Original Article

Association between Plasma Metal Levels and Diabetes Risk: a Case-control Study in China*

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Abstract

Objective Many metals, some of which have been classified as environmental endocrine disruptors, are used extensively in everyday consumer products and are ubiquitous in our living environment. In the present study, we aimed to explore the associations between the prevalence risk of type 2 diabetes and plasma levels of 20 trace elements as well as those of heavy metals in a Han Chinese population.

Methods We conducted a case-control study to investigate the associations between plasma concentrations of 20 metals and diabetes in Jiangsu province. A total of 122 newly diagnosed cases of type 2 diabetes and 429 matched controls were recruited from community physical examinations in Suzhou City of Jiangsu Province. Plasma metal levels were measured by inductively-coupled plasma mass spectrometry.

Results After adjusting for confounders, plasma vanadium, chromium, manganese, copper, zinc, arsenic, selenium, strontium, palladium, cadmium, cesium, and barium were associated with diabetes risk ($P < 0.05$). The adjusted *OR* increased with increasing concentration of vanadium, manganese, copper, zinc, and cesium.

Conclusion Many metals, including manganese, copper, zinc, arsenic, selenium, and cadmium in plasma, are associated with the morbidity of diabetes. Monitoring of environmental metal levels and further studies are urgently needed.

Key words: Metals; Diabetes; Chromium; Arsenic; Cadmium

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INTRODUCTION

One of the well-known independent risk factors for type 2 diabetes is fasting plasma glucose (FPG)[1], which may also increase the risk of cardiovascular disease (CVD)[2-4]. In recent years, epidemiological evidence has supported the idea that toxic heavy metals, including cobalt, arsenic, selenium, cadmium, iron, and copper, are associated with the prevalence of CVD[5-8]. In fact, some metals can persist in the living and working environment for several years, and some heavy metals (such as nickel, cadmium, arsenic, and argentum) even have biological half-lives of more than several years[9-11], which makes them a public health concern. Nevertheless, evidence for the association of heavy metals with diabetes or FPG is still limited or due to controversies.

Son et al.[12] found environmental exposure to cadmium in abandoned mine residents to be associated with diabetes. Barregard et al.[13] also found a significant interaction between high concentrations of blood cadmium (B-Cd) and diabetes mellitus (DM), providing support for the hypothesis that adults with DM have a higher risk of renal glomerular damage from cadmium exposure than those without DM. Shapiro et al.[14] observed dose-response relationships between four metals (lead, cadmium, mercury, and arsenic) and the incidence of gestational diabetes mellitus (GDM), only plasma arsenic levels displayed a significant association with GDM, but no statistically significant associations were observed between cadmium and GDM. A significant association was observed between cerebrovascular disease (CCVD) and urinary cobalt in a previous study in the USA[5], but in a study investigating the risk of diabetes and prediabetes among occupational workers, higher levels of urinary cobalt was associated with an increased risk of diabetes in male subjects only. Moreover, their research also uncovered significant associations between nickel, copper, and diabetes. Many of the above-mentioned chemicals are used extensively in everyday consumer products and are ubiquitous in our living environment. However, there are limited epidemiologic data regarding the risk of metabolic dysfunction associated with metal element exposure and a variety of metal levels in the blood of the Han Chinese population. Consequently, more studies are needed to confirm the observed associations and explore new findings.

Based on the above background information, we aimed to explore the associations of type 2 diabetes risk with the plasma levels of 20 trace elements as well as heavy metals in the present study, including vanadium, manganese, iron, chromium, cobalt, copper, nickel, zinc, arsenic, selenium, rubidium, strontium, ruthenium, rhodium, palladium, argentum, cadmium, cesium, barium, and lanthanum, among 551 Han Chinese adults recruited from a community physical examination clinic in Suzhou, Jiangsu Province, China.

MATERIALS AND METHODS

Study Participations

The subjects in our study were examined and recruited between April 2014 and July 2016. The source population consisted of community residents in Suzhou City. We selected both cases and controls from the same City for the reason of more similar living environment and dietary habits comparing to different cities, which may be confounders for type 2 diabetes.

The diagnostic criteria for new cases of diabetes were based on blood glucose levels, defined as random plasma glucose concentrations ≥ 11.1 mmol/L plus symptoms of diabetes, 2-hour post-load oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L, or fasting plasma glucose (FPG) ≥ 7.0 mmol/L. In addition, an HbA1c ≥ 6.5% has been accepted as a diagnostic criterion for DM. Adults who were selected as newly diagnosed cases should not have been previously diagnosed with type 2 diabetes by a physician and should not be current or past users of any oral hypoglycemic drugs or insulin. However, the definitions of newly diagnosed diabetes were determined after professional medical discussions with learned and experienced endocrinologists from the physical examination center.

Each subject donated 5-mL venous blood samples for subsequent blood testing. FPG was assayed with an automated biochemical analyzer (Randox Laboratories Ltd., UK) using the enzymatic colorimetric method. Clinical laboratory technicians working in Nanjing Prevention and Treatment Center for Occupational Diseases carried out the experiment according to standard operation procedures.

Questionnaire

Subject information was collected *via* questionnaire administered by trained interviewers

in the form of face-to-face interviews. The questionnaire generally included demographic data, past and present medical conditions, pharmaceutical preparations, physical activity and diet during daily life, hereditary factors, drinking status, and smoking and passive smoking status. In our study, ever drinkers were identified as subjects who drank a bottle of beer or 50 g of wine per day for at least one year, and everyone else was classified as a never drinker. Workers who had one cigarette per day for at least one year were identified as ever smokers, and all others were never smokers.

Exclusion Criteria

In the first round of selection, subjects who had been diagnosed with diabetes by professional endocrinologists and had being undergoing treatment or taking medication previously or presently were excluded from our study, as we sought newly diagnosed patients who had never undergone therapeutic treatment.

For the following analyses, we excluded subjects with missing blood samples, missing blood glucose data, or abnormal blood biochemical levels, which would probably have resulted in abnormal plasma outputs of metal elements. Adults whose blood did not qualify for plasma detection were also excluded. In addition, we excluded participants with missing investigative or physical examination data (e.g., missing height, weight, systolic or diastolic pressure, smoking or drinking status, total cholesterol or triglycerides, etc.).

Each recruited newly diagnosed case of type 2 diabetes was well matched with 1-4 controls. The cases were selected without any restriction on age or sex, while the controls, which were frequency-matched to the cases by age, gender, and BMI, consisted of individuals from the same community who were seeking health care from the Suzhou Center for Disease Control and Prevention at the same time. The final participant population consisted of 551 subjects (122 newly diagnosed cases of type 2 diabetes and 429 matched controls) from a community physical examination center in Suzhou city of Jiangsu Province, China.

Ethical Consideration

This project was approved by the Ethics Committee of Nanjing Medical University. Written informed consent was obtained from each individual. Ethical guidelines were followed throughout the whole study period.

Detection of Plasma Metal Contents

We determined the concentrations of 20 metals in plasma in the following steps. In brief, the frozen plasma samples were stored in a refrigerator at 5 °C 3 h before sample preparation and completely thawed at room temperature immediately before the experiment, followed by homogenizing on a vortex mixer. A 200-μL plasma sample was pipetted into a 10-mL centrifuge tube (LabServ. Thermo Fisher Scientific, USA) containing 200 μL of 100-μg/L interior label, and then the volume was adjusted to 4.0 mL with diluent prepared with 65% (v/v) highly purified Triton X-100 (Sigma-Aldrich), 65% nitric acid HNO_3 (Merck KGaA, Germany), and purified water (Wahaha Purified Water, China). When the final homogenization was complete, we measured metal concentrations in the composite samples with an inductively-coupled plasma mass spectrometer on the basis of an octupole-based collision/reaction cell (Thermo, iCAP-Q ICP-MS, USA). Furthermore, internal quality control samples with every batch were detected after standardization. The detection limits of all metal elements are demonstrated in Table 1.

Table 1. Detection Limits of ICP-MS for Metal Elements

Elements	Detection Limits (μg/L)
Vanadium	0.0040
Chromium	0.0153
Manganese	0.0213
Iron	0.4043
Cobalt	0.0015
Nickel	0.0540
Copper	0.0329
Zinc	0.3189
Arsenic	0.0181
Selenium	0.0000
Rubidium	0.0234
Strontium	0.0435
Ruthenium	0.0019
Rhodium	0.0002
Palladium	0.0073
Argentum	0.0054
Cadmium	0.0023
Cesium	0.0016
Barium	0.0642
Lanthanum	0.0011

Statistical Analysis

Measurement data are expressed as mean ± SD ($\bar{x} \pm s$), and data with a skewed distribution are described as median and interquartile ranges. Differences among groups were analyzed by nonparametric tests, student *t*-test, or one-way ANOVA. Qualitative data were described as percentages and analyzed using the chi-square (χ^2) test or Fisher's exact test as indicated. Crude and adjusted odds ratios (*OR*s) were determined with 95% confidence intervals (95% *CI*s) by multivariate logistic regression.

Results were considered statistically significant at $P < 0.05$. We entered all data into a computerized database using the statistical analysis software Epidata 3.1. All analyses were performed using the SPSS software (Version 22.0, SPSS Inc., USA) and SAS 9.1.3 (SAS Institute, Cary, NC).

RESULTS

Basic Participant Characteristics

Table 2 shows the basic characteristics of all subjects. A total of 551 participants were analyzed in this study. There were more female subjects than male ones in each group and in the total population. Approximately 216 (39.2%) out of 551 subjects were male, whereas the remaining 335 (60.8%) were female. The age range of all subjects was 40-92, and the mean age was 66.48, 66.25, and 66.43 years for controls, newly diagnosed type 2 diabetes patients, and the total population, respectively. Most of our population disapproved of smoking and drinking: 84.0% of study subjects were never smokers, and 16.0% were ever smokers. The ratio of never to ever drinkers was 89.7% and 10.3%, respectively. There were no significant differences between cases and controls with respect to age, gender, BMI, and smoking status; however, cases were more likely than controls to be ever drinkers. The percentage of current drinkers in cases was significantly higher than in controls (15.6% *vs.* 8.9%, $P < 0.05$). With respect to family history, the case group was more likely to have a family history of diabetes than the controls, with a prevalence of 14.8% in cases and 4.7% in controls. However, the mean level of FPG in newly diagnosed diabetes was significantly higher than that in controls (7.55 *vs.* 5.67 mmol/L, $P < 0.05$).

Table 2. Descriptive Characteristics of New Diagnosed Cases of Type 2 Diabetes and Controls

Variables	All (*N* = 551)	Cases (*N* = 122)	Controls (*N* = 429)	*P*
Gender, *n* (%)				
Male	216 (39.2)	43 (35.2)	173 (40.3)	0.310[a]
Female	335 (60.8)	79 (64.8)	256 (59.7)	
Age, years	66.43 ± 9.36	66.25 ± 9.46	66.48 ± 9.34	0.809[b]
< 66, *n* (%)	234 (42.5)	55 (45.1)	179 (41.7)	
66-70, *n* (%)	136 (24.7)	25 (20.5)	111 (25.9)	0.880[a]
> 70, *n* (%)	181 (32.8)	42 (34.4)	139 (32.4)	
BMI, kg/m^2	24.67 ± 3.32	25.08 ± 3.74	24.55 ± 3.18	0.151[b]
Smoking status, *n* (%)				
Never	463 (84.0)	100 (82.0)	363 (84.6)	0.481[a]
Ever	88 (16.0)	22 (18.0)	66 (15.4)	
Drinking status, *n* (%)				
Never	494 (89.7)	103 (84.4)	391 (91.1)	**0.032**[a]
Ever	57 (10.3)	19 (15.6)	38 (8.9)	
Family history, *n* (%)				
No	513 (93.1)	104 (85.2)	409 (95.3)	**0.000**[a]
Yes	38 (6.9)	18 (14.8)	20 (4.7)	
FPG, mmol/L	6.09 ± 3.18	7.55 ± 2.14	5.67 ± 3.30	**0.000**[b]

Note. [a]χ^2 test for the distribution between cases and controls. [b]Student *t*-test for mean comparison between cases and controls.

Plasma Metal Levels in Cases and Controls

Table 3 shows the blood levels of 20 metal elements in our study participants. There were significant differences between cases and controls in plasma vanadium concentration: the median concentration of vanadium was 0.234 μg/L in the case group and 0.177 μg/L in the control group ($P < 0.05$). Similarly, blood levels of chromium, manganese, copper, zinc, and cadmium were higher in cases than those in controls ($P < 0.05$): the corresponding concentrations were 2.286 μg/L in cases *vs.* 1.898 μg/L in controls for chromium, 2.725 μg/L *vs.* 1.828 μg/L for manganese, 932.164 μg/L *vs.* 786.388 μg/L for copper, 634.382 μg/L *vs.* 575.205 μg/L for zinc, and 0.096 μg/L *vs.* 0.065 μg/L for cadmium. Participants with diabetes had significantly higher concentrations of arsenic, selenium, strontium, palladium, cesium, and barium than those in the non-diabetic group ($P < 0.05$): their comparative plasma levels were 0.754 μg/L in diabetes *vs.* 0.536 μg/L in non-diabetes for arsenic, 18.565 μg/L *vs.* 15.447 μg/L for selenium, 33.248 μg/L *vs.* 30.539 μg/L for strontium, 0.373 μg/L *vs.* 0.231 μg/L for palladium, 0.957 μg/L *vs.* 0.779 μg/L for cesium, and 8.173 μg/L *vs.* 4.802 μg/L for barium. However, there was no significant difference in the blood concentrations of iron, cobalt, nickel, rubidium, ruthenium, rhodium, argentum, and lanthanum between cases and controls with respect to the median values.

Plasma Metals and Diabetes

We divided the subjects' plasma metal concentrations into tertiles to analyze the association between diabetes prevalence and metal content. Serum iron, cobalt, nickel, rubidium, ruthenium, rhodium, argentum, and lanthanum were not associated with diabetes risk (Table 4). However, for the other metals, we observed statistically significant correlations with increased diabetes risk. After adjusting for confounders, the adjusted *OR* values and 95% *CI* of diabetes of the third tertiles (the highest group) comparing minimum tertiles (the lowest group) for vanadium, chromium, manganese, copper, zinc, arsenic, selenium, strontium, palladium, cadmium, cesium, and

Table 3. Metal Concentrations in New Diagnosed Diabetes and Controls

Variables	All		Cases		Controls		P^a
	Median (μg/L)	Quartile Range (μg/L)	Median (μg/L)	Quartile Range (μg/L)	Median (μg/L)	Quartile Range (μg/L)	
Vanadium	0.191	0.138	0.234	0.180	0.177	0.125	**0.000**
Chromium	1.952	1.114	2.286	1.389	1.898	1.048	**0.000**
Manganese	1.954	1.242	2.725	1.930	1.828	0.944	**0.000**
Iron	1117.162	451.861	1174.648	459.733	1104.439	442.876	0.139
Cobalt	0.294	0.124	0.292	0.132	0.297	0.122	0.563
Nickel	6.478	3.640	5.968	3.903	6.551	3.570	0.191
Copper	815.755	261.226	932.164	268.340	786.388	244.672	**0.000**
Zinc	590.108	196.973	634.382	191.369	575.205	201.633	**0.000**
Arsenic	0.615	0.784	0.754	0.584	0.536	0.790	**0.002**
Selenium	16.390	11.875	18.565	9.279	15.447	12.538	**0.000**
Rubidium	277.661	82.564	274.967	66.249	278.579	93.801	0.501
Strontium	31.456	12.724	33.248	14.153	30.539	11.489	**0.000**
Ruthenium	0.043	0.061	0.046	0.069	0.042	0.057	0.398
Rhodium	0.000	0.003	0.000	0.003	0.000	0.003	0.545
Palladium	0.287	0.716	0.373	0.609	0.231	0.693	**0.002**
Argentum	0.411	0.462	0.503	0.398	0.390	0.497	0.730
Cadmium	0.071	0.065	0.096	0.102	0.065	0.061	**0.000**
Cesium	0.821	0.404	0.957	0.375	0.779	0.382	**0.000**
Barium	5.115	4.633	8.173	13.656	4.802	3.202	**0.000**
Lanthanum	0.035	0.034	0.038	0.032	0.035	0.036	0.333

Note. [a]Nonparametric test for the comparison of metal levels in abnormal distribution.

Table 4. Comparisons of Diabetes risk According to the Three Tertiles of Plasma Metals

Variables	Q1 (lowest) (μg/L)	Q2 (middle) (μg/L)	Q3 (highest) (μg/L)	*P*[b]
Vanadium	< 0.151	0.151-	0.235	
Case: *N* (%)	22 (18.03)	40 (32.79)	60 (49.18)	**0.000**
Control: *N* (%)	162 (37.76)	143 (33.33)	124 (28.91)	
All (%)	184 (33.39)	183 (33.22)	184 (33.39)	
Adjusted *OR* (95% *CI*s)[a]	1.000	2.100 (1.178-3.744)	3.589 (2.040-6.314)	
Chromium	< 1.623	1.623-2.321	> 2.321	
Case: *N* (%)	30 (24.59)	33 (27.05)	59 (48.36)	**0.000**
Control: *N* (%)	152 (35.43)	151 (35.20)	126 (29.37)	
All (%)	182 (33.03)	184 (33.39)	185 (33.58)	
Adjusted *OR* (95% *CI*s)[a]	1.000	1.066 (0.605-1.878)	2.219 (1.319-3.733)	
Manganese	< 1.671	1.671-2.416	> 2.416	
Case: *N* (%)	14 (11.48)	33 (27.05)	75 (61.47)	**0.000**
Control: *N* (%)	169 (39.39)	152 (35.43)	108 (25.18)	
All (%)	183 (33.21)	185 (33.58)	183 (33.21)	
Adjusted *OR* (95% *CI*s)[a]	1.000	2.528 (1.286-4.969)	7.880 (4.169-14.893)	
Iron	< 988.245	988.245-1293.406	> 1293.406	
Case: *N* (%)	34 (27.87)	45 (36.89)	43 (35.24)	0.246
Control: *N* (%)	150 (34.97)	139 (32.40)	140 (32.63)	
All (%)	184 (33.39)	184 (33.39)	183 (33.22)	
Adjusted *OR* (95% *CI*s)[a]	1.000	1.418 (0.847-2.373)	1.591(0.900-2.814)	
Cobalt	< 0.259	0.259-0.340	> 0.340	
Case: *N* (%)	45 (36.89)	38 (31.15)	39 (31.96)	0.520
Control: *N* (%)	140 (32.63)	147 (34.27)	142 (33.10)	
All (%)	185 (33.58)	185 (33.58)	181 (32.84)	
Adjusted *OR* (95% *CI*s)[a]	1.000	0.820 (0.495-1.357)	0.822 (0.496-1.364)	
Nickel	< 5.365	5.365-7.713	> 7.713	
Case: *N* (%)	53 (43.44)	30 (24.59)	39 (31.97)	0.074
Control: *N* (%)	130 (30.30)	154 (35.90)	145 (33.80)	
All (%)	183 (33.22)	184 (33.39)	184 (33.39)	
Adjusted *OR* (95% *CI*s)[a]	1.000	0.416 (0.245-0.706)	0.637 (0.383-1.060)	
Copper	< 729.661	729.661-901.400	> 901.400	
Case: *N* (%)	15 (12.30)	37 (30.32)	70 (57.38)	**0.000**
Control: *N* (%)	168 (39.16)	147 (34.27)	114 (26.57)	
All (%)	183 (33.22)	184 (33.39)	184 (33.39)	
Adjusted *OR* (95% *CI*s)[a]	1.000	2.796 (1.456-5.368)	6.862 (3.644-12.920)	
Zinc	< 529.777	529.777-649.232	> 649.232	
Case: *N* (%)	27 (22.13)	43 (35.25)	52 (42.62)	**0.002**
Control: *N* (%)	156 (36.36)	141 (32.87)	132 (30.77)	
All (%)	183 (33.22)	184 (33.39)	184 (33.39)	
Adjusted *OR* (95% *CI*s) [a]	1.000	1.964 (1.132-3.407)	2.261 (1.285-3.979)	
Arsenic	< 0.389	0.389-0.915	> 0.915	
Case: *N* (%)	22 (18.03)	57 (46.72)	43 (35.25)	**0.008**
Control: *N* (%)	162 (37.76)	127 (29.60)	140 (32.64)	
All (%)	184 (33.39)	184 (33.39)	183 (33.22)	
Adjusted *OR* (95% *CI*s)[a]	1.000	3.436 (1.956-6.037)	2.204 (1.244-3.905)	
Selenium	< 12.774	12.774-19.825	> 19.825	
Case: *N* (%)	13 (10.66)	60 (49.18)	49 (40.16)	**0.000**
Control: *N* (%)	171 (39.86)	124 (28.90)	134 (31.24)	
All (%)	184 (33.39)	184 (33.39)	183 (33.22)	
Adjusted *OR* (95% *CI*s)[a]	1.000	8.134 (4.088-16.182)	6.138 (3.012-12.509)	
Rubidium	< 251.164	251.164-300.669	> 300.669	

Continued

Variables	Q1 (lowest) (μg/L)	Q2 (middle) (μg/L)	Q3 (highest) (μg/L)	P^b
Case: *N* (%)	32 (26.23)	54 (44.26)	36 (29.51)	0.615
Control: *N* (%)	152 (35.43)	129 (30.07)	148 (34.50)	
All (%)	184 (33.39)	183 (33.22)	184 (33.39)	
Adjusted *OR* (95% *CI*s)[a]	1.000	2.286 (1.354-3.860)	1.057 (0.578-1.933)	
Strontium	< 28.225	28.225-36.059	> 36.059	
Case: *N* (%)	28 (22.95)	40 (32.79)	54 (44.26)	**0.001**
Control: *N* (%)	156 (36.36)	144 (33.57)	129 (30.07)	
All (%)	184 (33.39)	184 (33.39)	183 (33.22)	
Adjusted *OR* (95% *CI*s)[a]	1.000	1.505 (0.866-2.616)	2.151 (1.273-3.636)	
Ruthenium	< 0.027	0.027-0.065	> 0.065	
Case: *N* (%)	34 (27.87)	45 (36.89)	43 (35.24)	0.246
Control: *N* (%)	150 (34.97)	139 (32.40)	140 (32.63)	
All (%)	184 (33.39)	184 (33.39)	183 (33.22)	
Adjusted *OR* (95% *CI*s)[a]	1.000	1.349 (0.803-2.267)	1.277 (0.749-2.179)	
Rhodium	< 0.000	0.000-0.003	> 0.003	
Case: *N* (%)	64 (52.46)	37 (30.33)	21 (17.21)	0.286
Control: *N* (%)	227 (52.91)	87 (20.28)	115 (26.81)	
All (%)	291 (52.81)	124 (22.50)	136 (24.69)	
Adjusted *OR* (95% *CI*s)[a]	1.000	1.568 (0.962-2.557)	0.686 (0.394-1.194)	
Palladium	< 0.100	0.100-0.493	> 0.493	
Case: *N* (%)	23 (18.85)	53 (43.44)	46 (37.71)	**0.004**
Control: *N* (%)	160 (37.30)	131 (30.54)	138 (32.16)	
All (%)	183 (33.22)	184 (33.39)	184 (33.39)	
Adjusted *OR* (95% *CI*s)[a]	1.000	2.409 (1.370-4.237)	2.236 (1.266-3.952)	
Argentum	< 0.300	0.300-0.636	> 0.636	
Case: *N* (%)	36 (29.51)	48 (39.34)	38 (31.15)	0.801
Control: *N* (%)	147 (34.27)	137 (31.93)	145 (33.80)	
All (%)	183 (33.21)	185 (33.58)	183 (33.21)	
Adjusted *OR* (95% *CI*s)[a]	1.000	1.458 (0.870-2.442)	0.929 (0.544-1.587)	
Cadmium	< 0.051	0.051-0.096	> 0.096	
Case: *N* (%)	28 (22.95)	33 (27.05)	61 (50.00)	**0.000**
Control: *N* (%)	153 (35.66)	152 (35.43)	124 (28.91)	
All (%)	181 (32.84)	185 (33.58)	185 (33.58)	
Adjusted *OR* (95% *CI*s)[a]	1.000	1.086 (0.617-1.912)	2.511 (1.486-4.245)	
Cesium	< 0.700	0.700-0.951	> 0.951	
Case: *N* (%)	21 (17.21)	37 (30.33)	64 (52.46)	**0.000**
Control: *N* (%)	163 (38.00)	147 (34.27)	119 (27.73)	
All (%)	184 (33.39)	184 (33.39)	183 (33.22)	
Adjusted *OR* (95% *CI*s)[a]	1.000	1.847 (1.015-3.361)	3.908 (2.223-6.869)	
Barium	< 4.134	4.134-6.786	> 6.786	
Case: *N* (%)	18 (14.75)	28 (22.95)	76 (62.30)	**0.000**
Control: *N* (%)	165 (38.46)	157 (36.60)	107 (24.94)	
All (%)	183 (33.21)	185 (33.58)	183 (33.21)	
Adjusted *OR* (95% *CI*s)[a]	1.000	1.583 (0.823-3.046)	6.184 (3.448-11.093)	
Lanthanum	< 0.026	0.026-0.049	> 0.049	
Case: *N* (%)	36 (29.50)	43 (35.25)	43 (35.25)	0.379
Control: *N* (%)	148 (34.50)	140 (32.63)	141 (32.87)	
All (%)	184 (33.39)	183 (33.22)	184 (33.39)	
Adjusted *OR* (95% *CI*s)[a]	1.000	1.236 (0.741-2.062)	1.202 (0.712-2.029)	

Note. [a]Adjusted for age, gender, BMI, family history, smoking and drinking status in the logistic regression model. [b]χ^2 test for the distribution of different metal levels.

barium were 3.589 (2.040-6.314), 2.219 (1.319-3.733), 7.880 (4.169-14.893), 6.862 (3.644-12.920), 2.261 (1.285-3.979), 2.204 (1.244-3.905), 6.138 (3.012-12.509), 2.151 (1.273-3.636), 2.236 (1.266-3.952), 2.511 (1.486-4.245), 3.908 (2.223-6.869), and 6.184 (3.448-11.093), respectively, and the second tertiles (the middle group) comparing minimum tertiles for vanadium, manganese, copper, zinc, arsenic, selenium, palladium, and cesium were 2.100 (1.178-3.744), 2.528 (1.286-4.969), 2.796 (1.456-5.368), 1.964 (1.132-3.407), 3.436 (1.956-6.037), 8.134 (4.088-16.182), 2.409 (1.370-4.237), and 1.847 (1.015-3.361), respectively. Furthermore, the adjusted *OR* increased with increasing concentration of vanadium, manganese, copper, zinc, and cesium per tertile ($P < 0.05$).

DISCUSSION

The present study suggests that newly diagnosed diabetes patients were more likely to be drinkers and to have higher average blood concentrations of some metals (vanadium, chromium, manganese, copper, zinc, arsenic, selenium, strontium, palladium, cadmium, cesium, and barium) than control subjects without type 2 diabetes. This indicates that drinking may induce pancreatic β-cell dysfunction or an inability to produce insulin, which plays an important role in decreasing blood glucose. In previous studies, some metals (arsenic, cadmium, manganese, zinc, and mercury) are thought to have estrogenic activity and are consequently classified as EDCs (environmental endocrine disruptors)[15-18]. They can simulate some features of insulin secreted from pancreatic β-cells, disturbing normal insulin regulatory function with blood glucose and causing pathoglycemia or even more serious illness.

The plasma concentration results of heavy metals in this study are in partial agreement with those of a previous population-based study exploring the association of urinary metal profiles with diabetes risk[19-21]. However, it must be kept in mind that, in our research, we decided a priori to use metals in the blood rather than in the urine as the main outcome measure of metal burden, because there is diurnal variability in metal excretion, which is usually affected by urinary flow rate[22]. Therefore, the variability of metal levels in urine is substantial, despite their long half-lives. Taking this into account, urinary metals are not good biomarkers for many outcomes, because the excretion of metals varies far more due to other factors than to metal toxicity itself. Fortunately, blood metal levels were used in our study as a valid biomarker, which is not affected by the above factors, because metal levels in blood are steady unless individuals change their diet or living habits dramatically.

We did not find significant differences in palsma nickel concentration between the third and first tertiles, but the nickel level in the middle tertile was the protective factor against diabetes in the present study. Although it has been reported that the whole-body burden of nickel might be changed in diabetes, the results were inconsistent. Kazi et al.[23] showed no difference in blood levels of nickel between patients with diabetes and controls, whereas some other findings reported a higher concentration of plasma nickel in diabetics[24-28]. However, Yarat et al.[29] found a lower serum nickel concentration in patients with diabetes. A significant association between plasma arsenic and diabetes has been found in our study, which was in line with previous studies[30-33]. Some researchers with human and animal experimental evidence suggested that arsenic may impair pancreatic β-cells in the process of insulin synthesis and secretion, decreasing glucose uptake[34-37]. Skalnaya et al.[38] have evaluated serum levels of copper, zinc, and iron in diabetes patients. Our results also showed that elevated plasma copper and zinc levels were significantly correlated with increased diabetes risk. Unfortunately, we did not find iron to be associated with diabetes risk among subjects, which may suggest that current intake levels of iron may not affect the glucose metabolism. Our results showed that elevated plasma selenium levels were significantly correlated with increased diabetes risk; however, there was conflicting evidence linking selenium to glucose metabolism. Askari[39] suggest that blood Selenium concentration is significantly lower in patients with hyperglycemia than in those with euglycemia. In agreement with their results, high selenium status was associated with reduced diabetes prevalence in several prospective studies[40-42]. However, high serum and plasma selenium concentrations were associated with an increased prevalence of diabetes in other studies[43-46], and a non-significant association has also been found[47-49]. Our results also suggested that plasma cadmium was related to diabetes, which was in accordance with previous studies indicating that cadmium could cause diabetes through disruption of pancreatic β-cells and the presence of oxidative stress[50-52].

The present study has a number of strengths and limitations. The case group consists of newly diagnosed diabetes, and the diagnosis of type 2 diabetes was based on the professional medical opinions of endocrinologists from the physical examination center. Moreover, we focus on the metal concentrations in plasma and not in urine, a result that is easily affected by urinary flow rate. Regarding limitations, it should firstly be noted that this was a cross-sectional study, so we do not know whether diabetes results from the presence of these metals in the body or vice versa, because the cross-sectional design is a limitation regarding causality. Furthermore, the limited size of the final population (122 newly diagnosed cases of type 2 diabetes and 429 matched controls) is also a limitation. Finally, we cannot exclude the possibility of a false-positive result, because our results were obtained only as the plasma output of these metals; thus, the positive findings regarding metal levels and diabetes may have been due to chance. Therefore, the associations found in this study require further investigation in future studies.

Our results emphasized the need to monitor environmental metal levels in order to reduce metal exposure to humans. Further research is urgently needed to determine the role of metals in the development of diabetes.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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