

# Smoking causes the disorder of glucose metabolism under different levels of blood pressure in male occupational population

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## Abstract

Smoking is an important modifiable factor in the risk of type 2 diabetes. Type 2 diabetes and hypertension overlap in the population. The present study investigated effects of smoking on glucose metabolism under different blood pressure (BP) levels in occupational population. A smoking survey among occupational groups was conducted in 2018. The general linear model was used to analyze the differences of glucose metabolism indexes and BP indexes influenced by different smoking intensity (never 0, mild <10, moderate <20, heavy  $\geq$ 20 pack-years). Odds ratios of developing diabetes and  $\beta$ -cell deficiency were analyzed by using logistic regression model. BP was further taken into account in the relationship between smoking and glucose metabolism. As a result, 1730 male workers aged 21 to 60 years were included in the analysis finally. Compared to never smokers, heavy smokers had significantly increased fasting plasma glucose. Moderate and above smokers had significantly increased glycosylated hemoglobin, decreased fasting plasma insulin and  $\beta$ -cell function, after adjustment for covariates. Further, smoking intensity was found to have a dose-dependent relationship with impaired  $\beta$ -cell function and diabetes. In conclusion, smoking has a positive dose-dependent relationship with  $\beta$ -cell deficiency and diabetes. Male smoking workers, especially the moderate or higher smoking, with high-normal and high BP levels are at high risk of abnormal glucose metabolism.

Dan Wang, Deren Qiang, and Wenchao Xu contributed equally to this work.

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## KEYWORDS

blood pressure, cigarette smoking, glucose metabolism, type 2 diabetes,  $\beta$ -cell deficiency

## 1 | INTRODUCTION

Non-communicable diseases (NCDs) account for more than 70% of total deaths, according to the 2017 Global Burden of Disease Study.<sup>1</sup> Cardiovascular diseases (CVDs) account for the largest proportion (17.8 million or 43.3%) of deaths due to NCDs. Hypertension, diabetes, hypercholesterolemia, obesity, and smoking are the top five modifiable traditional cardiovascular risk factors.<sup>2,3</sup> The latest data from the Global Burden of Disease Study showed that hypertension, diabetes, and smoking remain among the five leading contributors to the global burden of disease.<sup>4</sup> Moreover, the interaction between these three risk factors is devastating.

Diabetes is considered the “epidemic of the 21st century.” Cigarette consumption in China has increased dramatically, with about two-thirds of Chinese men now smoking.<sup>5</sup> Academically, growing evidence have suggested the positive causal association<sup>6</sup> and dose-response relationship<sup>7,8</sup> between smoking and type 2 diabetes. It was also estimated that 10.3% in men and 2.2% in women of type 2 diabetes cases (approximately 25 million) worldwide were attributed to current smoking.<sup>9</sup> Additionally, type 2 diabetes and hypertension are often thought to co-exist.<sup>10,11</sup> A study of 318,664 people examining the causality between type 2 diabetes and hypertension in both directions implied that type 2 diabetes may causally affect hypertension.<sup>12</sup>

To clarify the relationship between smoking, type 2 diabetes and hypertension, we analyzed the difference in glycemic indices of smoking intensity, evaluated the effect of smoking on the risk of diabetes and key pathogenic factors of diabetes such as  $\beta$ -cell deficiency, and further investigated the effects of smoking on blood pressure (BP), and the difference in glycemic index of smoking under different BP levels. As recommended by the American Heart Association,<sup>13</sup> workplace health programs are an important strategy for preventing major risk factors for CVDs. Therefore, we conducted this study specifically for the occupational population in the hope of making the interaction between smoking and glucose metabolism and BP clearer and further improving blood glucose and BP control in our employees.

## 2 | METHODS

### 2.1 | Study design and participants

A sample of occupational population was selected using a multistage cluster random sampling method from the large chemical industries company during April to October in 2018. First stage: we selected three workshops according to type of work, number of occupational people, and occupational characteristics. Second stage: employees who have not the occupational risk factor exposure (such as the noise,

benzene, occupational dust exposure, and so on) were recruited. The last stage: all female employees were excluded. A total of 1772 male employees were recruited finally. We further excluded people with a history of diabetes medication use ( $n = 42$ ). The remaining 1730 participants were eligible for the analysis.

When we examined the relationship between smoking and BP, 183 cases who self-reported taking anti-hypertensive medications that might affect BP results were further excluded from the study. Individual person's data have not contained in any form (including any individual details, images or videos) in this manuscript. The protocol of this study was approved by the ethical review committee of the Jiangsu Provincial Center for Disease Control and Prevention (BL2015-B004-01). The procedures were in accordance with the standards of the ethics committee of Jiangsu Provincial Center for Disease Control and Prevention and with the Declaration of Helsinki (1975, revised 2013).

### 2.2 | Questionnaire survey

After the recruitment, trained investigators used the uniform questionnaire form to gather information of participants through the face-to-face interview, including demographic characteristics, lifestyle factors, and clinical indicators. Participants who gave a positive response to the question “Do you now smoke cigarettes?” were classified as “smokers.” The investigated smoking history included age at smoking initiation, duration of smoking, number of cigarettes smoked daily. Cumulative smoking dose was calculated in “pack-years” by multiplying the number of cigarettes packs per day by the number of smoking years. Four categories of smoking intensity were defined: never smokers (participants who reported not smoking at recruitment), mild smokers (participants who smoked for less than 10 pack years), moderate smokers (participants who smoked 10 pack years or more but less than 20 pack years), and heavy smokers (participants who had smoked for 20 pack years or more).<sup>14</sup> Drinking was defined as having consumed alcohol at least once a week during the 30 days prior to the survey.<sup>15</sup> According to the standards of the World Health Organization,<sup>16</sup> the intake of vegetables and fruits  $\leq 400$  g/d was defined as insufficient intake of vegetables and fruits.

### 2.3 | Anthropometric and BP measurements

Body height and waist circumference (WC) were measured to the closest 0.1 cm. Body weight was measured with light indoor clothing and without shoes. The body mass index (BMI) was calculated as  $[\text{weight}/(\text{height}^2)]$  ( $\text{kg}/\text{m}^2$ ). BP was measured by trained personnel after at least 5 min of rest in a relaxed sitting position, using

calibrated electronic sphygmomanometer (HEM-7200, Omron Corporation, Japan). Participants were seated quietly for 5 min, both feet on the floor with the arm supported at heart level. A correctly sized cuff with the air bladder encircling at least 2/3 of the arm was used. BP was measured twice at intervals of 1 min in each arm, and the average of two readings in the arm with the higher BP reading was used for final BP value. If the difference between the two measurements was greater than 5 mmHg, a third measurement was obtained; the last two measurements were recorded and used for all analyses. Hypertension was defined as systolic blood pressure (SBP)  $\geq 140$  mmHg, and/or diastolic blood pressure (DBP)  $\geq 90$  mmHg, and/or having taken anti-hypertensive medication.<sup>17</sup>

## 2.4 | Blood glucose, insulin, and lipid measurements

A total of 3–5 ml fasting blood samples were drawn from each participant. All blood samples were tested by Jiangsu Province Center for Disease Control and Prevention. The tests included fasting plasma glucose (FPG), fasting insulin (FINS), hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and creatinine (Cr). FPG and plasma lipid levels were detected with the enzymatic methods on an automatic biochemistry analyzer (Abbott Laboratories, USA), HbA1c was analyzed by high pressure liquid chromatography (HPLC) on a quantitative glycated hemoglobin analyzer (D-10, Bio-Rad Laboratories, USA), and serum insulin was measured by electrochemiluminescence immunoassay on a fully automated electrochemiluminescence analyzer (COBAS-E601, Roche Company, Switzerland), all under strict quality control.

$\beta$ -cell function (HOMA- $\beta$ ) and insulin resistance (HOMA-IR)<sup>18,19</sup> were calculated from FINS and FPG levels with the following formulas: HOMA- $\beta$  (%) =  $[FINS \text{ (mU/L)} \times 20] / [FPG \text{ (mmol/L)} - 3.5]$ ; HOMA-IR =  $[FINS \text{ (mU/L)} \times FPG \text{ (mmol/L)} / 22.5]$ . The cutoff points for  $\beta$ -cell deficiency and insulin resistance (IR) were HOMA- $\beta$  (%)  $< 50$  and HOMA-IR  $\geq 2.6$ , respectively. The main clinical indicator of renal function is the estimated glomerular filtration rate (eGFR). eGFR is calculated according to the Chinese modified simplified MDRD equation<sup>20</sup>:  $eGFR = 175 * (SCr)^{-1.234} * (Age)^{-0.179} (*0.79 \text{ female})$ . Diabetes was defined as FPG  $\geq 7.0$  mmol/L, and/or HbA1c  $\geq 6.5\%$ , and/or having taken glucose-lowering medication.<sup>21</sup> According to the Chinese guidelines on prevention and treatment of dyslipidemia in adults,<sup>22</sup> dyslipidemia was defined as TC  $\geq 6.22$  mmol/L, TG  $\geq 2.26$  mmol/L, HDL-C  $< 1.04$  mmol/L, and/or LDL-C  $\geq 4.14$  mmol/L, and/or having taken lipid-lowering medication.

## 2.5 | Statistical analysis

Smoking intensity is classified by cumulative dose for pack years. Quantitative variables with normal distribution were represented by mean  $\pm$  standard deviation, and analysis of variance was used for compar-

ison between multiple groups. Categorical variables were expressed as frequency and percentage (%), and  $\chi^2$  test was used for comparison between groups.

Unadjusted means and adjusted means with 95% confidence intervals (CIs) of FPG, FINS, HbA1c, HOMA-IR, HOMA- $\beta$ , SBP, DBP were calculated based on general linear model according to smoking intensity. Binary logistic regression analysis was used to compare risk estimates for Type 2 diabetes and  $\beta$ -cell deficiency and hypertension based on smoking intensity, with never smokers as the reference subgroup. Then stratified analysis was used to further explore the effects of smoking intensity on glucose metabolism under different BP levels. The adjustment covariates included age, BMI, WC, TC, TG, HDL-C, LDL-C, eGFR, drinking, dietary taste, adequate fruit and vegetable intake and hypertension. All statistical analyses were performed using SPSS (version 22.0), and double-tailed  $p$  value  $< 0.05$  was considered statistically significant. A restricted cubic spline smoothing technique was also used to interpolate the overall trend of risk across the range of smoking pack-years made by R software (version 4.1.2).

## 3 | RESULTS

### 3.1 | General characteristics of population with different smoking levels

The remaining 1730 participants were eligible for the analysis, including never smokers 644, mild smokers 381, moderate smokers 311, and heavy smokers 394. Table 1 showed the baseline quantitative characteristics of participants by smoking intensity. A total of 1730 male workers aged 21 to 60 years (average  $41.67 \pm 9.58$  years old) were finally included in the analysis. Table 2 showed that 680 (39.31%) had hypertension and 721 (41.68%) had dyslipidemia. As illustrated, heavy smokers were significantly older, had a higher WC, lower eGFR, initiated smoking earlier, duration of smoking for longer, were more likely to be drinkers, inclined to eat less fruit and vegetables, and were inclined to be less limited to their intake of foods in high fat and cholesterol.

### 3.2 | The effects of different smoking levels on glucose metabolic indices

The adjusted means with 95% CI for FPG in mild, moderate, and heavy smokers was 5.21 (95% CI 5.10–5.31), 5.38 (95% CI 5.26–5.49), and 5.48 (95% CI 5.38–5.59) relative to 5.33 (95% CI 5.25–5.42) in never smokers ( $P_{\text{heavy}}^a = 0.036$ , Table 3). Elevated HbA1c related to cumulative smoking intensity was statistically significant before and after adjustment for multiple factors (5.34 [95% CI 5.29–5.38], 5.34 [95% CI 5.28–5.39], 5.46 [95% CI 5.40–5.52], 5.57 [95% CI 5.51–5.63],  $P_{\text{mild}}^a = 0.958$ ,  $P_{\text{moderate}}^a = 0.003$ ,  $P_{\text{heavy}}^a < 0.001$ ). The growth trend was shown in Figure S1.

The adjusted means with 95% CI for FINS in Table 3 was 11.19 (95% CI 10.67–10.71), 10.36 (95% CI 9.79–10.93), 10.18 (95% CI

**TABLE 1** Basic quantitative characteristics of population with different smoking levels

Characteristics*	Entire population (n = 1730)	Never smokers (n = 644)	Mild smokers (n = 381)	Moderate smokers (n = 311)	Heavy smokers (n = 394)	p
Age at smoking initiation, year	23.86 ± 6.69	-	26.12 ± 7.37	23.96 ± 6.33	21.60 ± 5.42	<0.001
Duration of smoking, year	12.51 ± 12.13	-	11.28 ± 6.71	21.14 ± 6.45	27.32 ± 5.81	<0.001
Age, year	41.67 ± 9.58	38.10 ± 9.99	37.40 ± 9.15	45.10 ± 6.63	48.93 ± 4.90	<0.001
BMI, kg/m <sup>2</sup>	24.30 ± 3.18	24.05 ± 3.18	24.62 ± 3.68	24.45 ± 2.99	24.30 ± 2.76	0.035
WC, cm	84.50 ± 8.78	83.22 ± 8.78	84.91 ± 9.74	84.95 ± 8.03	85.84 ± 8.10	<0.001
TC, mmol/L	4.94 ± 0.91	4.81 ± 0.88	4.85 ± 0.94	5.05 ± 0.83	5.16 ± 0.94	<0.001
TG, mmol/L	1.73 ± 1.43	1.41 ± 0.98	1.74 ± 1.27	1.88 ± 1.58	2.15 ± 1.86	<0.001
HDL-C, mmol/L	1.15 ± 0.30	1.19 ± 0.29	1.10 ± 0.27	1.15 ± 0.35	1.12 ± 0.30	<0.001
LDL-C, mmol/L	2.54 ± 0.65	2.49 ± 0.64	2.51 ± 0.65	2.59 ± 0.59	2.62 ± 0.70	0.008
Cr, μmol/L	78.77 ± 10.98	79.12 ± 11.65	78.25 ± 9.67	79.24 ± 10.69	78.31 ± 11.27	0.427
Serum uric acid, μmol/L	320.47 ± 78.69	315.78 ± 76.70	326.66 ± 83.25	322.11 ± 81.22	320.84 ± 75.08	0.188
Urea nitrogen, mmol/L	5.04 ± 1.23	5.09 ± 1.34	4.93 ± 1.13	4.99 ± 1.17	5.12 ± 1.18	0.109
eGFR, ml/min/1.73m <sup>2</sup>	106.87 ± 18.88	108.36 ± 20.15	109.21 ± 16.67	104.12 ± 17.98	104.33 ± 18.95	<0.001

\*Data are expressed as the means ± SD.

**TABLE 2** Basic categorical characteristics of population with different smoking levels

Characteristics*	Entire population (n = 1730)	Never smokers (n = 644)	Mild smokers (n = 381)	Moderate smokers (n = 311)	Heavy smokers (n = 394)	p
BMI						
slim or normal, < 24.0	723 (41.79)	297 (46.12)	148 (38.85)	127 (40.84)	151 (38.32)	<0.001
overweight, 24.0-27.9	819 (47.34)	291 (45.19)	170 (44.62)	148 (47.59)	210 (53.30)	
fat, ≥28.0	188 (10.87)	56 (8.70)	63 (16.54)	36 (11.58)	33 (8.38)	
Drinking	599 (34.62)	136 (21.12)	129 (33.86)	124 (39.87)	210 (53.30)	<0.001
Dietary taste						
Light	327 (18.90)	156 (24.22)	59 (15.49)	55 (17.68)	57 (14.47)	<0.001
Medium	765 (44.22)	314 (48.76)	183 (48.03)	132 (42.44)	136 (34.52)	
Salty	638 (36.88)	174 (27.02)	139 (36.48)	124 (39.87)	201 (51.02)	
Limit intake of high-fat foods	637 (36.82)	245 (38.04)	140 (36.75)	117 (37.62)	135 (34.26)	0.658
Adequate fruit and vegetable intake	377 (21.79)	168 (26.09)	85 (22.31)	67 (21.54)	57 (14.47)	<0.001
Hypertension	680 (39.31)	223 (34.63)	125 (32.81)	134 (43.09)	198 (50.25)	<0.001
Dyslipidemia	721 (41.68)	209 (32.45)	185 (48.56)	142 (45.66)	185 (46.95)	<0.001

\*Data are expressed as n (%).

9.65–10.71) relative to 11.29 (95% CI 10.88–11.70) in never smokers ( $P_{\text{mild}}^a = 0.767$ ,  $P_{\text{moderate}}^a = 0.010$ ,  $P_{\text{heavy}}^a = 0.002$ ). The same dose relationship can be seen in HOMA-IR ( $P_{\text{mild}}^a = 0.236$ ,  $P_{\text{moderate}}^a = 0.047$ ,  $P_{\text{heavy}}^a = 0.035$ ) and HOMA- $\beta$  ( $P_{\text{mild}}^a = 0.016$ ,  $P_{\text{moderate}}^a = 0.004$ ,  $P_{\text{heavy}}^a = 0.001$ ). The downward trend was also shown in Figure S1.

### 3.3 | Associations between smoking intensity, diabetes and $\beta$ -cell deficiency

According to Table 4, smoking was found to have a dose-dependent relationship with diabetes ( $OR_{\text{mild}}^a = 0.84$  [0.42–1.70],  $OR_{\text{moderate}}^a$

**TABLE 3** The effects of different smoking levels on glucose metabolic indices

Variables	Never smokers (n = 644)		Mild smokers (n = 381)		Moderate smokers (n = 311)		Heavy smokers (n = 394)	
	Mean (95% CI)	Ad-Mean (95% CI) <sup>a</sup>	Mean (95% CI)	Ad-Mean (95% CI) <sup>b</sup>	Mean (95% CI)	Ad-Mean (95% CI) <sup>b</sup>	Mean (95% CI)	Ad-Mean (95% CI) <sup>a</sup>
FPG (mmol/L)	5.25 (5.17–5.33)	5.33 (5.25–5.42)	5.20 (5.09–5.31)	5.21 (5.10–5.31)	5.41 (5.29–5.53)	5.38 (5.26–5.49)	5.60 (5.49–5.70) <sup>b</sup>	5.48 (5.38–5.59) <sup>b</sup>
		<i>p</i> = 0.513	<i>p</i> = 0.058	<i>p</i> = 0.33	<i>p</i> = 0.33	<i>p</i> = 0.542	<i>p</i> < 0.001	<i>p</i> <sup>a</sup> = 0.036
HbA1c (%)	5.30 (5.26–5.35)	5.34 (5.29–5.38)	5.34 (5.28–5.40)	5.34 (5.28–5.39)	5.47 (5.40–5.53) <sup>b</sup>	5.46 (5.40–5.52) <sup>b</sup>	5.61 (5.55–5.67) <sup>b</sup>	5.57 (5.51–5.63) <sup>b</sup>
		<i>p</i> = 0.365	<i>p</i> = 0.958	<i>p</i> = 0.001	<i>p</i> < 0.001	<i>p</i> = 0.003	<i>p</i> < 0.001	<i>p</i> <sup>a</sup> < 0.001
FINS (mmol/L)	10.91 (10.48–11.34)	11.29 (10.88–11.70)	11.38 (10.82–11.94)	11.19 (10.67–11.71)	10.48 (9.86–11.10)	10.36 (9.79–10.93) <sup>b</sup>	10.54 (9.99–11.09)	10.18 (9.65–10.71) <sup>b</sup>
		<i>p</i> = 0.193	<i>p</i> = 0.767	<i>p</i> = 0.268	<i>p</i> = 0.010	<i>p</i> = 0.302	<i>p</i> <sup>a</sup> = 0.002	<i>p</i> <sup>a</sup> = 0.002
HOMA-IR	2.58 (2.46–2.70)	2.72 (2.61–2.83)	2.66 (2.50–2.81)	2.61 (2.47–2.75)	2.57 (2.40–2.74)	2.52 (2.37–2.68) <sup>b</sup>	2.66 (2.51–2.81)	2.52 (2.38–2.66) <sup>b</sup>
		<i>p</i> = 0.432	<i>p</i> = 0.236	<i>p</i> = 0.904	<i>p</i> = 0.047	<i>p</i> = 0.387	<i>p</i> <sup>a</sup> = 0.035	<i>p</i> <sup>a</sup> = 0.035
HOMA-β (%)	139.79 (133.36–146.22)	139.82 (133.36–146.28)	154.90 (146.54–163.26) <sup>b</sup>	152.67 (144.48–160.85) <sup>b</sup>	122.93 (113.68–132.19) <sup>b</sup>	123.39 (114.39–132.39) <sup>b</sup>	118.87 (110.65–127.09) <sup>b</sup>	120.63 (112.31–128.94) <sup>b</sup>
		<i>p</i> = 0.005	<i>p</i> = 0.016	<i>p</i> = 0.003	<i>p</i> = 0.004	<i>p</i> < 0.001	<i>p</i> <sup>a</sup> = 0.001	<i>p</i> <sup>a</sup> = 0.001

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; FINS, fasting insulin; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function.

<sup>a</sup>Adjusted for age, BMI, WC, TC, TG, HDL-C, LDL-C, eGFR, drinking, dietary taste, adequate fruit and vegetable intake and hypertension, using never smokers as references.

<sup>b</sup>Meaningful indicators are marked with it.

= 1.14 [0.56–2.32], OR<sup>a</sup><sub>heavy</sub> = 2.11 [1.15–3.87]) and impaired β-cell function (OR<sup>a</sup><sub>mild</sub> = 1.01 [0.56–1.81], OR<sup>a</sup><sub>moderate</sub> = 1.34 [0.76–2.37], OR<sup>a</sup><sub>heavy</sub> = 1.88 [1.12–3.17]), however, not with insulin resistance (OR<sup>a</sup><sub>mild</sub> = 0.90 [0.67–1.20], OR<sup>a</sup><sub>moderate</sub> = 0.79 [0.58–1.07], OR<sup>a</sup><sub>heavy</sub> = 0.83 [0.61–1.11]). These trends were vividly presented in Figure 1.

### 3.4 | Associations between smoking intensity and hypertension

Figure 2 showed unadjusted and adjusted means of BP in smokers. Only the unadjusted DBP increased steadily with increasing smoking intensity (*P*<sub>moderate</sub> = 0.033, *P*<sub>heavy</sub> < 0.001, Table S1). Further, no statistical correlation was found between smoking and hypertension in this study population (Table 5).

### 3.5 | BP-specific stratified analysis

The results revealed that, after a stratified analysis of BP (Table S2), the effect of smoking on the glycemic index FPG was particularly significant in those with high BP (*P*<sup>\*</sup><sub>heavy</sub> = 0.009). The effect of smoking on the glycemic index HbA1c was particularly significant in those with high-normal BP (*P*<sup>\*</sup><sub>heavy</sub> < 0.001) and those with high BP (*P*<sup>\*</sup><sub>moderate</sub> = 0.027, *P*<sup>\*</sup><sub>heavy</sub> < 0.001). And relative to people with normal BP levels, HbA1c also showed a differential higher state under the same smoking intensity with differential increase in BP (Figure 3).

In addition, FINS gradually reduced statistically with increasing smoking intensity under high-normal BP level (*P*<sup>\*</sup><sub>heavy</sub> = 0.020) and high BP level (*P*<sup>\*</sup><sub>mild</sub> = 0.096, *P*<sup>\*</sup><sub>moderate</sub> = 0.001, *P*<sup>\*</sup><sub>heavy</sub> = 0.028). β-cell function at different smoking intensities also showed such a downward trend. Under high BP level, the adjusted means with 95% CI for HOMA-β (%) were 151.66 (95% CI 138.35–164.98), 152.94 (95% CI 135.82–170.07), 113.67 (95% CI 96.01–131.33), 112.91 (95% CI 97.55–128.28). And relative to people with normal BP levels, β-cell function also showed a differential lower state under the same smoking intensity with differential increase in BP (Figure 3).

## 4 | DISCUSSION

It was found that, in this large occupational cohort in China, an increase in smoking intensity significantly increased FPG, HbA1c and significantly decreased FINS and β-cell function, showing that heavy smoking independently contributed to β-cell function deficiency and the development of diabetes mellitus. In addition, we found no statistically significant association between smoking and hypertension, and the presence of an association of smoking on diabetes was not directly related to BP, but smokers were at greater risk of developing diabetes in the presence of an increase in BP.

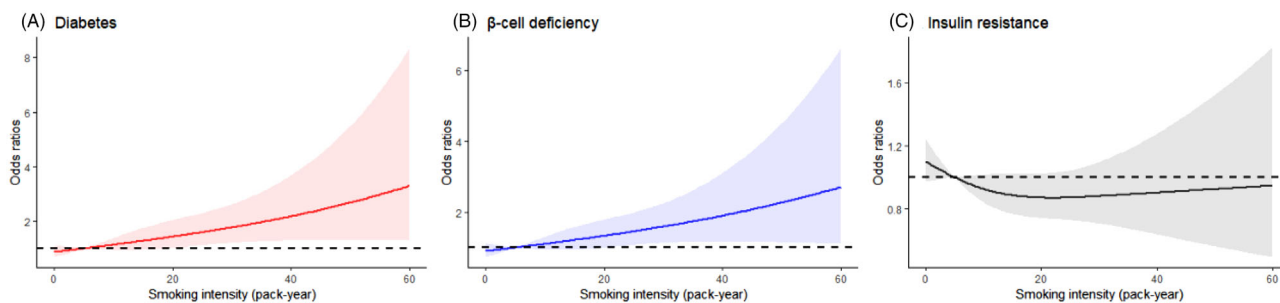
HbA1c is an indicator of long-term (2–3 months) glucose exposure. Several studies in middle-aged people have shown a strong, persistent association between HbA1c and subsequent diabetes risk.<sup>23–26</sup> Lipska

**TABLE 4** Associations between smoking intensity, diabetes and  $\beta$ -cell deficiency

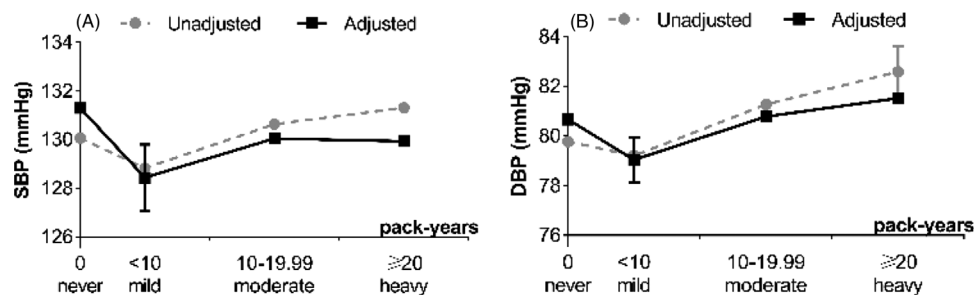
Disease	$\beta$	Never smokers	Mild smokers	Moderate smokers	Heavy smokers	<i>p</i>
Diabetes	<i>N</i> (%)	15 (2.33)	11 (2.89)	12 (3.86)	28 (7.11)	
	OR (95% CI) <sup>a</sup>	1.00	0.84 (0.42–1.70)	1.14 (0.56–2.32)	2.11 (1.15–3.87) <sup>b</sup>	0.016
$\beta$ -cell deficiency	<i>N</i> (%)	35 (5.43)	20 (5.25)	23 (7.40)	41 (10.41)	
	OR (95% CI) <sup>a</sup>	1.00	1.01 (0.56–1.81)	1.34 (0.76–2.37)	1.88 (1.12–3.17) <sup>b</sup>	0.017
Insulin resistance	<i>N</i> (%)	260 (40.37)	167 (43.83)	125 (40.19)	171 (43.40)	
	OR (95% CI) <sup>a</sup>	1.00	0.90 (0.67–1.20)	0.79 (0.58–1.07)	0.83 (0.61–1.11)	0.210

<sup>a</sup>Adjusted for age, BMI, WC, TC, TG, HDL-C, LDL-C, eGFR, drinking, dietary taste, adequate fruit and vegetable intake and hypertension, using never smokers as references.

<sup>b</sup>Meaningful indicators are marked with it.



**FIGURE 1** Adjusted odds ratios of diabetes,  $\beta$ -cell deficiency and Insulin resistance by smoking intensity (pack years). Adjusted for age, BMI, WC, TC, TG, HDL-C, LDL-C, eGFR, drinking, dietary taste, adequate fruit and vegetable intake and hypertension, using never smokers as references.



**FIGURE 2** Influence of smoking intensity on blood pressure index. Adjusted for age, BMI, WC, TC, TG, HDL-C, LDL-C, eGFR, drinking, dietary taste, adequate fruit and vegetable intake and diabetes, using never smokers as references. All statistically significant points showed both means and 95% CI. DBP, diastolic blood pressure; SBP, systolic blood pressure.

and colleagues<sup>27</sup> also found that effects of elevated HbA1c and IFG on the risk of diabetes in older adults were similar to those observed in younger adults, and elevated HbA1c seemed to be a stronger predictor, which supported the finding of the present study that moderate and above smokers ( $\geq 10$  pack years) had significantly higher HbA1c than never smokers.

The present study showed that smoking intensity and dose were associated with impaired  $\beta$ -cell function ( $\beta$ -cell function assessment in the homeostasis model),<sup>28,29</sup> and when the dose  $\geq 10$  pack-years,  $\beta$ -cell function already decreased significantly. Nicotine has been widely considered an important pathogenic factor of smoking exposure.<sup>30</sup>

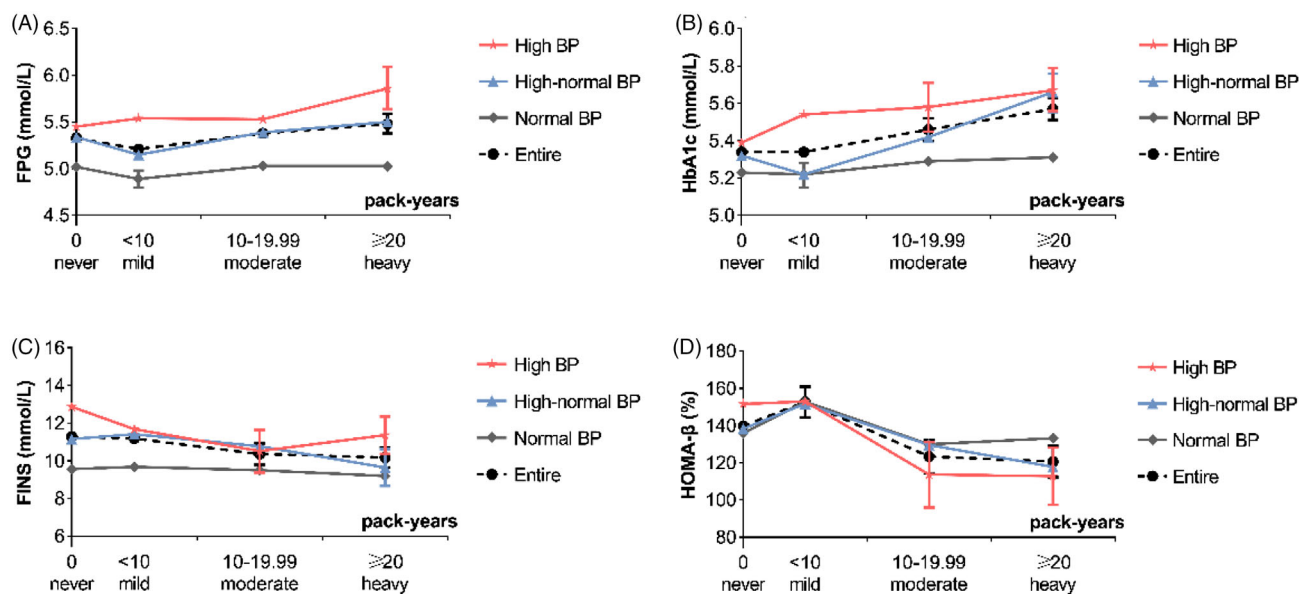
In animal models, smoking was found to cause elevated ceramide levels, which are associated with the activation of oxidative and endoplasmic reticulum stress. And at the mechanistic level, these changes caused reduced insulin production, impaired insulin processing, reduced insulin secretion, and reduced  $\beta$ -cell viability and proliferation.<sup>31</sup>

Smoking cessation and prevention is a crucial component of the management of hypertension and diabetes mellitus.<sup>32</sup> Although the present finding argued for previous studies that there was no significant dose-response relationship between smoking and hypertension,<sup>33,34</sup> it is seen that smoking and BP have a synergistic

**TABLE 5** Association between smoking intensity and hypertension

Disease	$\beta$	Never smokers	Mild smokers	Moderate smokers	Heavy smokers	<i>p</i>
Hypertension	<i>N</i> (%)	173 (29.12)	102 (28.49)	94 (34.69)	128 (39.51)	
	OR (95% CI) <sup>a</sup>	1.00	0.76 (0.55–1.04)	1.03 (0.74–1.44)	1.14 (0.82–1.58)	0.143

<sup>a</sup>Adjusted for age, BMI, WC, TC, TG, HDL-C, LDL-C, eGFR, drinking, dietary taste, adequate fruit and vegetable intake and diabetes, using never smokers as references.



**FIGURE 3** Influence of smoking intensity on FPG, HbA1c, FINS and HOMA- $\beta$  stratified by blood pressure levels. Adjusted for age, BMI, WC, TC, TG, HDL-C, LDL-C, eGFR, drinking, dietary taste, and adequate fruit and vegetable intake, using never smokers as references. #All statistically significant points showed both means and 95% CI. BP, blood pressure; FINS, fasting insulin; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HOMA- $\beta$ , homeostasis model assessment of  $\beta$ -cell function.

adverse effect on the risk of diabetes. On the other hand, context-specific smoking cessation interventions should be implemented, particularly in hypertensive and diabetic populations, considering the devastating interactions between smoking, hypertension and/or diabetes, resulting in dramatic increases in all-cause and CVDs morbidity and mortality.<sup>32,35</sup>

The occupational populations tend to be a “blind spot” in the prevention and treatment of diabetes and hypertension. A cross-sectional study of high-altitude working population in China found an overall crude prevalence of hypertension of 28.1%.<sup>36</sup> Shockey and colleagues<sup>37</sup> observed that the prevalence of diabetes is 6.4% among employed adults in the United States, which differed by occupation. A study of type 2 diabetes screening interventions in Canadian workplaces<sup>38</sup> showed that the prevalence of diabetes in the occupational population was 8% and that interventions with educational programs were effective in reducing the level of diabetes risk among employees. In the present occupational cohort, the prevalence of diabetes and hypertension was 7.1% and 39.3% in male workers. Tsimihodimos and colleagues<sup>39</sup> observed that the development of hypertension and diabetes tracked each other over time and diabetic

patients with BP values near the upper limit of normal should be monitored for the development of hypertension.

Strengths of our study include 1) an occupation-based sample population, as workplace hypertension management programs have proven to have greater coverage and better accessibility among employees,<sup>40</sup> 2) extensive data on potential confounders, 3) an updated version of the HOMA calculator (iHOMA2) providing better estimates of insulin sensitivity and pancreatic  $\beta$ -cell function, and 4) simultaneous analysis of the triangular relationship between BP, smoking and glucose metabolism. Our study also has slight shortcomings in that it was a cross-sectional study that focused on analyzing the differences in glucose metabolism caused by smoking under different BP levels, and we could not rule out residual confusion or infer causality.

In conclusion, moderate to heavy smoking can significantly increase HbA1c and decrease FINS and HOMA- $\beta$ , and heavy smoking can significantly increase FPG. Smoking has a positive dose-dependent relationship with impaired  $\beta$ -cell and diabetes mellitus. Meanwhile, BP control should not be neglected, and good management of BP along with smoking cessation can effectively reduce the risk of developing diabetes among occupational people.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

Dan Wang, Deren Qiang, Wenchao Xu, Yu Qin, Yongqing Zhang, Qizhan Liu, and Quanyong Xiang designed the study. Dan Wang, Deren Qiang, Wenchao Xu, Jiaqi Wang, Jiali Liu, Yu Qin, and Quanyong Xiang collected the data. Dan Wang, Deren Qiang, Wenchao Xu, Jiaqi Wang, Jiali Liu, Yu Qin, Qizhan Liu, and Quanyong Xiang analyzed the data. Dan Wang drafted the manuscript. Wenchao Xu, Yu Qin, Yongqing Zhang, Qizhan Liu, and Quanyong Xiang revised the manuscript. Yu Qin and Yongqing Zhang provided technical or material support. Quanyong Xiang obtained funding and was responsible for study supervision.

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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