalence of diabetes, even at the relatively low levels seen in the U.S. general population. Also, cobalt was positively associated with diabetes, but the association was not robust to different modeling strategies. Conversely, we found no evidence of an association between barium, cadmium, cesium, lead, and thallium with diabetes prevalence. Barium, molybdenum, and antimony were positively associated with HOMA-IR; cesium was negatively associated with HOMA-IR; and cadmium, cobalt, lead, thallium, tungsten, and uranium were not associated with HOMA-IR.

Molybdenum
We found strong associations of molybdenum with diabetes and HOMA-IR among all participants and those without diabetes. Molybdenum is an essential nutrient needed for certain enzymes (25). Humans are exposed to it primarily through ingestion of food but may also be

Table 2—Multivariable-adjusted[†] geometric mean (95% CI) HOMA-IR by quartile of urinary metals (N = 4,294): NHANES 1999–2010

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}
Barium					
Overall	2.00 (1.88, 2.13)	2.04 (1.91, 2.18)	2.05 (1.93, 2.19)	2.26 (2.10, 2.43)	<0.01
Participants without diabetes	1.86 (1.75, 1.98)	1.86 (1.73, 2.00)	1.89 (1.77, 2.02)	2.08 (1.93, 2.24)	0.01
Cadmium					
Overall	2.11 (1.92, 2.32)	2.07 (1.96, 2.20)	2.08 (1.95, 2.23)	2.09 (1.96, 2.22)	0.47
Participants without diabetes	1.90 (1.75, 2.07)	1.90 (1.80, 2.02)	1.95 (1.82, 2.07)	1.93 (1.82, 2.05)	0.71
Cobalt					
Overall	2.01 (1.86, 2.16)	2.07 (1.95, 2.19)	2.16 (2.04, 2.29)	2.11 (1.96, 2.27)	0.46
Participants without diabetes	1.88 (1.74, 2.03)	1.91 (1.79, 2.03)	1.99 (1.87, 2.12)	1.90 (1.77, 2.04)	0.95
Cesium					
Overall	2.23 (2.07, 2.39)	2.07 (1.93, 2.22)	2.13 (2.01, 2.26)	1.95 (1.82, 2.09)	0.01
Participants without diabetes	2.06 (1.92, 2.21)	1.89 (1.76, 2.02)	1.97 (1.86, 2.09)	1.80 (1.68, 1.93)	0.02
Molybdenum					
Overall	1.98 (1.87, 2.10)	2.03 (1.91, 2.16)	2.08 (1.95, 2.21)	2.30 (2.13, 2.49)	<0.01
Participants without diabetes	1.85 (1.74, 1.96)	1.88 (1.77, 2.00)	1.89 (1.77, 2.01)	2.11 (1.94, 2.29)	0.01
Lead					
Overall	2.05 (1.92, 2.20)	2.04 (1.91, 2.17)	2.09 (1.96, 2.24)	2.16 (2.03, 2.30)	0.74
Participants without diabetes	1.88 (1.76, 2.01)	1.91 (1.80, 2.04)	1.93 (1.79, 2.07)	1.96 (1.85, 2.09)	0.91
Antimony					
Overall	1.90 (1.76, 2.06)	1.93 (1.82, 2.05)	2.26 (2.12, 2.41)	2.25 (2.08, 2.44)	<0.01
Participants without diabetes	1.80 (1.67, 1.93)	1.82 (1.70, 1.94)	2.07 (1.95, 2.20)	2.00 (1.86, 2.15)	0.04
Thallium					
Overall	2.16 (1.99, 2.34)	2.04 (1.92, 2.18)	2.17 (2.03, 2.32)	2.00 (1.86, 2.14)	0.20
Participants without diabetes	2.01 (1.85, 2.17)	1.90 (1.79, 2.03)	1.99 (1.86, 2.13)	1.83 (1.70, 1.97)	0.14
Tungsten					
Overall	1.89 (1.77, 2.03)	2.14 (2.04, 2.25)	2.11 (1.99, 2.24)	2.05 (1.90, 2.22)	0.89
Participants without diabetes	1.81 (1.68, 1.94)	2.00 (1.90, 2.09)	1.94 (1.83, 2.06)	1.85 (1.71, 1.99)	0.30
Uranium					
Overall	2.03 (1.88, 2.18)	1.98 (1.84, 2.14)	2.02 (1.88, 2.16)	2.07 (1.90, 2.26)	0.96
Participants without diabetes	1.88 (1.76, 2.00)	1.83 (1.70, 1.98)	1.88 (1.75, 2.03)	1.87 (1.71, 2.05)	0.71

†Multivariable adjustment included age, race/ethnicity, sex, menopausal status, education, income, smoking status, pack-years smoked, alcohol consumption, waist circumference, CRP, high ALT, high GGT, daily calories consumed, percent of calories from saturated fat, and urinary creatinine.

exposed to it through vitamin supplements, water, and ambient air (26). Some excess molybdenum is excreted in urine, but it also accumulates in the liver, kidneys, and bones (26,27).

Although molybdenum is an essential element, high levels of molybdenum may have toxic effects, which may vary depending on the chemical form. High levels of molybdenum exposure have been associated with high uric acid and gout-like symptoms in humans and numerous health outcomes in animal studies, including kidney and liver damage, anemia, diarrhea, slow growth, and bone abnormalities (26). Molybdenum can also inhibit intestinal copper absorption (26). Molybdenum was not associated with obesity in a recent study of the U.S. general population (8).

Antimony
Antimony is used in the manufacturing of electronics, metal alloys, fire-retardant materials, glass, and ceramics (28). Ingestion of large amounts of antimony has substantial gastrointestinal effects including vomiting, nausea, and diarrhea. Antimony is also a metalloestrogen and may

affect health, including diabetes risk, through hormone disruption (19). Studies in the U.S. general population have found that higher levels of antimony were associated with peripheral arterial disease and prevalent self-reported cardiovascular and cerebrovascular disease (7,29) but not obesity (8). Our study adds diabetes to the health outcomes associated with antimony.

Tungsten
Tungsten is commonly used in metal alloys (e.g., cemented carbide) and in numerous tools, automotive parts, and other products. The widespread use of tungsten alloys makes low-level occupational exposure common, but it usually involves coexposure with other metals (30). Environmental exposure to tungsten also occurs commonly through water, food, and ambient air.

Our study found that higher levels of urine tungsten were associated with diabetes but not with insulin resistance in the U.S. general population. We were unable to locate any other studies of tungsten and diabetes. A previous study conducted in the U.S. general population found that tungsten was not associated with BMI or waist

circumference (8). Studies in the U.S. general population have found that higher levels of tungsten were associated with peripheral arterial disease (29) and a self-reported previous diagnosis of cardiovascular disease (7).

Uranium

Humans are commonly exposed to naturally occurring uranium and depleted uranium, which has been increasingly used in munitions in recent years (31). Radioactive toxicity of uranium decreases as enrichment decreases, while the chemical toxicity of uranium is not related to enrichment. Therefore, the chemical toxicity is a much greater concern than radioactivity in naturally occurring uranium and depleted uranium.

In our study, higher levels of urinary uranium were associated with diabetes but not insulin resistance. We were not able to locate any other epidemiologic studies investigating uranium exposure and diabetes. However, a previous study conducted in the U.S. general population found that biomarkers of uranium exposure were associated with asthma, congestive heart failure, emphysema, and liver disease (32). Studies in occupationally exposed people suggest uranium may increase the risk of other disease including kidney disease and cancer (33,34).

Cadmium

Cadmium is a widespread toxic and carcinogenic metal (35). Humans are commonly exposed to cadmium via smoking and the consumption of contaminated food and water (36,37). Urine cadmium was not associated with diabetes in our study. In contrast, several previous studies have found an association between biomarkers of cadmium exposure and diabetes. In a previous cross-sectional study of the U.S. general population, urine cadmium was positively associated with diabetes (38). In a cross-sectional study of the Korean general population, blood cadmium was associated with the metabolic syndrome (39) but not diabetes (11). In a case-control study in Pakistan, participants with diabetes had higher levels of hair cadmium than those without diabetes (13). In a study of environmental exposure to cadmium in Thailand, those with continued high exposure throughout the 5-year study were more likely to develop diabetes than those with reduced exposure (10). In a prospective study of women without diabetes at baseline, blood and urine cadmium were not associated with developing diabetes after 5 years of follow-up (40). It is not clear why this association differed in these studies, but it should be noted that cadmium levels were lower in the 1999–2010 NHANES than most of these previous studies (41).

Other Metals

We could not identify epidemiologic studies investigating biomarkers of barium, cesium, or thallium with diabetes. In our study, these metals were not associated with diabetes. However, we found that higher levels of barium were associated with greater HOMA-IR. A previous cross-sectional study found that barium was positively associated with obesity (8). Since both studies were cross-sectional, we cannot determine whether barium causes obesity and subsequently insulin resistance or whether obesity causes both insulin resistance and increased urine barium excretion.

We found that urine lead was not associated with diabetes or with insulin resistance. Most (12,13,15,42) but not all (11,14) previous studies investigating lead and diabetes have found a positive association. In our study, lead was measured in urine, which has not been validated as a measure of external exposure to lead (43) and may not reflect long-term exposure to lead.

Finally, urine cobalt was associated with diabetes when modeled continuously but not when categorized into quartiles. It was not associated with HOMA-IR. In a previous study of 1,470 women, hair cobalt was similar between healthy-weight nondiabetic women and obese nondiabetic women, but cobalt concentrations were lower in women with diabetes (44). Cobalt is a component of vitamin B12, which is an essential nutrient for people. Biguanide medication use is associated with reduced vitamin B12 absorption and could affect cobalt concentrations in people using biguanides for diabetes (45).

Limitations and Strengths

Our study is essentially exploratory considering the limitations of previous literature in this area and the cross-sectional nature of the study. We cannot rule out the possibility that changes in metabolism, lifestyle, or medication use after the development of diabetes affected exposure, absorption, or excretion of some metals. Of particular concern is that decreased kidney function resulted in greater excretion of metals among people with diabetes, but our results were consistent after the exclusion of people with chronic kidney disease. Another limitation is the use of a single urine metal measurement, which may not reflect cumulative exposure and does not address the route of exposure or different forms of the metals. A 24-h urine sample may have been preferable to a spot urine sample, but we adjusted for creatinine to control for concentration dilution of urine. We may have been able to improve the characterization of metal exposure with measurement in other tissues such as hair or nails, but they were not available in NHANES. Also, the use of only A1C to determine undiagnosed diabetes may have missed some people who would have been considered to have diabetes based on fasting glucose or 2-h glucose after a glucose challenge. Another limitation is that we were not able to adjust for physical activity or exercise in our study because these data were not collected consistently throughout NHANES. Finally, exposure to these metals may involve coexposure to other potentially harmful substances, and we cannot rule out confounding by substances not measured or not adequately measured in the 1999–2010 NHANES.

Despite these limitations, our study maintained a number of strengths. The 1999–2010 NHANES was a large study collected using a rigorous study protocol with extensive quality-control procedures by technicians trained and

certified in data collection procedures. The results of our study are generalizable to the U.S. noninstitutionalized civilian population. To our knowledge, the relationship between many of the metals included in our study and diabetes has never been investigated in a large population-based study.

Conclusions

We found evidence of an association of urine levels of molybdenum, antimony, tungsten, and uranium with the prevalence of diabetes, even at the relatively low levels seen in the U.S. general population. Additionally, barium, molybdenum, and antimony were positively associated with HOMA-IR in our study. Metals associated with diabetes, if causal, may also increase the risk of diabetes through pathways unrelated to insulin resistance, such as directly damaging the β-cells (17). Considering that our study included a nationally representative sample of the U.S. population, our results may have important public health implications, as the concentrations of metals in our study may be typical or lower than what is seen in other populations around the world. Our study provides impetus to further study metals, especially molybdenum, antimony, tungsten, and uranium, as risk factors for diabetes in future prospective studies.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
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