Nickel exposure is associated with the prevalence of type 2 diabetes in Chinese adults

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Abstract

Background: Nickel exposure can induce hyperglycaemia in rodents, but little is known about its association with abnormal glucose metabolism in humans. We aimed to investigate the association of nickel exposure with the prevalence of type 2 diabetes in Chinese adults.

Methods: A total of 2115 non-institutionalized men and women aged 55 to 76 years from Beijing and Shanghai were included, and urinary nickel concentration was assessed by inductively coupled plasma mass spectroscopy. The prevalence of type 2 diabetes was compared across urinary nickel quartiles. Fasting plasma glucose, insulin, lipids, C-reactive protein and glycated haemoglobin A1c, as well as urinary albumin and creatinine were measured.

Results: The median concentration of urinary nickel was 3.63 μg/l (interquartile range: 2.29–5.89 μg/l), and the prevalence of diabetes was 35.3% (747 cases/2115 persons). Elevated levels of urinary nickel were associated with higher fasting glucose, glycated haemoglobin A1c, insulin and homeostatic model assessment of insulin resistance (all \( P < 0.01 \)). The odds ratios (95% confidence interval) for diabetes across the increasing urinary nickel quartiles were 1.27 (0.97–1.67), 1.78 (1.36–2.32) and 1.68 (1.29–2.20), respectively (referencing to 1.00), after multivariate adjustment including lifestyle factors, body mass index and family history of diabetes (\( P \) for trend \(< 0.001\)). The association remained unchanged after further controlling for urinary creatinine and C-reactive protein (\( P \) for trend \(< 0.001\)).

Conclusions: Increased urinary nickel concentration is associated with elevated prevalence of type 2 diabetes in humans.

Key words: Nickel exposure, epidemiology, type 2 diabetes
Introduction

The type 2 diabetes (T2D) epidemic has been evidenced worldwide, especially in many developing countries. Among the top 10 countries with high T2D prevalence, five are Asian countries including China, India, Pakistan, Indonesia and Bangladesh. For instance, the prevalence of T2D in the adults in China was less than 1% in 1980 and reached 11.6% in 2010. Although excess energy intake and sedentary lifestyle are well-recognized risk factors for diabetes, growing evidence has suggested that environmental exposures such as heavy metals may contribute to the pathogenesis of T2D.

As a heavy metal, nickel is widely distributed in the environment and can be released into ambient air and soil when burning coal, fuel oil and waste or discharging sewage. Nickel and its compounds are also commonly used in many industries such as electroplating, alloy production and the production of nickel-cadmium batteries. Therefore, the general public are exposed to nickel from air, foods and drinking water. Other sources of nickel exposure may come from use of tobacco, dental or orthopaedic implants, stainless steel kitchen utensils, inexpensive jewellery and nickel-releasing coins. Most absorbed nickel is excreted in the urine regardless of its exposure route and urinary nickel concentration, hence, is commonly used to assess nickel exposure levels.

To date, it remains largely unclear whether nickel exposure is associated with diabetes risk in humans. Several animal studies have indicated that nickel exposure can induce hyperglycaemia, likely due to its effects in promoting hepatic glycolysis and pancreatic glucagon release and decreasing peripheral utilization of glucose. However, evidence from human studies is limited regarding whether nickel exposure is associated with dysregulation of glucose homeostasis. In this study, we investigated the levels of nickel exposure in a Chinese population and analysed its association with T2D.

Methods

Study population

A population-based sample was obtained from the Nutrition and Health of Aging Population in China study (NHAPC) to examine environmental and genetic factors related to chronic diseases. A total of 3289 Chinese (1458 men and 1831 women) aged 50 to 70 years were recruited in 2005 from Beijing and Shanghai, which were selected as representative cities in northern and southern China. In each city, one rural district and two urban districts were sampled to represent populations of low, middle or high socioeconomic level. In 2011, a total of 2529 (76.9%) eligible participants who attended the baseline survey were successfully followed up, details were previously reported. The present study is a cross-sectional analysis of the 2011 follow-up visits when urine samples were collected. After excluding those without urine samples (n = 335), or with missing information on covariates (n = 79), a total of 2115 individuals were eligible for the present analyses. The study was approved by the Institutional Review Board of the Institute for Nutritional Sciences, and all participants provided informed consent.

Data collection

A face-to-face interview was conducted by trained health workers with standard questionnaires in 2011 to obtain data on demographics, health status, lifestyle and physical activities. Education attainment (0–6 years, 7–9 years or ≥10 years), current smoking status, alcohol drinking (yes or no), physical activity (low, moderate or high) and family history of chronic diseases (yes or no) were previously defined. After overnight fasting, all participants were invited to undergo physical examination, and their height, weight, waist circumference and blood pressure were measured by trained medical professionals according to standard protocols. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres and categorized as normal weight (<24.0 kg/m²), overweight (24.0 to 27.9 kg/m²) or obesity (≥28.0 kg/m²), according to the criteria for Chinese individuals.

Laboratory measurements

Fasting peripheral venous blood samples were collected by EDTA-contained tubes and centrifuged to separate plasma,
buffy coat and erythrocytes and then stored at −80°C until analysis. Plasma glucose, triglyceride, total cholesterol, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol were measured using an automatic analyser (Hitachi 7080, Tokyo, Japan) with reagents purchased from Wako Pure Chemical Industries (Osaka, Japan). Urinary albumin and creatinine were also measured by the automatic analyser with reagents from Roche Diagnostics (Mannheim, Germany). Fasting insulin was assessed by radioimmunoassay with kits from Merck Millipore (Billerica, MA). The insulin resistance index [homeostasis model assessment of insulin resistance (HOMA-IR)] was calculated using the original homeostasis model assessment method of Matthews et al.23 Plasma high-sensitive C-reactive protein (CRP) was measured by a particle-enhanced immunoturbidimetric assay (UltrAsensitive CRP kit; Orion Diagnostica, Espoo, Finland). Glycated haemoglobin A1c (HbA1c) from resolved erythrocytes was measured with an automated immunoassay (Tina-Quant Hemoglobin A1C II; Roche Diagnostics, Indianapolis, IN).

Measurement of urinary nickel concentration

First morning urine samples were collected with clean containers and stored at -80°C until analysis. Each 1 ml of the urine samples was mixed with 1 ml 2% HNO₃, and then centrifuged at 4000 rpm for 10 min. The supernatants were injected into an Agilent 7700x inductively coupled plasma mass spectroscopy system (ICP-MS, Agilent Technologies, Tokyo, Japan). All the containers or tubes were pre-cleaned by overnight soaking in ultrapure grade 2% HNO₃ solution.8 Quality control was performed (1 out of 20 samples), and the inter- and intra-assay coefficients of variation were <10% and <8%, respectively. All participants had urinary nickel levels above the detection limit (0.084 µg/l).

Definition of type 2 diabetes

T2D was defined as fasting plasma glucose concentration of 7.0 mmol/l or higher, self-reported physician-diagnosed diabetes or receipt of antidiabetic medications.

Statistical analysis

Analysis of covariance for continuous variables and multivariate logistic regression analysis for categorical variables were applied for the comparison across urinary nickel quartiles. Whenever appropriate, log₁₀ transformations of skewed variables were used in analyses. A logistic regression model was used to test odds ratios (ORs) and confidence intervals (CIs) of T2D for each urinary nickel quartile compared with the lowest quartile, with adjustment for age (continuous), sex, region (Beijing, Shanghai), residence (urban, rural), education (<6, 6–9 or ≥10 years), current smoking status (yes, no), alcohol drinking (yes, no), physical activity (low, moderate, high), family history of diabetes (yes, no), BMI (continuous) and urinary creatinine concentration (log-transformed continuous variable). Tests of linear trend across increasing nickel quartiles were conducted by assigning the median value to each quartile and treating it as a continuous variable. Plasma CRP was further adjusted to test influence of inflammatory status on the association. The log-linear dose-response relationship was estimated by applying a restricted cubic spline regression model with 3 knots at the 5th (1.27 µg/l), 50th (3.64 µg/l) and 95th (22.9 µg/l) percentiles.24 Stratified analyses were performed according to age (<65, ≥65), sex, region, residence, current smoking status, BMI category (normal weight, overweight and obesity) and physical activity. Likelihood ratio tests were conducted to examine interactions.

Because duration of diabetes may influence nickel metabolism, and diabetes may be accompanied with deteriorated renal function leading to increased nickel leak into urine, we have conducted sensitivity analyses by including diabetes duration (0–6, ≥6 years) and albuminuria (defined as albumin to creatinine ratio ≥30 mg/g as indicator of renal damage)25 in stratified analyses. In addition, nickel may coexist or interact with other elements, such as arsenic (As) and cadmium (Cd),8,11 which were reported to be associated with T2D.26,27 Therefore, these elements were additionally adjusted as continuous variables (log₁₀-transformed) on the basis of the final model aforementioned. Finally, HbA1c ≥6.5% was also employed as a diabetes diagnosis criterion in sensitivity testing. All analyses were performed with SAS (version 9.3; SAS Institute Inc., Cary, NC).

Results

As shown in Table 1, the median concentration of urinary nickel was 3.63 µg/l (interquartile range: 2.29–5.89 µg/l), and 35.3% (747/2115) of the participants had T2D. Participants with higher urinary nickel concentrations were more likely to be men and Shanghai residents. Furthermore, participants with increased urinary nickel concentration tended to have elevated levels of glucose, HbA1c, insulin and HOMA-IR, as well as urinary albumin and creatinine (all P for trend <0.05).

Compared with those without T2D, participants with T2D had elevated urinary nickel concentration (median: 4.03 µg/l in T2D vs 3.40 µg/l in non-T2D subjects,
The ORs (95% CIs) for T2D from the lowest to the highest urinary nickel quartiles were 1.28 (0.98–1.67), 1.81 (1.39–2.36) and 1.69 (1.30–2.20), respectively (referencing to 1.00) (P for trend <0.001) (Table 2), after adjusting for age, sex, region and residence (model 1). The nickel-diabetes association was not materially changed (P for trend <0.001) by further controlling for lifestyle covariates and family history of diabetes (model 2), as well as...
as additionally adjusting for urinary creatinine (log-transformed) (model 3) and CRP (model 4) (all \( P \) for trends <0.001). The strength of the association was attenuated, but all \( P \) for trends remained <0.01, when using creatinine-corrected nickel concentration in the models (see Supplementary Table S1, available as Supplementary data at IJE online). A positive log-linear dose–response relationship was evident in the cubic spline regression model (Figure 1, \( P < 0.01 \) for linearity).

When urinary nickel concentration was considered as a continuous variable, the overall OR (95% CI) of having diabetes was 1.33 (1.06–1.67) per unit increment of log-transformed nickel concentration. In the stratified analyses, the nickel-diabetes association was slightly stronger in men, urban and Beijing residents, current smokers and individuals with lower physical activity levels as compared with their counterparts (Figure 2). However, no interaction was detected with any of the variables (all \( P \) for interaction >0.10).

The nickel-diabetes association remained when stratified according to diabetes duration (0–6, ≥6 years) and having albuminuria (see Supplementary Table S2, available as Supplementary data at IJE online). Moreover, the association persisted when including As and Cd levels in the model (OR, 1.71 compared the highest with the lowest quartile; 95% CI, 1.27–2.29; \( P \) for trend =0.001).

The association was not materially changed when including HbA1c ≥6.5% as an additional diagnosis criteria for T2D (see Supplementary Table S3, available as Supplementary data at IJE online).

**Discussion**

To our knowledge, this is the first population-based study showing that elevated urinary nickel concentrations were associated with an increased risk of having T2D. The association was independent of traditional diabetes risk factors including lifestyle, BMI, family history of diabetes and inflammatory biomarkers.

**Nickel exposure**

The median concentration of urinary nickel in our population was 3.63 \( \mu \)g/l (interquartile range: 2.29–5.89 \( \mu \)g/l). In most previously published studies, urinary nickel values, however, varied from 0.6 to 2.4 \( \mu \)g/l among people living in Italy, Denmark, Germany, Norway, Japan (women only) and USA, except in a Finnish study in which the geometric mean was 4.8 \( \mu \)g/l. Although the US Center for Disease Control Agency for Toxic Substances and Disease Registry (CDC/ATSDR) has used 1–3.0 \( \mu \)g/l as a reference value, currently there is no internationally...
acceptable value or range for urinary nickel concentration in the general population. Thus, it remains to be elucidated whether or to what extent the discrepancies regarding urinary nickel concentrations could be explained by its exposure levels, effects of genetic predisposition and other predisposing factors on its metabolism, between-laboratory differences in methods (ICP-MS vs electrothermal atomic absorption spectrometry) and measurement errors, or variations in population characteristics among studies.

The main sources of nickel exposure among the general population are contaminated drinking water and foods.\textsuperscript{8,9,36} Some studies found high amounts of nickel

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**Figure 2.** Stratified analyses of the associations [odds ratio (95% confidence interval)] between urinary nickel concentrations and type 2 diabetes.

<table>
<thead>
<tr>
<th>Participant subgroup</th>
<th>Participants with diabetes</th>
<th>Participants without diabetes</th>
<th>Odds ratio ( a ) (95% confidence interval)</th>
<th>( P ) for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>3.87 (2.52-6.06)</td>
<td>3.45 (2.11-5.81)</td>
<td>1.30 (0.95-1.77)</td>
<td>0.50</td>
</tr>
<tr>
<td>≥65</td>
<td>4.16 (2.72-6.53)</td>
<td>3.39 (2.30-5.58)</td>
<td>1.43 (1.01-2.01)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>4.04 (2.63-6.62)</td>
<td>3.52 (2.31-6.04)</td>
<td>1.53 (1.07-2.19)</td>
<td>0.81</td>
</tr>
<tr>
<td>Women</td>
<td>4.01 (2.58-6.01)</td>
<td>3.38 (2.11-5.46)</td>
<td>1.23 (0.91-1.66)</td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Beijing</td>
<td>3.99 (2.51-6.21)</td>
<td>3.19 (2.10-5.27)</td>
<td>1.63 (1.13-2.34)</td>
<td>0.30</td>
</tr>
<tr>
<td>Shanghai</td>
<td>4.09 (2.70-6.53)</td>
<td>3.67 (2.28-6.04)</td>
<td>1.20 (0.88-1.64)</td>
<td></td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>4.18 (2.84-6.53)</td>
<td>3.36 (2.04-5.73)</td>
<td>1.50 (1.08-2.09)</td>
<td>0.52</td>
</tr>
<tr>
<td>Rural</td>
<td>3.84 (2.38-6.15)</td>
<td>3.47 (2.31-5.66)</td>
<td>1.23 (0.89-1.69)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4.14 (2.56-6.84)</td>
<td>3.53 (2.41-6.04)</td>
<td>1.64 (1.00-2.68)</td>
<td>0.93</td>
</tr>
<tr>
<td>No</td>
<td>4.02 (2.63-6.06)</td>
<td>3.39 (2.12-5.54)</td>
<td>1.28 (0.98-1.66)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24</td>
<td>4.03 (2.63-6.06)</td>
<td>3.44 (2.22-5.81)</td>
<td>1.29 (0.91-1.83)</td>
<td>0.51</td>
</tr>
<tr>
<td>24-27.9</td>
<td>3.80 (2.42-6.09)</td>
<td>3.28 (2.11-5.54)</td>
<td>1.58 (1.10-2.29)</td>
<td></td>
</tr>
<tr>
<td>≥28</td>
<td>4.44 (2.90-6.83)</td>
<td>3.67 (2.34-5.75)</td>
<td>1.13 (0.63-2.04)</td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>4.04 (2.60-6.36)</td>
<td>3.38 (2.15-5.52)</td>
<td>1.41 (1.07-1.87)</td>
<td>0.72</td>
</tr>
<tr>
<td>Moderate</td>
<td>4.42 (2.76-6.71)</td>
<td>3.41 (2.11-6.26)</td>
<td>1.37 (0.84-2.24)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>3.77 (2.57-5.72)</td>
<td>3.54 (2.50-5.84)</td>
<td>1.07 (0.53-2.16)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>4.03 (2.60-6.31)</td>
<td>3.40 (2.19-5.66)</td>
<td>1.33 (1.06-1.67)</td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \text{Adjusted for age, sex, region, residence, current smoking status, BMI, education, alcohol drinking, physical activity, family history of diabetes, urinary creatinine level (log-transformed) and C-reactive protein, stratifying factors excepted.} \)
in foods like spinach, cocoa, oatmeal, dark chocolate and dry legumes. However, we did not observe correlations between urinary nickel concentrations and consumption of rice, wheat or seafood (data not shown). In addition, tobacco smoking is another small but important source of non-occupational nickel exposure. In line with this idea, we found that both the median concentration of urinary nickel and the OR for having T2D were higher in smokers than in their non-smoking counterparts (Figure 2). Certainly, more studies are needed to clarify the major sources of nickel exposure and its health outcomes in different populations.

Association between nickel and T2D

In our study, elevated levels of urinary nickel were associated with not only elevated prevalence of T2D, but also increased levels of fasting plasma glucose, insulin, HbA1C and HOMA-IR. Although there has been no large-scale population study designed to investigate the association of nickel exposure with diabetes, higher blood and urinary nickel concentrations were reported in Pakistan diabetic patients \((n = 257)\) compared with non-diabetic controls \((n = 166)\) (blood nickel concentrations were \(2.7 \pm 0.86\) vs \(2.2 \pm 0.56\) \(\mu\)g/l in men, and \(2.5 \pm 0.6\) vs \(2.02 \pm 0.7\) \(\mu\)g/l in women, respectively, age range 46–60). However, another case-control study by Forte et al. showed that patients with type 2 diabetes \((n = 68,\) mean age 68.4 years) had lower blood nickel levels than non-diabetic controls \((n = 59,\) mean age 57.2 years) (blood nickel concentrations were 0.78 (0.66–0.87) vs 0.89 (0.74–1.15) \(\mu\)g/l, respectively). A previous study showed that blood nickel had a direct correlation with urine nickel \((r = 0.3)\). However, compared with urinary nickel, blood nickel level may mainly reflect recent exposure due to the short half-life of nickel in this compartment. Moreover, it remains unclear whether or to what degree such discrepancies between these studies could be explained by differences in participant characteristics (such as disease duration, medication use or magnitude of renal damage), sample size, nickel exposure levels, measurement methods (sector field inductively coupled plasma mass spectrometry vs atomic absorption spectrometer), or other factors that may influence blood nickel metabolism. Therefore, more large-scale population-based studies are needed to clarify the role of nickel exposure in the pathogenesis of type 2 diabetes in the future. Evidence from studies in rodent models demonstrated that nickel exposure was more potent than other divalent metals in affecting glucose homeostasis and inducing hyperglycaemia by impairing islet function, increasing hepatic glycogenolysis and pancreatic release of glucagon, reducing peripheral utilization of glucose and altering gluconeogenesis.

The underlying mechanism of nickel exposure in the pathogenesis of T2D is not yet fully elucidated. Das et al. reported that nickel treatment of rats could increase hepatic lipid peroxides and reduce several antioxidant enzymes including superoxide dismutase, catalase and glutathione peroxidase, as well as hepatic glutathione concentration. It was also reported that nickel might damage insulin function and induce glucose deregulation through the reactive oxygen species (ROS) pathway. Moreover, Gupta et al. found that nickel could also raise nitric oxide synthase (NOS) levels in rats, along with an increase in cyclic guanosine monophosphate, which might lead to hyperglycaemia by stimulating endocrine secretion. However, whether these findings in animal models can explain the association of nickel exposure with diabetes in humans needs thorough investigation in the future.

Strengths and limitations

To our knowledge, this is the first relatively large-scale population study that has revealed the association of nickel exposure with T2D. Comprehensive information regarding potential confounders were carefully analysed and controlled in our statistical analyses.

There were certain limitations in our study. First, due to the cross-sectional nature, a causal relationship between nickel and diabetes cannot be established, and a reverse causality is also possible in that elevated urinary nickel could be a consequence of diabetic renal damage. Thus, it is critical to carry out prospective studies in the future. Second, a single measurement of urinary nickel may not reflect long-term exposure. However, based on results from the German Environmental Survey in children, Wilhelm et al. suggested that under steady state conditions, a single urine measurement seems to be acceptable as it can reflect long-term nickel exposure when continuously consumed nickel-rich foods are presumably consistent with urine nickel levels. Third, first morning spot urine rather than 24-h urine samples were used in our study; thus the results might be influenced by biorhythm or collection time. However, it is generally not feasible to collect 24-h urine samples in large-scale epidemiological studies, and available studies suggest that spot urine is acceptable for measuring exposure levels of heavy metals such as arsenic. In the current study, we adjusted for urinary creatinine as a covariate to account for urine dilution. As an alternative, creatinine-corrected nickel concentration was also used in the models and the results remained largely unchanged. Finally, it is noteworthy that other environmental confounding factors may affect our
conclusions and such factors, if discovered, need to be taken into account in future analyses.

Conclusions
Our study showed for the first time that elevated urinary nickel concentrations were associated with increased prevalence of T2D in a Chinese population. From the perspective of public health, it is interesting and important to confirm whether there is a causal role of nickel exposure during the pathogenesis of diabetes in humans. Therefore, more studies in the general population, particularly with prospective designs, are warranted. Studies are also needed to elucidate the potential mechanisms underlying the relation between nickel exposure and diabetes in humans.

Supplementary Data
Supplementary data are available at IJE online.

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Conflict of interest: None declared.

References
Commentary:
Environmental chemicals and diabetes: which ones are we missing?

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