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Environmental Nickel Exposure and Diabetes in a Nationally Representative Sample of US Adults

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Abstract

Laboratory studies have shown that nickel exposure may adversely affect glucose metabolism. However, studies about the effects of environmental nickel exposure on diabetes pathogenesis in humans are sparse. We aimed to evaluate the association of urinary nickel concentrations, as a biomarker of environmental nickel exposure, and diabetes in a nationally representative sample of US adults. The data from a nationally representative population (n = 1585) in the National Health and Nutrition Examination Survey 2017–18 were used. Diabetes (n = 330) was defined as self-reported physician's diagnosis, HbA1c ≥ 6.5%, fasting plasma glucose ≥ 126 mg/dL, or 2-h plasma glucose ≥ 200 mg/dL. Urinary nickel concentrations were determined by inductively coupled plasma mass spectrometry. Logistic regression with sample weights was used to estimate the odds ratios (ORs) of diabetes and 95% confidence intervals (CIs). Urinary nickel concentrations were higher in individuals with diabetes (weighted median 1.23 μg/L) than those without diabetes (1.01 μg/L). After adjustment for urinary creatinine and other risk factors for diabetes, the OR of diabetes comparing the highest with lowest quartile of urinary nickel

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Code Availability Code for data cleaning and analysis will be made available once the paper has been conditionally accepted.

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Consent to Participate Informed consent was obtained from all individual participants included in the study.

Consent for Publication The authors affirm that human research participants provided informed consent for publication of the aggregate data produced in the study.

concentrations was 2.70 (95% CI 1.39–5.24; P_{trend} = 0.03). Environmental nickel exposure is positively and significantly associated with diabetes in U.S. adults.

Keywords

Diabetes; Nickel; Epidemiology; US adults

Introduction

Diabetes has become a growing pandemic that poses an enormous public health challenge worldwide. In the United States, the prevalence of diabetes in 2018 was estimated to be 10.5%, affecting 34.2 million individuals (CDC 2020). The global prevalence is estimated to grow to 578 million by the year 2030 (IDF 2019). Although physical activity and excess energy intake are well-known risk factors for diabetes, growing evidence suggests that exposure to heavy metals may be associated with diabetes pathogenesis (Rana 2014; Chen et al. 2009). Identification of environmental risk factors for diabetes is urgently needed because they are modifiable risk factors that can be used to mitigate future growth in diabetes prevalence.

Nickel is a silver-white ferromagnetic heavy metal that is commonly used in electroplating, alloy production, and nickel–cadmium battery industries (ATSDR 2005). These industries as well as the oil and coal power, trash incinerating, and mining industries release nickel into the environment. Food is the most common non-occupational source of nickel exposure in the general population followed by air, drinking water, and tobacco (Genchi et al. 2020). The average dietary intake of nickel in the United States ranges from 69 to 162 μg/day (Pennington and Jones 1987).

Nickel exposure may adversely affect glucose metabolism and play an important role in diabetes pathogenesis. Animal studies have consistently demonstrated the hyperglycemic effect of nickel (Kadota and Kurita 1955; Peligero et al. 1985; Kubrak et al. 2012). However, studies about the impact of nickel exposure on diabetes in humans are sparse and the findings have been inconsistent. Two studies of Chinese adults observed that nickel exposure is associated with increased prevalence of diabetes (Liu et al. 2015; Feng et al. 2015); however, nested case–control studies of multiethnic US adult women and Chinese senior adults did not find significant associations between urinary or plasma nickel and diabetes, respectively (Wang et al. 2020; Yuan et al. 2018). Additional studies are needed to further clarify the association of nickel exposure and diabetes.

In the present study, we used the data from the National Health and Nutrition Examination Survey (NHANES) to examine the association of urinary nickel concentrations, as a biomarker of environmental nickel exposure (McNeely et al. 1972), with diabetes in a nationally representative sample of U.S. adults.

Methods

Study Population

The NHANES is a complex, multistage probability sampling survey, administered by the National Center for Health Statistics, Centers for Disease Control and Prevention (CDC), with the data representing the nationwide noninstitutionalized US population. As part of NHANES, abundant data on demographics, socioeconomic status, lifestyle, diet, and medical conditions are collected. In addition, extensive health examinations are performed and specimens are collected for laboratory tests as part of NHANES. The NHANES data are released publicly every 2 years. The National Center for Health Statistics Ethics Review Board has approved NHANES. Written informed consent was obtained from all participants.

In the present study, we used the data from NHANES 2017–18 because urinary concentrations of nickel were only measured in this cycle. In total, diabetes and urinary nickel concentrations data were available for 1622 adults aged ≥ 20 years. Based on the visual inspection of box and QQ plots, outliers of urinary nickel concentrations were excluded ($n = 3$). After additionally excluding individuals diagnosed with diabetes at < 20 years of age ($n = 6$), individuals whose body mass index (BMI) data were unavailable ($n = 26$), and individuals with missing covariate information ($n = 2$), 1585 adult participants were included in the study.

Exposure Assessment

Concentrations of nickel in urine samples were measured using the inductively coupled plasma–dynamic reaction cell–mass spectrometry at the Inorganic and Radiation Analytical Toxicology Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention (Atlanta, GA, USA). The lower limit of detection (LLOD) of urine nickel was 0.31 μg/L. According to NHANES analytic guidance, analytic results (7.3%) that are below the LLOD were assigned values of the LLOD divided by the square root of 2 (CDC 2018). To account for variable urine dilution, we adjusted for urinary creatinine in all analyses, as recommended (Barr et al. 2005).

Outcome Ascertainment

Diabetes was defined based on the self-reported physician diagnosis, plasma fasting glucose concentrations ≥ 126 mg/dL, HbA1c ≥ 6.5%, or a 2-h plasma glucose concentration ≥ 200 mg/dL (Menke et al. 2015). Trained interviewers collected information of self-reported previous diagnosis of diabetes. Certified technologists measured HbA1c and plasma fasting glucose concentrations and administered a 2-h oral glucose tolerance test.

Potential Confounders

Standardized questionnaires were used to collect the data on age, sex, race/ethnicity, education, family income, dietary information, smoking status, alcohol consumption, physical activity, smoking status, and medical conditions (Johnson et al. 2013). Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic (Mexican and non-Mexican Hispanic), and other mixed races/ethnicities. Education was categorized as less than high school, high school, and higher than high school (college or associates

(AA) degree and college graduate or higher). Family income-to-poverty ratio was grouped as ≤ 1.30, 1.31–3.50, and > 3.50 (Johnson et al. 2013). The total energy intake was calculated using the US Department of Agriculture automated multiple-pass method (http://www.ars.usda.gov/ba/bhnrc/fsrg). Never smokers were defined as individuals who smoked less than 100 cigarettes in their lifetime. Among those who smoked more than 100 cigarettes, adults who did not smoke at the time of the survey were considered former smokers, whereas those who smoked cigarettes at the time of the survey were classified as current smokers (CDC 2017). Alcohol intake was categorized as 0, 0.1–27.9, and ≥ 28 g/day for males, and 0, 0.1–13.9, and ≥ 14 g/day for females (USDA & HHS 2015). Physical activity was assessed using the Global Physical Activity Questionnaire (WHO 2014). Metabolic equivalents of task (MET) minutes per week were derived to take into account both the duration and intensity of different activities (WHO 2014). Weight and height were measured and used to calculate BMI. The 2015 healthy eating index (HEI-2015) score was calculated to represent diet quality, with a higher score indicating a better diet (Reedy et al. 2018). Urinary creatinine was determined enzymatically using a Coba 6000 analyzer (Roche Diagnostics, Indianapolis, IN, USA) (CDC 2018). Whole blood concentrations of cadmium and lead were measured using the inductively coupled plasma–dynamic reaction cell–mass spectrometry (CDC 2018).

Statistical Analysis

All analyses were conducted according to NHANES analytical guidelines (Johnson et al. 2013). Appropriate weights and the Taylor series linearization method were used to represent the non-institutionalized U.S. population (Johnson et al. 2013). Chi-square tests and analysis of variance (ANOVA) were used to compare categorical variables and continuous variables, respectively. Logistic regression was used to estimate odds ratios (ORs) of diabetes according to quartiles of urinary nickel concentrations. We adjusted for age, sex, race/ethnicity, and urinary creatinine in Model 1. We additionally adjusted for family income-to-poverty ratios, education, physical activity, smoking status, alcohol intake, total energy intake, HEI-2015, family history of diabetes, and blood concentrations of cadmium and lead in Model 2. Because heavy metals are linked to diabetes (Leff et al. 2018; Tinkov et al. 2017), blood concentrations of cadmium and lead were included as confounders. Model 3 was additionally adjusted for BMI. The missing data of categorical variables were grouped into a subcategory. To assess linear trends across quartiles of urinary nickel concentrations, the median of log-transformed nickel concentrations for each category was calculated and the median was fitted as a continuous variable in models.

To evaluate effect modification, we conducted interaction and stratified analyses by sex, race/ethnicity, and smoking status (because cigarette smoking is an important route of nickel exposure in the general population). Because chronic kidney disease could affect urinary nickel excretion, we conducted a sensitivity analysis by excluding individuals with chronic kidney disease to test the robustness of our findings. The NHANES data did not distinguish diabetes subtypes, so another sensitivity analysis was conducted including participants who were diagnosed with diabetes before 20 years of age (i.e., more likely to have type 1 diabetes). In addition, we performed a third sensitivity analysis excluding diabetes cases who did not report physicians' diagnosed diabetes.

All statistical analyses were performed using survey procedures of the SAS 9.4 package (SAS Institute, Cary, NC, USA). The level of statistical significance (α) was set at 0.05.

Results

The final sample consisted of 1585 participants (49.4% male, mean (± SEM) age 47.7 ± 1.0 years; 50.6% female, mean age 49.8 ± 1.2 years). The median urinary nickel concentration was 1.04 μg/L (interquartile range [IQR] 0.59–1.73), and weighted prevalence of diabetes was 14.2% (SEM 1.2%). Urinary concentrations of nickel were higher in non-Hispanic blacks, those with higher blood concentrations of lead and cadmium, and those lower family incomes, energy intake, alcohol intake, diet quality (Table 1). The weighted median (IQR) concentrations of nickel in individuals with diabetes compared to those without diabetes were 1.23 (0.81–1.80) μg/L and 1.01 (0.57–1.71) μg/L, respectively; however, these values were not significant different (P = 0.09). Urinary nickel concentrations according to population characteristics are given in Table S1, available as Supplementary Material to this paper.

There was a significant association of environmental nickel exposure and diabetes prevalence in this population. After adjustment for age, sex, race/ethnicity, and urinary creatinine concentrations, the OR (95% CI) of diabetes was 1.83 (0.95–3.54) comparing the highest with the lowest quartile of nickel (P_{trend} = 0.21; Table 2). This association was significant after further adjustment for additional demographic, socioeconomic, and lifestyle factors, the OR (95% CI) of diabetes was 2.70 (1.39–5.24) comparing the highest with the lowest quartile of nickel in fully adjusted models (P_{trend} = 0.03).

Although the association appeared stronger among females compared to males, among whites as compared to nonwhites, and among never smokers compared to ever (current or past) smokers, no significant interactions were found (P for interaction > 0.05 for each; Table 3). The OR (95% CI) of diabetes comparing the highest and lowest quartiles of urinary nickel concentration was 4.15 (1.89–9.12) among females (P_{trend} = 0.008) compared to 2.06 (0.71–6.03) among males (P_{trend} = 0.26). The OR (95% CI) of diabetes was 5.61 (1.71–18.4) among whites (P_{trend} = 0.07) compared to 1.90 (1.02–3.53) among nonwhites (P_{trend} = 0.08). The OR (95% CI) of diabetes was 4.00 (1.43–11.2) among never smokers (P_{trend} = 0.02) compared to 1.70 (0.62–4.68) among ever (current or past) smokers (P_{trend} = 0.52). The associations of urinary nickel concentrations with diabetes did not change appreciably in sensitivity analyses when excluding individuals with chronic kidney disease, when including individuals who were diagnosed with diabetes before 20 years of age, or when excluding individuals without physicians' diagnosis of diabetes (Tables S2–S4).

Discussion

In the present study, higher urinary nickel concentrations were significantly associated with an elevated prevalence of diabetes in US adults, including after adjustment for other major risk factors of diabetes including age, sex, socioeconomic status, diet, lifestyle, and BMI.

Owing to the widespread nickel throughout the environment, humans are widely exposed to nickel. The general population is exposed to nickel through food, contaminated drinking

water, air, and tobacco (Genchi et al. 2020). In this study, nickel was detected above the LLOD in 92.7% of urine samples, which is slightly below the 96–100% detection rates observed in Canada, China, and in a multiethnic cohort of US adult women (Saravanabhavan et al. 2017; Liu et al. 2015; Wang et al. 2020).

Our study represents the first in a nationally representative sample to examine the association between environmental nickel exposure and diabetes in the general U.S. adult population. Consistent with our findings, Liu et al., (2015) in a cross-sectional study among Chinese adults showed a significant association between urinary nickel levels and diabetes prevalence; the ORs (95% CI) of the third and fourth quartiles compared to the first were 1.77 (1.34–2.36) and 1.69 (1.27–2.26), respectively in Chinese adults. Similarly, a cross-sectional study of adults in China by Feng et al. (2015) observed significant risk of diabetes when comparing the extreme quartiles with an OR (95% CI) of 1.65 (1.04–2.64). To date, only two longitudinal studies have evaluated the association of nickel exposure and diabetes incidence. A nested case–control study by Wang et al. (2020) found a positive, but nonsignificant association of urinary nickel and risk of diabetes, with an HR (95% CI) of 1.15 (0.98–1.35) in a multiethnic cohort of adult women in the U.S. However, the number of diabetes cases (n = 102) was relatively small in the study by Wang et al. (2020), with larger sample size it is possible that the association of urinary nickel and incident diabetes would be significant. In addition, a nested case–control study by Yuan et al. (2018) found no association of plasma nickel and risk of diabetes in a cohort of senior adults in China. Of note, the urinary nickel concentrations are, on average, lower in the present study compared to the studies among adults in China (Liu et al. 2015; Feng et al. 2015) and the nested case–control study among multiethnic adult women in the US (Wang et al. 2020).

Interestingly, possible race/ethnic and sex differences for the association between nickel exposure and diabetes were observed. The association appeared stronger among whites compared with nonwhites and among females as compared to males, although the interaction effects were not statistically significant for either comparison. In contrast, Liu et al. (2015) observed that the association between urinary nickel and diabetes appears stronger among Chinese adult males compared to females. Taken together, these observations suggest that nickel may have race/ethnicity and sex-specific associations with diabetes. Supporting this hypothesis are the results from a multiethnic cohort of U.S. adult women that observed significant differences in nickel exposure by race/ethnicity (Wang et al. 2019), and a study that demonstrated different inflammatory responses to nickel exposure between male and female mice (You et al. 2020).

Cigarette smoking is a major source of nickel exposure among the general population (Genchi et al. 2020); therefore, there might be a concern that the observed findings between nickel exposure and diabetes could be confounded by concomitant toxins in cigarettes. However, in this study, the association between nickel exposure and diabetes appeared even stronger among never smokers, which does not support confounding by smoking in the association between nickel exposure and diabetes in this study population.

The significant association between nickel exposure and diabetes is biologically plausible. Animal studies have consistently found that acute and subchronic nickel exposure causes

hyperglycemia, possibly by inducing glycogenolysis (Tikare et al. 2008; Kubrak et al. 2012), hyperglucagonemia (Horak et al. 1978; Cartana and Arola 1992; Horak and Sunderman 1975a), hypoinsulinemia (Cartana and Arola 1992; Bwititi and Ashorobi 1998; Alvarez et al. 1993; Clary 1975), or gluconeogenesis (Cartana and Arola 1992). Rats acutely injected with nickel chloride have elevated plasma glucose values within 30 min that correspond to reduced insulin:glucagon plasma ratios (Cartana and Arola 1992; Alvarez et al. 1993) and are attenuated by co-administration of exogenous insulin (Clary 1975; Horak and Sunderman 1975b). Hypophysectomy, adrenalectomy, or administration of select α-adrenergic antagonists prevents nickel-induced hyperglycemia in rats (Alvarez et al. 1993; Horak and Sunderman 1975b). Furthermore, nickel exposure increases nitric oxide synthase levels in rat brain, adrenal glands, and pancreas and the hyperglycemic response is attenuated by nitric oxide synthase inhibition (Gupta et al. 2000). Taken together, these observations suggest that the hyperglycemic effect of nickel is a stress-related response.

The strengths of this analysis include the use of nationally representative data from NHANES that includes comprehensive information about demographic, socioeconomic, and lifestyle factors, which allows adjustment for confounding from a variety of diabetes-related risk factors and generalization of the findings to a broader population. There are also several limitations to the present study. First, we could not establish a temporal relationship or draw causal inference from the observed associations. Longitudinal studies are needed to confirm our findings. Second, spot urine samples were collected to measure nickel concentrations instead of 24-h urine samples due to the perceived challenges and difficulties with sample collection. Third, although we adjusted for many potential confounders, we cannot rule out the possibility of residual confounding by other unknown factors such as nickel exposure from jewelry or canned food. Fourth, the NHANES dataset does not differentiate type 1 from type 2 diabetes, so we cannot rule out possible confounding from residual type 1 cases.

In this nationally representative sample of US adults, we found that environmental nickel exposure was significantly associated with diabetes. These findings suggest that nickel may be a novel risk factor for diabetes. More research is needed to identify potential mechanisms, evaluate sex and race/ethnicity differences, and characterize relevant exposure pathways.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Availability of data and material

The dataset analyzed for this study can be found in: https://www.cdc.gov/nchs/nhanes/index.htm.

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Table 1

Characteristics of the study population from the National Health and Nutrition Examination Survey (NHANES) 2017–18 according to quartiles of urinary nickel concentrations

	Urinary nickel quartiles (μg/L)				
	Q1 (< 0.65)	**Q2 (0.65–1.17)**	**Q3 (1.17–1.94)**	**Q4 (> 1.94)**	***p* value**
No. Participants	397	396	402	390	
Age (years)	48.0 ± 1.56	48.2 ± 1.37	48.9 ± 0.98	50.1 ± 1.51	0.31
Gender					
Male	47.9 (5.1)	49.2 (3.7)	55.1 (3.3)	44.7 (2.8)	0.35
Female	52.1 (5.1)	50.8 (3.7)	44.9 (3.3)	55.3 (2.8)	
Race/ethnicity					
Non-Hispanic white	64.6 (4.6)	65.6 (4.1)	64.1 (3.6)	54.9 (4.4)	0.03
Hispanic	15.3 (1.9)	16.1 (3.0)	15.2 (2.8)	15.7 (2.9)	
Non-Hispanic black	8.1 (1.5)	9.8 (1.9)	13.1 (2.8)	14.4 (1.5)	
Other	12.0 (2.9)	8.5 (1.8)	7.7 (1.5)	15.0 (2.6)	
Education					
Less than high school	10.0 (1.4)	9.6 (2.1)	13.8 (3.0)	15.2 (2.3)	0.06
High school	23.2 (4.2)	28.3 (3.0)	34.2 (3.3)	29.1 (3.7)	
College or higher	66.8 (4.1)	62.1 (3.8)	52.0 (4.6)	55.7 (4.3)	
Smoking					
Never smoker	54.5 (4.8)	52.9 (3.6)	62.8 (5.0)	54.3 (4.9)	0.35
Current smoker	16.5 (2.6)	14.7 (2.7)	14.0 (3.0)	21.2 (3.9)	
Past smoker	29.1 (4.9)	32.5 (3.8)	23.2 (3.5)	24.5 (4.1)	
Family income-to-poverty ratio					
< 1.3	14.2 (1.7)	17.7 (2.2)	20.8 (2.7)	23.8 (2.5)	0.07
1.3–3.5	28.3 (3.9)	35.0 (3.7)	29.1 (4.0)	33.4 (3.6)	
≥ 3.5	48.0 (4.3)	38.4 (5.0)	36.0 (5.8)	30.8 (4.6)	
Missing	9.5 (2.2)	8.8 (1.9)	14.1 (3.5)	12.0 (2.5)	
Physical activity (MET-min/week)					
< 600	33.0 (3.0)	30.5 (3.8)	34.0 (3.5)	34.9 (2.7)	0.72
600–1199	10.9 (2.3)	8.0 (1.9)	7.7 (1.6)	7.0 (1.7)	

	Urinary nickel quartiles (μg/L)				
	Q1 (< 0.65)	**Q2 (0.65–1.17)**	**Q3 (1.17–1.94)**	**Q4 (> 1.94)**	***p* value**
> 1200	56.0 (3.2)	61.5 (3.1)	57.3 (3.7)	58.1 (3.0)	
Alcohol (g/day)	11.2 ± 1.62	13.1 ± 2.33	8.7 ± 1.88	8.7 ± 1.05	0.04
Total energy intake (kcal/day)	2227.2 ± 59.0	2045.3 ± 69.8	2182.1 ± 53.6	2157.2 ± 53.1	0.04
HEI-2015	51.4 ± 1.52	49.5 ± 1.16	48.8 ± 1.12	50.6 ± 0.91	0.02
BMI (kg/m^2)					
< 25.0	30.2 (4.1)	25.0 (4.1)	18.4 (2.4)	22.3 (3.1)	0.17
25–29.9	31.0 (3.9)	30.4 (2.8)	34.4 (3.3)	27.0 (3.3)	
≥ 30.0	38.7 (3.6)	44.7 (4.5)	47.2 (3.3)	50.7 (4.4)	
Family history of diabetes					
Yes	49.7 (2.6)	45.9 (4.4)	44.2 (3.2)	40.2 (4.3)	0.28
No	50.3 (2.6)	54.1 (4.4)	55.8 (3.2)	59.8 (4.3)	
Blood cadmium (μg/L)	0.44 ± 0.04	0.43 ± 0.03	0.39 ± 0.04	0.54 ± 0.05	0.005
Blood lead (μg/dL)	1.02 ± 0.04	1.08 ± 0.06	1.22 ± 0.07	1.22 ± 0.07	0.003
Diabetes					
Yes	9.1 (2.0)	14.6 (2.5)	18.4 (2.6)	15.6 (2.2)	0.04
No	90.9 (2.0)	85.4 (2.5)	81.6 (2.6)	84.4 (2.2)	

Unless indicated otherwise, data are given as the weighted mean ± SEM for continuous variables and weighted percentages (SEs) for categorical variables

BMI body mass index, *HEI-2015* 2015 healthy eating index, *MET* metabolic equivalent of task, *PIR* family income-to-poverty ratio

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Table 2

Associations of urinary nickel concentration with diabetes in US adults

	Urinary nickel quartiles (μg/L)				P_{trend}
	Q1 (< 0.65)	**Q2 (0.65–1.17)**	**Q3 (1.17–1.94)**	**Q4 (> 1.94)**	
Median, μg/L	0.43	0.89	1.49	2.66	
No. of cases/participants	58/397	89/396	84/402	99/390	
Model 1	1 (reference)	1.75 (0.80–3.82)	2.46 (1.00–6.09)	1.83 (0.95–3.54)	0.21
Model 2	1 (reference)	2.03 (0.97–4.23)	3.48 (1.63–7.44)	2.48 (1.47–5.48)	0.02
Model 3	1 (reference)	1.83 (0.84–3.99)	3.58 (1.67–7.70)	2.70 (1.39–5.24)	0.03

The data show odds ratios (OR) with 95% confidence intervals (CI) in parentheses.

Model 1: adjusted for age (years), sex (male, female), race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black, and other race), and urinary creatinine (quartiles).

Model 2: adjusted for all factors in Model 1 plus education (less than high school, high school, college, or higher), family income (family income-to-poverty ratio: < 1.3, 1.3–3.5, ≥ 3.5, or missing), cigarette smoking (never, past, and current), physical activity (< 600, 600–1199, ≥ 1200 MET-min/week), alcohol intake (0, 0.1–27.9, ≥ 28 g/day for males; 0, 0.1–13.9, ≥ 14 g/day for females), total energy intake (quartiles), 2015 healthy eating index (HEI-2015) score (quartiles), family history of diabetes (yes, no), blood cadmium levels, and blood lead levels

Model 3: adjusted for all factors in Model 2 plus body mass index (< 25.0, 25.0–29.9, ≥ 30.0 kg/m^2)

Table 3

Associations of urinary nickel concentrations with diabetes in US adults by sex and race/ethnicity

	Urinary nickel quartiles				P_{trend}	$P_{interaction}$
	Q1	**Q2**	**Q3**	**Q4**		
Sex						
Male	1 (reference)	1.42 (0.47–4.27)	2.98 (0.98–9.08)	2.06 (0.71–6.03)	0.26	0.66
No. of cases/participants	27/185	35/189	50/216	56/198		
Female	1 (reference)	2.17 (0.96–4.89)	4.29 (1.67–11.0)	4.15 (1.89–9.12)	0.008	
No. of cases/participants	31/212	54/207	34/186	43/192		
Race						
White	1 (reference)	2.90 (0.78–10.8)	6.26 (2.48–15.8)	5.61 (1.71–18.4)	0.07	0.76
No. of cases/participants	14/128	26/138	25/140	33/132		
Nonwhite	1 (reference)	1.34 (0.73–2.47)	2.04 (1.08–3.85)	1.90 (1.02–3.53)	0.08	
No. of cases/participants	44/269	63/258	59/262	66/258		
Smoking status						
Never smokers	1 (reference)	1.98 (0.78–5.00)	6.50 (2.15–19.7)	4.00 (1.43–11.2)	0.02	0.26
No. of cases/participants	29/231	47/224	49/234	55/211		
Ever (current and past) smokers	1 (reference)	1.76 (0.56–5.52)	1.30 (0.49–3.44)	1.70 (0.62–4.68)	0.52	
No. of cases/participants	29/166	42/172	35/168	44/179		

The data show odds ratios with 95% confidence intervals in parentheses

Models were adjusted for the same covariates as given in Model 3 in Table 2, except for the stratified variable