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Multiple metals exposure, elevated blood glucose and dysglycemia among Chinese occupational workers

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ABSTRACT

Aims: Exposure to metals may adversely affect cardiometabolic health. The aim of this study is to directly evaluate the roles of multiple metals exposure in glucose homeostasis, the dysfunction of which has been linked to diabetes and cardiovascular diseases (CVDs).
Methods: We performed a cross-sectional analysis of baseline data from 464 metal-exposed workers who participated in a large prospective occupational study in China (Jinchang Cohort). The logistic regression model was used to evaluate the association between urinary metal levels and high fasting plasma glucose (high-FPG) (≥ 75th percentile) and dysglycemia.
Results: Increasing levels of urinary nickel were prospectively associated with high-FPG: multivariable odds ratios (ORs) were 1.00 for the 1st quartile (lowest), 1.20 (95% confidence interval [CI]: 0.60–2.43) for the 2nd quartile, 1.64 (0.78–3.49) for the 3rd quartile and 3.17 (1.38–7.30) for the 4th quartile (highest) (P-trend = 0.004). The positive associations were also observed between urinary zinc and high-FPG (4th vs. 1st quartile = 2.71, 95%CI: 1.26–5.84, P-trend = 0.01). Inverse associations between urinary cobalt and risk of high-FPG and dysglycemia were observed (P-trend <0.05). For dysglycemia, the positive trends of increasing levels of urinary nickel and zinc still remained, although urinary nickel was no longer statistically significant. A significant association between urinary arsenic and dysglycemia was also found. However, no associations were observed between urinary copper, cadmium, and risk of high-FPG or dysglycemia.
Conclusion: Multiple urinary metals, particularly arsenic, nickel, zinc, and cobalt, were associated with elevated blood glucose among Chinese occupational workers, supporting the notion that metal exposure plays a critical role in the development of diabetes.

1. Introduction

Exposure to metals may adversely affect cardiometabolic health, although evidence for the association between metal exposure and dysregulation of glucose homeostasis is limited or conflicting (Järup, 2003). Toxic metals, such as arsenic (As) and cadmium (Cd), may play a role in the development of dysglycemia (elevated fasting plasma glucose [FPG], impaired fasting glucose [IFG] and diabetes) (Afridi, Kazi, Kazi, et al., 2008; Chen, Yang, Huang, et al., 2009; Feng, Cui, Liu, et al., 2015). Compared with some well-established risk factors of diabetes, such as diet and physical activity, the impact of metals on diabetes development has been grossly under-researched and their effects possibly underestimated (Kuo & Navas-Acien, 2015).

Some previous studies (Feng et al., 2015; Kuo, Howard, Umans, et al., 2015; Navas-Acien, Silbergeld, Pastor-Barriuso, et al., 2009), but not all (Steinmaus, Yuan, Liaw, et al., 2009; Zierold, Knobeloch, & Anderson, 2004), suggested that exposure to high urinary As level was related to increased risk of type 2 diabetes (T2D), while urinary Cd was inconsistently associated with altered high FPG and IFG (Feng et al., 2015; Swaddiwudhipong, Mahasakpan, Limpatanachote, et al., 2010). Additionally, some heavy metals, including cobalt (Co), copper

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(Cu), nickel (Ni) and zinc (Zn), are also considered essential nutrients that are involved in various metabolic pathways and biological functions (Fraga, 2005). Both deficiencies and excesses of these elements are frequently related to T2D risk (Chen et al., 2009; Feng et al., 2015). Specifically, Ni may coexist or interact with other metals, such as As and Cd, which also have been associated with T2D (Liu, Sun, Pan, et al., 2015). However, relatively low exposure in the general population in the U.S. precluded them from being evaluated in relation to T2D risk.

Occupational exposure to metals occurs predominantly in mining, refining, alloy production and welding. However, except As, no information is available on links between other metals and diabetes risk in occupational populations or highly exposed general populations. Recent studies, including our own, have implicated that occupational metal exposures affect T2D risk (Liu, Feng, Wang, et al., 2016; Yang, Cheng, Pu, et al., 2015), but the effects of interactions due to multiple metals exposure were not addressed (Kuo & Navas-Acien, 2015). The Jinchang nonferrous metal industry is located at Jinchang city, Gansu province, China. It is the third largest nickel and second largest cobalt manufacturing enterprise in the world. Workers of the Jinchang Industry are routinely exposed to nickel as well as several other metals at high levels that have been measured in their urine. At present, little data are available directly evaluating the roles of multiple metals exposure in glucose and lipid homeostasis whose dysfunctions are known pathways to diabetes and cardiovascular diseases (CVDs). The objective of this study was to examine the associations of elevated FPG and dysglycemia with multiple urinary metals, including As, Cd, Co, Cu, Ni and Zn, among those occupational workers.

2. Material and methods

2.1. Study population

This study was based on data obtained from the baseline survey of the Jinchang Cohort Study, an ongoing perspective metal-exposed workers study in the Jinchang Nonferrous Metal Industry. The rationale, design, and methods of the cohort have been detailed elsewhere (Bai, Yang, Pu, et al., 2014). Briefly, we began the baseline survey from June 2011 to December 2013, after which all workers in the cohort participated in medical exams every other year that include in-person interviews, comprehensive physical exams, lab-based tests, and biosample collection. In the current study, a total of 464 occupational workers aged 20 to 50 years were included; they were randomly selected and matched by age from the specific occupation subgroups (office workers, mining/production workers, and smelting workers) of the Jinchang Industry (Yang et al., 2015). All subjects had given written informed consent and the study protocol was approved by the Ethical Committees of Workers' Hospital of the Jinchang industry and the Ethical Committees of the Public Health School of Lanzhou University.

2.2. Data collection

We collected several types of data in this study including questionnaire data obtained from in-person interviews, clinical data from physical, and biochemical examinations. In-person interviews were conducted by trained interviewers using a standardized questionnaire that included questions pertaining to prior use of tobacco and alcohol, family history of T2D, medical history, as well as other demographic, socioeconomic and lifestyle factors. The physical examination was performed by clinicians at the Worker's Hospital of the Jinchang Industry after the completion of the in-person interview. The examination included a measurement of weight, height and blood pressure. Automatic recording instruments (SK-X80/TCS-160D-W/H, Sonka, China) were used to measure weight and height. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Arterial blood pressure was measured three times at the end of the physical examination, with the participant in the seated position after 5 min of rest.

The biochemical examinations were measured using a clinical chemistry automatic analyzer (Hitachi 7600-020, Kyoto, Japan) during the morning, which included FPG, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). The blood glucose levels were measured by the glucose oxidase method. Plasma high-sensitive C-reactive protein (CRP) was measured by latex-enhanced immunoturbidimetric assay (MS-CRP test kit; Medical System, Zhejiang, China).

2.3. Urinary metal assessment

Spot urine specimens were collected in cryogenic tubes, stored at −40 °C, and then shipped on dry ice to the Public Health School of Lanzhou University. Urinary metals were detected using Inductively Coupled Plasma Mass Spectrometry (ICP-MS, Agilent 7700, Agilent Technologies, Santa Clara, CA, USA). All urine samples were coded and analyzed by lab personnel blind to their origin. Each 1 mL of the urine samples was mixed with 3.0% HNO3 to the final volume of 2.5 ml for overnight nitrification. The standard reference material human urine (SRM2670A, National Institute of Standards and Technology, Gaithersburg, MD, USA) was used as an external quality control, and sample spike-recoveries were used to confirm analytical recovery, which was 95%. The intra-day and inter-day coefficient of variation was within 5%. Urine creatinine concentrations were measured by the Sarcosine Oxidase Methods (Suzuki, 1994) with a Mindray BS-200 CREA Kit (Shenzhen Mindray Bio-medical Electronics Co., Ltd., Shenzhen, China).

2.4. Definitions

The outcomes of this analysis included high-FPG and dysglycemia. The cutoff point for high-FPG in this study was determined as 93.6 mg/dL (5.2 mmol/L), which corresponded as the 75th percentile. Dysglycemia was defined as IFG or T2D. IFG was defined as fasting plasma glucose 100–125 mg/dL (5.6–6.9 mmol/L). T2D was defined as fasting plasma glucose ≥126 mg/dL (≥ 7.0 mmol/L) or those who were on anti-diabetic medications at the time of the baseline interview.(Association, 2014) A pack year was defined as twenty cigarettes smoked every day for one year, which is equivalent to 7300 cigarettes smoked(Bernaards, Twisk, Snel, et al., 2001). Current drinker was defined as subject who drank hard liquor, beer, or wine at least one time per week during the past six months. Hypertension was defined as systolic ≥140 mmHg or diastolic ≥90 mmHg, or self-reported treatment for hypertension. Family history of T2D was defined as having at least one parent, sibling, or offspring with T2D. Abnormal lipid measurements were defined as (CDS, 2004): TG ≥ 1.70 mmol/L (150 mg/dL) or HDL-C < 0.9 mmol/L (35 mg/dL) in men and <1.0 mmol/L (39 mg/dL) in women.

2.5. Statistical analysis

Descriptive statistics were used to describe the frequency and proportion, mean and standard deviation (SD) of the demographic and clinical characteristics. Logistic regression model was used to test odds ratios (ORs) and confidence intervals (CIs) of high-FPG for each urinary metals quartile compared with the lowest quartile. Tests of linear trend across increasing quartiles of urinary metals were conducted by assigning the medians of metals in quartiles treated as a continuous variable. Basic models were adjusted for other known risk factors for T2D or high-FPG, including age, sex, years of education (<10, 10–12, and >12 years), occupation (office, mining/production, and smelting workers), BMI (<25 or ≥25 kg/m^2), smoking pack-years,

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current drinker (yes or no), family history of T2D, abnormal lipid, CRP, and urinary creatinine level. Smoking pack-years were categorized into tertiles (< 5, 5–15, and >15 pack-years). We additionally controlled the other urinary metals measured in the study when assessing the association between one of the measured metals. Pearson's correlation was calculated to explore the inter-metal relationships. Lastly, we examined the association of urinary metals with dysglycemia. Statistical analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC). All reported *P* values were made on the basis of two-side tests with a significance level of 0.05.

3. Results

Table 1 showed the characteristics of workers with (n = 130) and without high-FPG (n = 334). Among 464 workers, the mean age was 38.0 and 35.6 years for workers with and without high-FPG, respectively. The average of FPG in participants was 90.0 mg/dL. Workers with high-FPG were more likely to be male workers, smokers and alcohol drinkers. High-FPG was also associated with abnormal lipid and hypertension. Occupation, education and BMI did not differ significantly across high-FPG.

The median urinary levels of metals were 60.55 μg/L for As, 0.68 μg/L for Cd, 0.69 μg/L for Co, 16.60 μg/L for Cu, 5.29 μg/L for Ni and 361.83 μg/L for Zn. The detailed distribution of urinary metal concentrations, including unadjusted and adjusted for urinary creatinine, was given in Supplemental Table A. Except Zn with arsenic and nickel, many of metals were correlated with each other; a particularly strong positive correlation was observed for Ni and Co (r = 0.58, $P < 0.001$) (Supplemental Table B).

Table 2 showed adjusted ORs for high-FPG according to quartiles of urinary levels of metals. In model 1, after adjustment for demographic, lifestyle covariates (i.e. sex, age, education, occupation, smoking pack-years, current drinker), and clinical variables (i.e. BMI, family history of T2D, abnormal lipid, CRP, hypertension and urinary creatinine level), the ORs (95% CI) of high-FPG for increasing quartiles of urinary Ni were 1.00 (reference), 0.96 (0.51–1.81), 1.11 (0.58–2.10), and 1.64 (0.85–3.15), respectively (P for trend = 0.05). The positive associations were also observed between urinary Zn and high-FPG (P for trend = 0.03). Workers in the 2nd quartile of urinary arsenic had significantly higher FPG levels compared with participants in the 1st quartile (OR = 1.92, 95% CI: 1.03–3.59). Following additional adjustment for multiple metals measured in this study (model 2), an inverse association between higher levels of urinary Co and high-FPG was observed (4th quartile vs. 1st quartile: OR = 0.22, 95% CI: 0.08–0.63), P for trend = 0.01). The ORs (95% CIs) for high-FPG with quartiles of urinary Ni were 1.00 (reference), 1.20 (0.60–2.43), 1.64 (0.78–3.49), 3.17 (1.38–7.30), respectively (P for trend = 0.004). A statistically significant association between higher levels of urinary Zn and high-FPG was still observed (P for trend = 0.01). However, we did not observe a significant relationship between high-FPG and levels of urinary As, Cd and Cu.

Among 464 workers in this study, there were 44 (9.5%) workers with IFG and 11 (2.4%) workers with T2D. We further examined the relationship between levels of urinary metal and dysglycemia risk (Fig. 1). Overall, after adjusting for all demographic, lifestyle, and clinical covariates as well as multiple urinary metals, urinary levels of Co were inversely associated with dysglycemia risk (4th quartile vs. 1st quartile = 0.09 (95% CI: 0.02–0.44), P for trend = 0.04). Increasing levels of urinary Zn quartiles were also positively associated with IFG risk (P for trend = 0.02). For urinary Ni, the positive trend in the current study still remained, although it was no longer statistically significant at the conventional $P = 0.05$. The ORs (95%CI) for dysglycemia in the 2nd and 4th quartiles of urinary As were 6.42 (2.28–18.1) and 4.78 (1.44–15.87), respectively.

Table 1
Basic characteristics and clinical parameters among 464 workers in a population-based occupational cohort.

Variables[a]	High-FPG (≥ 93.6 mg/dL)	Non High-FPG (< 93.6 mg/dL)	Total
Sex	130 (25.0)	334 (75.0)	464 (100.0)
Men	81 (62.3)	155 (46.4)	236 (50.9)
Women	49 (37.7)	179 (53.6)	228 (49.1)
Age (years)	38.0 (7.3)	35.6 (7.4)	36.3 (7.4)
Occupation			
Office workers	20 (15.4)	76 (22.8)	96 (20.7)
Mining/production workers	54 (41.5)	123 (36.8)	177 (38.1)
Smelting workers	56 (43.1)	135 (40.4)	191 (41.2)
Cigarettes smoked per day	6.2 (10.1)	4.1 (7.3)	4.7 (8.2)
Smoking years	6.8 (10.1)	4.7 (8.1)	5.3 (8.8)
Pack-years of smoking			
Non-smoker	81 (62.3)	230 (68.9)	311 (67.0)
<5	10 (7.7)	41 (12.3)	51 (11.0)
5–15	20 (15.4)	34 (10.2)	54 (11.6)
>15	19 (14.6)	29 (8.7)	48 (10.3)
Current drinking			
Yes	29 (22.3)	52 (15.6)	81 (17.4)
No	101 (77.7)	282 (84.4)	383 (82.6)
BMI (kg/m^2)	23.4 (2.8)	22.1 (3.0)	22.4 (3.0)
<25	93 (71.5)	277 (82.9)	370 (79.7)
≥30	37 (28.5)	57 (17.1)	94 (20.3)
Total cholesterol (mmol/L)	4.7 (0.9)	4.5 (0.9)	4.5 (0.9)
Triglyceride (mmol/L)	2.1 (1.6)	1.6 (1.4)	1.7 (1.4)
H-DLC (mmol/L)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)
L-DLC (mmol/L)	3.0 (0.6)	2.9 (0.6)	2.9 (0.6)
CRP (mg/L)	1.4 (1.6)	1.3 (0.9)	1.3 (1.1)
Glucose (mg/dL)	106.2 (27.0)	82.8 (5.4)	90.0 (18.0)
Family history of diabetes	20 (15.4)	59 (17.7)	79 (17.0)
Abnormal lipid	64 (49.2)	109 (32.6)	173 (37.3)
Hypertension	26 (13.4)	36 (10.8)	62 (13.4)

BMI: body mass index; H-DLC: high-density lipoprotein cholesterol; LDL-cholesterol: low-density lipoprotein cholesterol; CRP: C-reactive protein.
[a] Data were presented as Means (SD) or n (%).

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Table 2
Multivariable adjusted odds ratios of high-FPG according to quartiles of urinary metal levels among 464 workers in a population-based occupational cohort study.

ORs (95% CI)	Quartile of Urinary Metal Levels (μg/L)				
	Q1 (Lowest)	Q2	Q3	Q4 (Highest)	*P* for trend
Arsenic	< 36.79	36.79–60.55	60.55–114.47	≥ 114.47	
n (cases/non-case)	29/86	41/74	27/90	33/84	
Crud ORs	1.00	1.64 (0.93–2.9)	0.89 (0.49–1.62)	1.17 (0.65–2.09)	0.71
Model 1[a]	1.00	1.92 (1.03–3.59)	1.06 (0.54–2.07)	1.59 (0.82–3.06)	0.41
Model 2[b]	1.00	1.97 (0.99–3.90)	1.12 (0.54–2.35)	1.89 (0.90–3.97)	0.31
Cadmium	< 0.43	0.43–0.68	0.68–1.17	≥ 1.17	
n (cases/non-case)	31/86	34/87	29/84	36/77	
Crud ORs	1.00	1.08 (0.61–1.92)	0.96 (0.53–1.73)	1.3 (0.73–2.29)	0.05
Model 1	1.00	1.28 (0.67–2.43)	1.14 (0.58–2.27)	1.19 (0.58–2.44)	0.74
Model 2	1.00	1.12 (0.55–2.27)	1.09 (0.51–2.35)	1.04 (0.46–2.38)	0.93
Cobalt	< 0.46	0.46–0.69	0.69–1.21	≥ 1.21	
n (cases/non-case)	40/76	37/79	30/88	23/91	
Crud ORs	1.00	0.89 (0.52–1.54)	0.65 (0.37–1.14)	0.48 (0.26–0.87)	0.01
Model 1	1.00	0.84 (0.46–1.54)	0.70 (0.35–1.4)	0.50 (0.22–1.11)	0.14
Model 2	1.00	0.60 (0.30–1.22)	0.46 (0.20–1.06)	0.22 (0.08–0.63)	0.01
Cupper	< 12.14	12.14–16.60	16.60–21.99	≥ 21.99	
n (cases/non-case)	34/78	34/80	27/94	35/82	
Crud ORs	1.00	0.98 (0.55–1.72)	0.66 (0.37–1.19)	0.98 (0.56–1.72)	0.90
Model 1	1.00	0.89 (0.48–1.63)	0.55 (0.28–1.05)	0.79 (0.40–1.59)	0.59
Model 2	1.00	0.83 (0.42–1.62)	0.41 (0.20–0.87)	0.63 (0.28–1.42)	0.26
Nickel	< 3.43	3.43–5.29	5.29–9.06	≥ 9.06	
n (cases/non-case)	32/84	27/88	33/85	38/77	
Crud ORs	1.00	0.81 (0.45–1.46)	1.02 (0.58–1.81)	1.3 (0.74–2.27)	0.68
Model 1	1.00	0.96 (0.51–1.81)	1.11 (0.58–2.1)	1.64 (0.85–3.15)	0.05
Model 2	1.00	1.20 (0.60–2.43)	1.64 (0.78–3.49)	3.17 (1.38–7.30)	0.004
Zinc	< 219.74	219.74–361.83	361.83–584.43	≥ 584.43	
n (cases/non-case)	22/95	30/87	38/82	40/70	
Crud ORs	1.00	1.49 (0.8–2.77)	2 (1.1–3.66)	2.47 (1.35–4.52)	0.001
Model 1	1.00	1.40 (0.72–2.72)	1.69 (0.88–3.23)	2.10 (1.04–4.23)	0.03
Model 2	1.00	1.48 (0.72–3.02)	2.07 (1.02–4.19)	2.71 (1.26–5.84)	0.01

[a] Model 1: adjusted for sex, age, education, occupation, BMI, pack-years, current drinker, family history of diabetes, abnormal lipid, C-reactive protein, hypertension, and urinary creatinine level.
[b] Model 2: additionally adjusted for arsenic, cadmium, cobalt, copper, nickel and zinc fitted simultaneously.

4. Discussion

In this occupational population-based study, elevated levels of urinary Ni, As and Zn were positively associated with increased blood glucose or dysglycemia, and urinary Co was inversely associated with risk of high-FPG and dysglycemia. We observed a strong positive correlation between urinary Ni and Co but no statistically significant associations between urinary Cu and Cd, and risk of high-FPG and dysglycemia.

Several strengths and limitations need to be kept in mind when interpreting these findings. First, because of the occupational nature of our study, we have achieved an objective assessment of multiple metals exposure simultaneously in these workers, allowing the examination of which metal in particular may be driving the increased blood glucose and lipid levels in these workers. Second, comprehensive information regarding potential confounders was also carefully measured and analyzed, thus minimizing the probability of bias. A limitation of the current study was the small sample size. Nevertheless, even with limited sample size, we were still able to observe the associations of multiple metals exposure with elevated blood glucose and dysglycemia risk in this hypotheses-generating study. Another limitation was that urinary metal concentration reflects the amount of metal that gets into the body by all routes of exposure, which may not reflect the actual level of occupational exposure. However, urine is an ideal specimen for many types of exposure assessment in occupational studies, because urine samples can be collected non-invasively and pose almost no risk to humans (Li, Ma, van der Kuijp, et al., 2014). There might be other relevant exposures aside from metals that could increase risk of high-FPG and FPG.

4.1. Metal exposure levels

Urinary levels of As, Co and Ni mainly reflect recent exposures (2010, USCDC, 2009, WHO, 2001). Cd level in urine best reflects cumulative environmental exposure. Workers in certain occupational settings, such as mining, smelting, welding, or the manufacture of Cu and Zn alloys, may be exposed to higher amount of Cu and Zn (Clark, Teschke, Rideout, et al., 2007). Compared with the general populations, the median level of urinary As in nonferrous metal workers was approximately two times higher than that of the Chinese general population (60.55 vs. 28.43 μg/L) (Feng et al., 2015), eight times higher than the level in US general population (USCDC, 2009) (60.55 vs. 7.90 μg/L) and six times higher than the level in Canadian general population (60.55 vs. 11.67) (2010). The levels of urinary Co, Ni, Cu and Zn were also higher than other reported general and occupational populations (Table 3). So far, there are no internationally acceptable references for these urinary levels of metals in occupational or general populations (Wilhelm, Ewers, & Schulz, 2004). By studying metal-exposed workers at high levels in the Jinchang Cohort Study, it is a practical and cost-effective way to evaluate the effect of multiple metals exposure and its link with T2D. In this study, we observed strong positive correlation between urinary Ni and Co, implicating that there might exist potential inter-metal effects due to multiple metal exposures in affecting risk of high-FPG and dysglycemia.

4.2. Ni and Co

For Ni, growing evidence suggested that elevated level of urinary Ni was associated with T2D or elevated FPG risk (Feng et al., 2015; Liu

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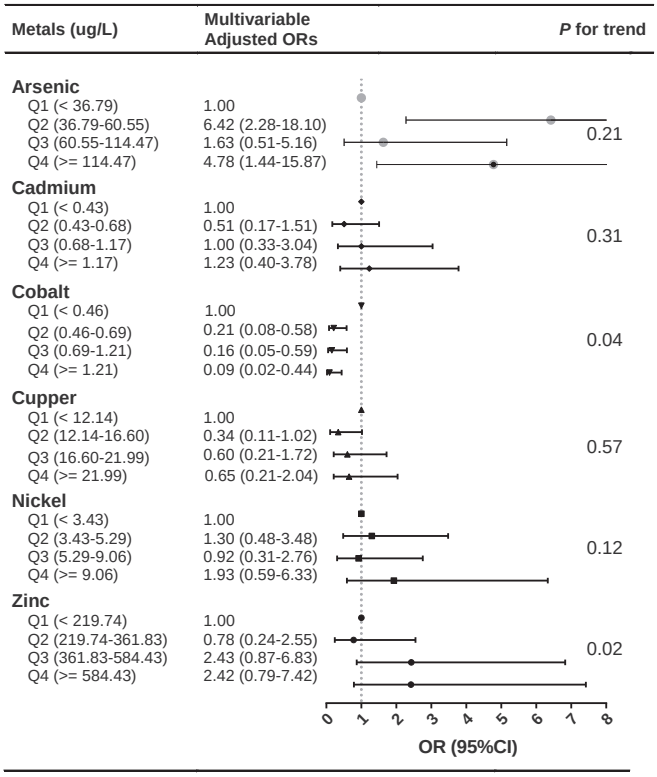

Fig. 1. Associations (OR, 95% CI) between urinary levels of metals and dysglycemia risk among 464 workers in a population-based occupational cohort study. Q = quartile. Data were presented as odds ratio (OR) and 95% confidence interval (95% CI). Adjusted for sex, age, education, occupation, BMI, pack-years, current drinker, family history of diabetes, abnormal lipid C-reactive protein, hypertension, urinary creatinine level, arsenic, cadmium, cobalt, copper, nickel and zinc fitted simultaneously.

et al., 2015). No information is available on the link between Ni exposure and diabetes or dysglycemia in occupational populations. Liu et al. (2015)) reported a cross-sectional association between urinary Ni with the prevalence of diabetes among 2155 people in the Chinese general population in 2015. This was the first study formally assessing the association between nickel exposure and diabetes risk (Kuo & Navas-Acien, 2015). However, the effect of multi-exposure was not evaluated in this study, which is under potentially diabetogenic. In the current study, when adjusting for traditional risk factors, such as age, BMI, smoking and drinking, we did not observe statistically significant association of urinary Ni with high-FPG risk, but additionally adjusting for other 5 urinary metals, the relation of urinary Ni with high-FPG risk was observed. Consistent with previous report (Kazi, Afridi, Kazi, et al., 2008a, 2008b), our study indicated that urinary Co was inversely associated with high-FPG risk. We also observed a strong positive correlation between urinary Ni and Co in this study, suggesting that urinary nickel in particular may be driving the increased risk of high-FPG and dysglycemia. Future studies investigating Ni exposure as a risk factor for diabetes should adequately account for the impact of Co exposure.

The underlying mechanism of Ni in the pathogenesis of dysglycemia is not yet fully understood. Some studies in animal models indicated that Ni may damage insulin function, increase hepatic glycolysis and pancreatic glucagon release, and increase plasma glucose levels (Kubrak, Rovenko, Husak, et al., 2012; Tikare, Das Gupta, Dhundasi, et al., 2008). Cobalt is acutely toxic in large doses and in cumulative and long-term exposure (Simonsen, Harbak, & Bennekou, 2012). Cobalt also is an essential micronutrient in the form of vitamin B12 (Taylor, Hancock, Hincapie, et al., 1978). An animal study reported that the glycemia-lowering effect of cobalt chloride ($CoCl_2$) decreased systemic glucose production and increased tissue glucose uptake, and increased expression of glucose transporter 1 (GLUT1) and inhibition gluconeogenesis (Saker, Ybarra, Leahy, et al., 1998). Future research in humans is needed to examine these findings.

4.3. As, Cu, and Cd

The association between arsenic exposure and diabetes risk has received special attention for more than two decades (Kuo & Navas-Acien, 2015). Epidemiological studies from occupational populations to general populations strongly supported that exposure to As was an independent risk factor for T2D (Bräuner, Nordsborg, Andersen, et al., 2014; Kuo, Moon, Thayer, et al., 2013; Sung, Huang, & Guo, 2015). We observed a significant association between urinary arsenic and dysglycemia risk. Experimental studies suggested that As could affect β-cell function and insulin sensitivity through oxidative stress, glucose uptake and transport, gluconeogenesis and adipocyte differentiation (Druwe & Vaillancourt, 2010); act as an endocrine disrupter affecting the function of hormone receptors (Davey, Bodwell, Gosse, et al., 2007); and impact diabetes through epigenetic mechanisms (Smeester, Rager, Bailey, et al., 2011). For Cu, the deficiency of Cu could decrease insulin response and increase glucose response (Siddiqui, Bawazeer, & Scaria Joy, 2014). However, no association was observed between urinary copper and elevated FPG or dysglycemia risk in this study, which was in line with recent studies (Ekmekcioglu, Prohaska, Pomazal, et al., 2001; Kazi et al., 2008a, 2008b). Cd is not physiologically or biochemically essential to an organism. Findings from animal studies indicated that Cd could cause high blood glucose through the induction of oxidative stress and disruption of pancreatic β-cell function (Satarug & Moore, 2012). One previous study reported that prevalence of IFG and T2D increased proportionally with increasing urinary cadmium levels (Stewart, Killeen, Naquin, et al., 2003).

Table 3
Comparison of urinary levels of metals from nonferrous metal workers in China and levels reported other populations.

Variables	Present Study	Feng et al., 2015[a]	US[b]/Canada H., 2010[c]
Population	Chinese nonferrous metal workers	Chinese general population	US/Canada general population
Sample size (n)	464	2242	2329/5319
Testing method	ICP-MS	ICP-MS	ICP-MS
Urinary levels of metals (μg/L), Median (interquartile range)			
Arsenic	60.55 (36.79–114.47)	28.43 (17.17–46.47)	7.90/11.67 (5.85–23.77)
Cadmium	0.68 (0.43–1.17)	0.89 (0.53–1.42)	0.27/0.38 (0.20–0.68)
Cobalt	0.69 (0.46–1.21)	0.24 (0.16–0.40)	0.30 (0.46–1.06)[b]
Copper	16.60 (12.14–21.99)	7.40 (5.20–10.71)	0.38 (0.20–0.68)[c]
Nickel	5.29 (3.43–9.06)	2.26 (1.48–3.52)	1.16 (0.65–2.03)[c]
Zinc	361.83 (219.74–584.43)	270.49 (168.04–412.42)	274.33 (136.98–524.69)[c]

[a] Chinese general population (18–80 years) in Wuhan City (2011).
[b] US general population (≥ 20 years), The Fourth National Report on Human Exposure to Environmental Chemicals (2011–2012), (Updated February 2015).
[c] Canada general population (6–79 years), Report on Human Expose to Environmental Chemicals in Canada, (2001–2009).

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4.4. Zn

Zn plays an important role in glucose metabolism (Isbir, Tamer, Taylor, et al., 1994). A meta-analysis showed that Zn supplementation has beneficial effects on glycemic control, and increased utilization of glucose by muscle and fat cells (Jayawardena, Ranasinghe, Galappatthy, et al., 2012). Clinical and epidemiological studies suggested that lower serum Zn levels are usually found in diabetics due to hyperglycemia, which interferes with the active transport of Zn back into the renal tubular cells and, thus, may lead to loss of Zn via the urine of diabetes patients (Aguilar, Saavedra, Arrieta, et al., 2007; Chausmer, 1998; Ferdousi & Mia, 2012). In accordance with previous studies, we observed that urinary Zn was strongly associated with increased risk of FPG and dysglycemia (Feng et al., 2015; Kazi et al., 2008a, 2008b).

In summary, multiple urinary metals, particularly Ni, As, Zn, and Co, were associated with elevated blood glucose, impaired fasting glucose, and diabetes among Chinese occupational workers, indicating that metal exposure may play a role in the development of diabetes. Further prospective studies with large sample sizes are needed to validate these associations.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jdiacomp.2016.07.022.

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