



Original Article

# Occupational exposure to heavy metals, alcohol intake, and risk of type 2 diabetes and prediabetes among Chinese male workers

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## Abstract

**Objective:** Both exposure to heavy metals and alcohol intake have been related to the risk of type 2 diabetes (T2D). In this study, we aimed to assess the potential interactions between metal exposure and alcohol intake on the risk of T2D and prediabetes in a cohort of Chinese male workers.

**Methods:** We conducted a cross-sectional analysis of 26,008 Chinese male workers in an occupational cohort study from 2011 to 2013. We assessed metal exposure and alcohol consumption at baseline in these workers who were aged  $\geq 20$  years. Based on occupations which were categorized according to measured urine metal levels, multiple logistic regression analyses were used to evaluate the independent and joint effects of metal and alcohol exposure on the risk of T2D and prediabetes.

**Results:** Risks of T2D ( $P_{\text{trend}} = 0.001$ ) and prediabetes ( $P_{\text{trend}} = 0.001$ ) were significantly elevated with increasing number of standard drinks per week, years of drinking, and lifetime alcohol consumption. An adjusted odds ratio (OR) of 6.1 (95% confidence interval [CI]: 4.8–7.8) was observed for the smelting/refining workers (highest metal exposure levels) who had the highest lifetime alcohol consumption ( $>873$  kg) ( $P_{\text{interaction}} = 0.018$ ), whereas no statistically significant joint effect was found for prediabetes ( $P_{\text{interaction}} = 0.515$ ).

**Conclusions:** Both exposures to metal and heavy alcohol intake were associated with the risk of diabetes in this large cohort of male workers. There was a strong interaction between these two exposures in affecting diabetes risk that needs to be confirmed in future studies.

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**Keywords:** Metals; Alcohol; Type 2 diabetes; Prediabetes; Interaction

## Introduction

Type 2 diabetes (T2D) is approaching epidemic proportions and is becoming a major public health problem.<sup>1</sup> T2D is strongly influenced by some well-established risk factors, including family history of diabetes, obesity, physical inactivity, tobacco use, and alcohol consumption.<sup>2</sup> The relationship between alcohol consumption and the increased risk of T2D has been studied in numerous prospective studies. Several previous studies,<sup>3–6</sup> but not all<sup>7,8</sup> showed that the risk of T2D was influenced by alcohol intake.<sup>9</sup> Identification of novel preventable risk factors is of utter importance, because the established risk factors do not fully account for the rapid increase in T2D rate.

Besides the traditional risk factors for T2D, such as alcohol intake, diet and physical activity, the role of environmental factors, particularly heavy metals, has gained considerable attention worldwide.<sup>10–12</sup> Recent studies showed that the exposure to heavy metals was associated with an increased risk of T2D.<sup>13–17</sup> The results of our previous studies also implied that occupations associated with higher levels of metal exposure were related with an increased risk of T2D.<sup>18–20</sup> However, few studies to date have analyzed the potential joint interactive effects of heavy metal exposure and alcohol intake on the risk of T2D or prediabetes. In this study, we assessed the potential interactions between metal exposure and alcohol intake, and the risk of T2D and prediabetes in 26,008 Chinese male workers exposed to heavy metals.

## Materials and methods

### *Study population*

This study was a part of an ongoing occupational cohort study – the Jinchang Cohort Study, which is a large prospective study of about 45,000 metal-exposed workers aged  $\geq 20$  years in the Jinchang Nonferrous Metal Industry, China. The details of the study rationale and profile have been described elsewhere.<sup>21</sup> In brief, a total of 42,122 participants were included from the baseline survey of the cohort; 26,008 (61.7%) were men and 16,114 (38.3%) were women. Approximately 36.6% of the men ( $n = 9511$ ) consumed alcohol, whereas 97.6%

( $n = 15734$ ) of the women did not consume alcohol. Given the low alcohol intake prevalence among the female workers, we conducted this cross-sectional analysis of the joint effects of alcohol intake and metal exposure on the risks of T2D and prediabetes in men only. This study also obtained the approval from the Ethical Committee of the Public Health School of Lanzhou University and the written informed consent from the participants.

### *Data collection*

The baseline survey was performed by trained interviewers via face-to-face interviews using a standardized and structured questionnaire that included questions pertaining to prior use of alcohol and tobacco, an assessment of lifetime occupational history, medical history, and other demographic, socioeconomic, and lifestyle factors. The clinical data were obtained through physical and biochemical examinations performed by clinicians at the Worker's Hospital of the Jinchang Company. These included blood pressure level, height, weight, and levels of fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Based on the World Health Organization (WHO) standards<sup>22</sup>: T2D was defined as a FPG level  $\geq 7.0$  mmol/L, and/or use of insulin or oral hypoglycemic agents at the time of the baseline survey. Prediabetes was defined as a FPG level between 5.6 mmol/L and 6.9 mmol/L in male workers without a prior diabetes diagnosis.

### *Alcohol intake and metal exposure assessment*

The questions regarding alcohol intake assessed the current drinking status, age of drinking initiation, alcohol content, and specific amount; the frequency and volume of alcohol intake were determined for all types of alcoholic beverages, including hard liquor, beer, and wine. One standard drink was converted to 14.0 grams of pure alcohol.<sup>23</sup> Non-drinkers were defined as those subjects who always drank less than once per week, or not at all. The number of standard drinks per week was categorized into four groups on the basis of quartile distributions in all of the cohort members:  $\leq 9$  drinks/week, 10–24 drinks/week,

25–56 drinks/week, and >56 drinks/week. The lifetime consumption of alcohol was measured as a drinking index, which was defined as kilograms of drinking per year multiplied by drinking years (kg × year). This metric was divided and analyzed based on the quartile distribution of all participants (the lowest quartile ≤99 kg, second quartile 100–322 kg, third quartile 323–873 kg, and highest quartile of intake >873 kg).

The estimation of the likely level of occupational metal exposure for each male worker of the cohort was based on the process of production in the company. The detailed method of occupational metal exposure assessment has been described in a previous publication.<sup>19</sup> Briefly, occupations related with possible metal exposure were assigned into three categories based on the possible level of exposure: office (low level), metal mining/production (intermediate level), and smelting/refining (high level) occupations. These three categories of occupations were validated through obtaining the urinary metal levels in a subgroup of 150 male workers, aged 20–50 years, matched by age. We used the occupational history information obtained from the baseline survey of the cohort to assign male workers into these 3 categories. The occupational categorization for those with T2D was based on the occupation at the time of diagnosis, whereas those male workers who did not have T2D were assigned to the occupational category that they had spent the longest time working in. Relatively few subjects (<10%) had worked in more than one of the three occupational categories in their lifetime (Fig. 1). For example, among the workers with T2D with more than one occupation in their lifetime, only 9.6% (n = 117) had worked in different occupational categories among the three we evaluated

in this study. Among the non-diabetic male workers with >1 occupation in their lifetime, 7.7% (n = 765) had worked in different occupational categories.

Statistical analyses

Multivariable logistic regression analysis was conducted to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) between the occupational groups, alcohol intake and the risks of T2D and prediabetes adjusting for potential confounders that included age (≤60, >60 years), body mass index (BMI) category (normal weight [<25], overweight [25–29.9] and obesity [≥30]),<sup>24</sup> abnormal lipids (yes, no), family history of diabetes (yes, no), and smoking status (non-smoker, current, former). Abnormal lipid levels were defined as: TG level >1.70 mmol/L (150 mg/dL) or HDL-C <0.9 mmol/L (35 mg/dL). We also tested for a trend in relation to the drinking by assigning median values of the intake quartiles as continuous variables in the model. The interaction effects between the occupational groups and alcohol intake were evaluated by including cross-product terms in the model. Data were analyzed using SAS 9.3 (SAS Institute, Cary, NC, USA). All reported P values were made on the basis of two-sided tests with a significance level of 0.05.

Results

Table 1 shows the characteristics of the participants according to the occupations associated with a higher level of metal exposure. The prevalences of T2D and prediabetes in office, mining/production, and smelting/refining workers were 6.2% and 14.4%, 7.7% and 20.2%, and 13.6% and 14.6%, respectively.

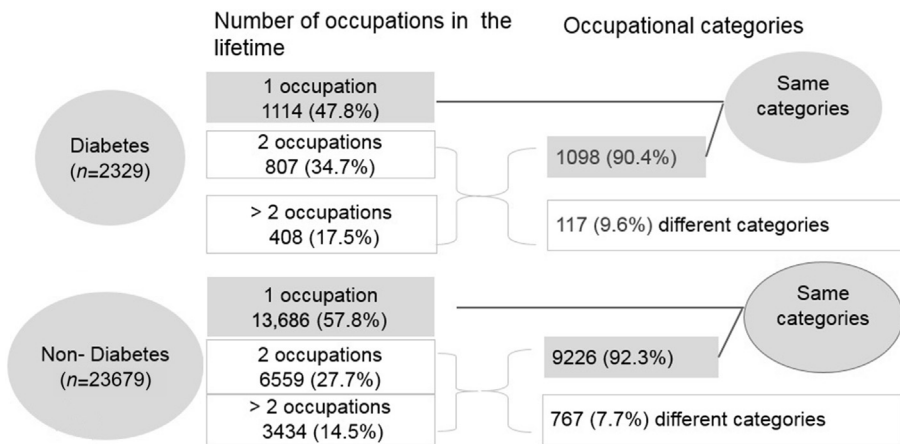


Fig. 1. The lifetime work histories in 26,008 Chinese male workers according to the presence of type 2 diabetes.

Table 1  
Participants' characteristics by occupations in 26,008 male workers (n, %).

Characteristics	Occupations <sup>a</sup>		
	Office	Mining/Production	Smelting/Refining
Participants	7210 (27.7)	11,450 (44.0)	7348 (28.3)
Age, years			
20–39	1966 (27.3)	3799 (33.2)	3062 (41.7)
40–60	3735 (51.8)	5112 (44.6)	3331 (45.3)
>60	1509 (20.9)	2539 (22.2)	955 (13.0)
Education			
Middle school or less	2423 (33.6)	4333 (37.8)	2606 (35.5)
High school	1651 (22.9)	3252 (28.4)	2341 (31.9)
College or higher	3136 (43.5)	3865 (33.8)	2401 (32.7)
Monthly household income, USD <sup>b</sup>			
<160	3348 (46.4)	6315 (55.2)	3947 (53.7)
160–800	3675 (51.0)	4945 (43.2)	3308 (45.0)
>800	187 (2.6)	190 (1.7)	93 (1.3)
BMI, kg/m <sup>2</sup>			
<25	4415 (61.2)	6923 (60.5)	5073 (69.0)
25–29.9	2550 (35.4)	4105 (35.9)	2054 (28.0)
≥30	245 (3.4)	422 (3.7)	221 (3.0)
Current smoker	4001 (55.5)	6784 (59.2)	4538 (61.8)
Former smoker	1037 (14.4)	1681 (14.7)	837 (11.4)
Type 2 diabetes	447 (6.2)	885 (7.7)	997 (13.6)
Prediabetes	1546 (21.4)	2309 (20.2)	1076 (14.6)
Abnormal lipid <sup>c</sup>	4100 (56.9)	6260 (54.7)	3752 (51.1)
Family history of diabetes	817 (11.3)	1574 (13.7)	1098 (14.9)
Hypertension	2488 (34.5)	3714 (32.4)	2302 (31.3)

BMI: body mass index.

<sup>a</sup> Occupations related with possible metal exposure were assigned into 3 categories: office (low level), metal mining/production (intermediate level), and smelting/refining (high level).

<sup>b</sup> 1 USD = 6.23 CNY in 2012.

<sup>c</sup> Abnormal lipid was defined as triglyceride level  $\geq 1.70$  mmol/L (150 mg/dL) or high-density lipoprotein cholesterol level  $< 0.9$  mmol/L (35 mg/dL).

Fig. 2 shows the urinary metal levels in these male workers based on their occupations. The median concentrations of urinary nickel among the office, mining/production, and smelting/refining workers were 4.15  $\mu\text{g/L}$ , 7.82  $\mu\text{g/L}$  and 9.89  $\mu\text{g/L}$ , respectively. The

corresponding urinary copper concentrations were 87.78  $\mu\text{g/L}$ , 209.29  $\mu\text{g/L}$  and 542.88  $\mu\text{g/L}$ , respectively, and the corresponding urinary cobalt concentrations were 0.51  $\mu\text{g/L}$ , 0.64  $\mu\text{g/L}$ , and 0.83  $\mu\text{g/L}$ , respectively. The levels of all three metals were

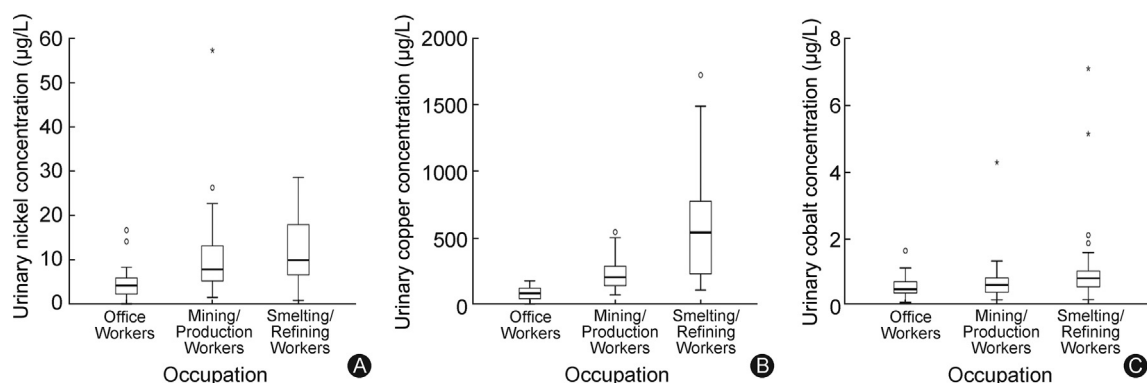


Fig. 2. Urinary metal concentration by occupations. (A) Nickel; (B) copper; (C) cobalt.

significantly different across the three occupational categories ( $P = 0.001$ ).

Table 2 shows the associations between alcohol consumption and the risks of T2D and prediabetes in male workers of the Jinchang Cohort Study. The multivariable-adjusted ORs for T2D risk were 1.3 (95% CI, 1.1–1.7) for  $\leq 9$  drinks/week, 1.2 (95% CI, 0.9–1.4) for 10–24 drinks/week, 1.7 (95% CI, 1.4–2.1) for 25–56 drinks/week, and 1.9 (95% CI, 1.6–2.2) for  $>56$  drinks/week (in comparison to non-drinkers,  $P_{\text{trend}} = 0.001$ ). The adjusted OR for prediabetes risk was similarly and significantly elevated with the increasing number of drinks per week ( $P_{\text{trend}} = 0.001$ ). The risks of T2D ( $P_{\text{trend}} = 0.001$ ) and prediabetes ( $P_{\text{trend}} = 0.001$ ) were also significantly elevated with the increasing number of drinking years and lifetime alcohol consumption. Compared to those of non-drinkers, the adjusted ORs for diabetes were 1.9 (95% CI, 1.6–2.2) for the highest category of total drinking years ( $>28$  years) and 1.7 (95% CI, 1.4–1.9) for lifetime alcohol consumption ( $>873$  kg), while the corresponding ORs for prediabetes risk associated with these metrics were 1.8 (95% CI, 1.6–2.1) and 1.5 (95% CI, 1.4–1.7), respectively.

Table 3 shows the multiplicative interaction between the occupational exposure to metals and alcohol consumption in affecting the risks of T2D and

prediabetes. We observed a statistically significant interaction between the occupations associated with high level of metal exposure and alcohol intake, and the diabetes risk. The highest risk of diabetes was observed in the smelting/refining workers (highest metal exposure levels) who had the highest lifetime alcohol consumption (i.e.  $> 873$  kg; OR = 6.1; 95% CI, 4.8–7.8;  $P_{\text{interaction}} = 0.018$ ). However, we did not observe a statistically significant interaction between drinking and the metal exposure level on the risk of prediabetes ( $P_{\text{interaction}} = 0.515$ ).

## Discussion

We observed that an increased number of drinks per week, drinking years, and lifetime alcohol consumption were associated with the risk of diabetes. The strongest risk for T2D was observed in the smelting/refining workers who consumed the highest amount of alcohol. These results suggest that both exposure to alcohol and heavy metals are associated with an increased risk of T2D. The magnitude of the risk in these male workers could be reduced by introducing lifestyle modifications related to the alcohol use.

Several limitations of this study need to be considered. First, we could not determine which

Table 2

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for type 2 diabetes and prediabetes among 26,008 male workers.<sup>a</sup>

Alcohol drink	Normal ( $n = 18,748$ )	Type 2 diabetes ( $n = 2329$ )		Prediabetes ( $n = 4931$ )	
		$n$	OR <sup>b</sup> (95% CI)	$n$	OR <sup>b</sup> (95% CI)
Non-drinkers	12,155	1399	Reference	2943	Reference
Standard drinks per week (1 drink = 14 g)					
$\leq 9$	1857	402	1.3 (1.1–1.7)	158	1.3 (1.1–1.5)
10–24	1688	479	1.2 (0.9–1.4)	173	1.5 (1.3–1.7)
25–56	1623	493	1.7 (1.4–2.1)	261	1.5 (1.3–1.7)
$>56$	1425	614	1.9 (1.6–2.2)	338	1.8 (1.6–2.1)
$P_{\text{trend}}$	–		0.001		0.001
Years of drink					
$\leq 13$	2062	345	0.7 (0.6–0.9)	103	1.0 (0.9–1.2)
13–21	1843	471	1.1 (0.9–1.4)	176	1.4 (1.2–1.6)
21–28	1443	498	1.8 (1.5–2.1)	240	1.7 (1.5–2.0)
$>28$	1245	674	1.9 (1.6–2.2)	411	1.8 (1.6–2.1)
$P_{\text{trend}}$	–		0.001		0.001
Lifetime alcohol consumption (kg)					
$\leq 99$	1948	115	0.7 (0.6–0.9)	319	0.8 (0.7–0.9)
100–322	1721	160	0.8 (0.7–1.0)	487	1.2 (1.1–1.4)
323–873	1584	258	1.3 (1.1–1.5)	543	1.4 (1.2–1.5)
$>873$	1340	397	1.7 (1.4–1.9)	639	1.5 (1.4–1.7)
$P_{\text{trend}}$	–		0.001		0.001

–: not applicable.

<sup>a</sup> Referent group in all sections is “non-drinkers”.

<sup>b</sup> Adjusted for age, smoking status, occupation category, body mass index, hypertension, abnormal lipid, and family history of diabetes.

Table 3

Multiplicative interaction between occupation-associated level of metal exposure and alcohol intake, and the risks of type 2 diabetes and prediabetes.

Lifetime alcohol consumption, kg	Occupational category, <i>OR</i> <sup>a</sup> (95% <i>CI</i> )		
	Office workers	Mining/production workers	Smelting/refining workers
<b>Diabetes</b>			
Non-drinkers	Reference	1.4 (1.2–1.6)	2.9 (2.4–3.4)
≤99	1.2 (0.8–1.8)	0.9 (0.7–1.3)	1.6 (1.1–2.3)
100–322	0.9 (0.6–1.4)	1.3 (0.9–1.7)	2.2 (1.6–3.1)
323–873	1.3 (0.9–1.7)	1.7 (1.3–2.2)	3.4 (2.6–4.4)
>873	1.4 (1.1–1.9)	1.9 (1.5–2.4)	6.1 (4.8–7.8)
<i>P</i> <sub>trend</sub> <sup>b</sup>	0.556	0.008	0.001
<i>P</i> <sub>interaction</sub>		0.018	
<b>Prediabetes</b>			
Non-drinkers	Reference	1.0 (0.9–1.1)	0.8 (0.7–1.0)
≤99	1.0 (0.7–1.2)	0.7 (0.6–0.9)	0.7 (0.5–0.9)
100–322	1.2 (1.0–1.5)	1.2 (1.0–1.4)	1.0 (0.8–1.2)
323–873	1.2 (1.0–1.5)	1.4 (1.2–1.7)	1.1 (0.9–1.4)
>873	1.4 (1.2–1.7)	1.5 (1.3–1.8)	1.4 (1.2–1.8)
<i>P</i> <sub>trend</sub> <sup>b</sup>	0.103	0.001	0.021
<i>P</i> <sub>interaction</sub>		0.515	

<sup>a</sup> Adjusted for age, smoke status, BMI, hypertension, abnormal lipid, and family history of diabetes.

<sup>b</sup> “Non-drinkers” is the reference within each occupational category.

specific metal might have been responsible for the increased risk of type 2 diabetes. Studies on quantitative evaluation on metal exposures, and the relationship between an individual metal and the diabetes risk will be further conducted in this prospective cohort study. Second, there is an exposure misclassification due to the use of occupations validated by determining urinary metal levels in a small subsample to estimate the likely levels of metal exposure for each male worker. Another limitation was the cross-sectional nature of the study, due to which we cannot establish a cause–effect association. However, the ongoing follow-up of each member every other year in the Jinchang Cohort should allow comprehensive evaluation of the exposure to alcohol, metals and diabetes in future years.

There remain some uncertainties regarding the role of alcohol intake in the development of T2D. In a meta-analysis that included 20 cohort studies, a U-shaped relationship between alcohol intake and the risk of T2D was reported, with moderate and high intakes being protective and hazardous, respectively.<sup>25,26</sup> However, these associations have not been consistent across studies, with some showing none, negative or positive relations between alcohol intake and the risk of T2D.<sup>9</sup> We observed a protective effect of T2D and prediabetes for drinkers with lifetime alcohol consumption ≤99 kg. In contrast, male workers with high alcohol intake (>873 kg) had an increased risk of T2D

and prediabetes (*OR* [95% *CI*]: 1.7 [1.4–1.9] and 1.5 [1.4–1.7], respectively). The results from our previous study showed that male workers with high levels of metal exposure, particularly smelting/refining workers, were associated with an increased risk of T2D or dysglycemia.<sup>18,20</sup> In the current study, we also found evidence for a joint effect between the high lifetime alcohol consumption and higher metal exposure on the risk of diabetes.

The mechanisms underlying the associations of alcohol intake and exposure to metals with the risk of T2D remain to be elucidated. Some beneficial effect of moderate alcohol intake has been related to an alcohol induced improvement of insulin sensitivity<sup>27,28</sup> and blood lipids<sup>29</sup>. However, binge drinking and intake of spirits have been shown to increase the risk of T2D,<sup>30–32</sup> a finding consistently observed in our cohort of men who were heavy drinkers of spirits. The potential mechanism of heavy alcohol intake on the risk of diabetes remains uncertain, although some evidence suggests that heavy alcohol consumption may be not associated with an increased risk of T2D.<sup>9</sup> Few studies have assessed the interaction between alcohol intake and metal exposure, and the risk of T2D. Heavy metals may disrupt the glucose uptake and alter the related molecular mechanism in glucose regulation.<sup>15</sup> However, metallic elements also play an important role in the alcoholic beverages.<sup>33</sup> Alcoholic beverages are

important metal sources of human intake, including raw materials, brewing, process type and equipment, bottling, storage and adulteration.<sup>34</sup> Additionally, alcohol, in particular beer, has high amounts of carbohydrates, which can raise blood sugar levels. Also, drinking heavily can make body less sensitive to insulin, which can cause T2D. It may partly explain the interaction between the metal exposure and alcohol intake in affecting the risk of T2D.

We did not observe an interaction between alcohol intake and metal exposure, and the risk of prediabetes in this study. In our previous study, we also did not find an association between metal exposure and the risk of prediabetes in men of the Jinchang Cohort.<sup>18</sup> So far, no data are available for exploring the interactions between alcohol intake and exposure to metals with the risk of prediabetes. More studies are needed to investigate the role of alcohol consumption in the risk of prediabetes among metal-exposed workers.

## Conclusions

In this large occupational cohort of Chinese male workers, it was found that the exposure to alcohol intake and heavy metals appears to significantly affect the risk of T2D. Concerning the significant adverse effects due to the interaction between occupational exposure to metals and alcohol intake, and the risk of T2D, strategies need to be developed to further investigate this joint effect in future prospective follow-up.

## Conflicts of interest

None declared.

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