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Original Article

Assessing the impact of cigarette smoking on β-cell function and risk for type 2 diabetes in a non-diabetic Chinese cohort

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Abstract: Although the impact of cigarette smoking on glucose homeostasis has been extensively studied, the results, however, are still not conclusive. We, therefore, conducted a cross-sectional analysis of a non-diabetic Chinese cohort collected by the China Health and Nutrition Survey (CHNS 2009) to comprehensively assess the relationship between smoking, Hemoglobin A1c, β-cell function and insulin sensitivity. The cohort included a total of 5965 individuals (47.4% male) with a mean age of 49.23 years, and 4140 of which were non-smokers (69.4%), 834 were current light smokers (13.9%) and 991 were current heavy smokers (16.6%). Current smokers were predominantly males (93.6%) with a lower BMI (22.95 versus 23.42 kg/m^2). HbA1c levels were dose-dependently increased with smoking exposure (5.39%, 5.42% and 5.45%, respectively, $P = 0.007$). Non-smokers were served as a referent, the adjusted ORs for type 2 diabetes were 1.12 ($P = 0.256$, light smokers) and 1.26 ($P = 0.014$, heavy smokers), indicating a positive relationship between cigarette smoking and incidence of diabetes. HOMA%B was decreased in a dose-responsive manner with cigarette smoking (4.80, 4.79 and 4.76, $P = 0.036$), suggesting an adverse effect of smoking on β-cell function. Collectively, cigarette smoking is dose-dependently associated with decreased HOMA%B, and current smokers were clearly in a higher risk for diabetes as manifested by the elevated HbA1c.

Keywords: Cigarette smoking, type 2 diabetes, HbA1c, β-cell function, insulin sensitivity, Chinese

Introduction

The prevalence of type 2 diabetes (T2D) is steadily increasing worldwide. According to the World Health Organization, diabetes will become the 7th leading cause of death by 2030, which renders this metabolic disorder to be a major public health burden on society [1]. Although previous studies provided suggestive evidence that cigarette smoking could be an independent risk factor for the development of type 2 diabetes [2], but no conclusive result has been reached thus far. Therefore, understanding the role of smoking in the pathogenesis of diabetes would provide help to make better decisions in clinical settings for intervention and control of diabetes.

Generally, glycosylated hemoglobin (HbA1c) is an indicator of long-term (2-3 months) glycemic exposure, which is commonly used to identify individuals at high risk for developing diabetes [3]. As a result, elucidating the role of smoking in HbA1c may help to elucidate the impact of smoking on diabetes risk. Indeed, cigarette smoking has been proposed contributing to type 2 diabetes by affecting insulin resistance and insulin secretion [4], but its exact impact on normal-glycemic individuals still remains controversial [5-9]. Similarly, no consistent results have been reached thus far in terms of the effect of cigarette smoking on β-cell function [10-14]. Practically, nicotine is the key pathogenic factor of smoking exposure, which was proposed to impair β-cell function and in-

duce β-cell apoptosis *via* the mitochondrial or the death receptor pathway in animal models [15-17]. In fact, some clinical and population-based studies have implicated adverse effects of cigarette smoking on β-cell function [10, 12]. However, other studies otherwise failed to detect a perceptible impact of smoking on β-cell function [13], or even increased insulin secretion in normal-glycemic smokers [11]. Ethnic differences in β-cell function have been suggested as an explanation for the discrepancies among previous studies [18, 19].

To systematically address the above question, we herein employed a large cohort which contains 5,965 participants collected by the China Health and Nutrition Survey (CHNS) for the study. In this context, we aimed to examine the effect of cigarette smoking on glycemic control and on the risk of diabetes as assessed by HbA1c, and to evaluate the impact of smoking exposure on the key pathogenic factors of diabetes such as β-cell function and insulin resistance.

Materials and methods

Study population and methods

We employed a large cohort collected by the China Health and Nutrition Survey (CHNS), which is publically available online (http://www.cpc.unc.edu/projects/china). The CHNS is an ongoing longitudinal study that was designed to examine whether China's economic, demographic and social change affect the health status and behaviors of the Chinese population. It used a stratified multistage, random cluster process to select representative sample of the Chinese non-institutionalized population from nine provinces of China, which varied widely in geography, socio-economic status and health profiles. The study was approved by the institutional review boards of the University of North Carolina at Chapel Hill (UNC-CH) and the National Institute for Nutrition and Health (NINH). The purpose and procedures of the study were fully explained to subjects and written informed consent was obtained from each participant. Detailed information on survey methodology and procedures of the CHNS has been described elsewhere [20].

Briefly, respondents were required to fill in a structured questionnaire relating to their demographic and socioeconomic characteristics, dietary habits, health status, life style, medical history and drug use, etc. They were then asked to take physical measurements and get a blood test. Participants were included in our analysis if they were adults (18-85 years old) who finished both the questionnaire survey and the blood examination in 2009. Exclusion criteria were 1) pregnancy; 2) not fasting at blood drawn; 3) HbA1c ≥ 6.5% or self-reported diabetes or taking anti-diabetic medications; 4) missing data on age, gender, HbA1c, glucose, waist circumference or smoking status. We further excluded subjects with extreme measurements (HbA1c < 3.5% or BMI < 14 kg/m^2 or BMI ≥ 40 kg/m^2) and ruled out individuals with anemia or chronic kidney disease that might have interference with our primary outcomes, the remaining 5,965 participants were eligible for this analysis.

Biochemical measurements

Blood samples were collected after an overnight fast for at least 8 hours and transported to a national central lab in Beijing for testing. HbA1c levels were measured using the method of ion-exchange high-performance liquid chromatography (HLC-723 G7, Tosoh, Japan). Glucose, Triglycerides (TG) and HDL-C concentrations were measured on a Hitachi 7600 analyzer using the GOD-PAP or enzymatic method. Insulin levels were determined by the radioimmunology assay (Gamma counter XH-6020, China). Plasma creatinine levels were measured on a Hitachi 7600 analyzer using the picric acid assay. Plasma Hemoglobin levels were determined by the VCS system (Beckman Coulter LH751/750). β-cell function (HOMA%B) and insulin sensitivity (HOMA%S) were calculated based on fasting insulin and fasting plasma glucose levels using the iHOMA2 software (Version 8.8.2.R2, University of Oxford, UK), the input limits for insulin were 20-400 pmol/L to ensure steady-state conditions.

Smoking status

The assessment of smoking status was based on self-report. Respondents who answered "no" to the question "Have you ever smoked cigarettes?" were classified as non-smokers. Subjects were defined as current smokers if they were reported to have ever smoked and have not quit smoking at the time of the inter-

Table 1. Characteristics of Chinese non-diabetic adults in CHNS 2009 according to smoking status

	All (n = 5965)	Non-smoker (n = 4140)	Current light smoker (n = 834)	Current heavy smoker (n = 991)	*p*-value
Age (years)	49.23 ± 0.18	49.14 ± 0.22	50.02 ± 0.53	48.94 ± 0.37	0.217
Male (%)	2827 (47.4%)	1118 (27.0%)	754 (90.4%)*	955 (96.4%)*,#	0.000
≤ Middle School Education (%)	4476 (75.1%)	3091 (74.7%)	615 (73.8%)	770 (77.9%)	0.081
Alcohol consumption (%)	2015 (33.8%)	794 (19.2%)	543 (65.1%)*	678 (68.4%)*	0.000
Medical insurance (%)	5417 (90.8%)	3762 (90.9%)	746 (89.4%)	909 (91.7%)	0.239
Hypertension (%)	1696 (28.4%)	1152 (27.8%)	267 (32.0%)	277 (28.0%)	0.050
Waist circumference (cm)	82.33 ± 0.12	81.91 ± 0.15	82.95 ± 0.34*	83.58 ± 0.30*	0.000
BMI (kg/m^2)	23.28 ± 0.04	23.42 ± 0.05	22.95 ± 0.11*	22.96 ± 0.10*	0.000
FPG (mmol/L)	5.12 ± 0.01	5.12 ± 0.01	5.06 ± 0.02*	5.14 ± 0.02#	0.006
HbA1c (%)	5.44 ± 0.01	5.43 ± 0.01	5.45 ± 0.01	5.46 ± 0.01	0.200
Insulin (ulU/mL)	2.45 ± 0.01	2.47 ± 0.01	2.40 ± 0.02*	2.41 ± 0.01*	0.000
Triglycerides (mmol/L)	1.57 ± 0.01	1.52 ± 0.01	1.66 ± 0.04*	1.72 ± 0.04*	0.000
HDL cholesterol (mmol/L)	1.44 ± 0.01	1.46 ± 0.01	1.41 ± 0.01*	1.40 ± 0.01*	0.000

Data are expressed as Mean ± SE or Number of participants (%). *p*-value is based on ANOVA test or Chi-square test as appropriate; *represent P < 0.05 as compared with non-smokers; #represent P < 0.05 as compared with current light-smokers. The data of insulin was log-transformed to approximate normal distribution. N = 5964 on Alcohol consumption; N = 5958 on Education.

view. Current smokers were further divided into two subgroups according to smoking intensity: current light smokers (≤ 15 cigarettes per day) and current heavy smokers (> 15 cigarettes per day).

Diabetes

Respondents were considered to have diabetes if they had: 1) a medical history of physician-diagnosed diabetes; or 2) an HbA1c ≥ 6.5%; or 3) initiated anti-diabetic treatment at the time of the interview. Impaired fasting glucose (IFG) was defined as fasting plasma glucose (FPG) value ranging from 5.6 to 6.9 mmol/L based on the ADA (2017) guideline [21]. Individuals who had a FPG < 5.6 mmol/L were categorized as normal fasting glucose (NFG). HbA1c ≥ 5.7% was used as the cut-off point for identifying participants at high risk of developing diabetes according to the 2017 ADA standards [21]. The optimal cut-off points for isolated impaired insulin secretion (i-IIS) and isolated insulin resistance (i-IR) were respectively 4.72 and 4.21, which were determined by the maximum Youden index.

Data analysis

Clinical and demographic characteristics were compared by smoking status; differences among groups were assessed using the one-way analysis of variance (ANOVA) for continuous variables or the chi-squared test for categorical data. The Scheffe's test was employed for post hoc comparison when the variances were equal across groups; otherwise, the Dunnett's T3 test was performed. Insulin, HOMA%B and HOMA%S were log-transformed for its skewed distribution before analysis. Data was presented as mean ± SE for continuous variables or number (percentage) for categorical variables as appropriate. Univariate analysis was conducted to calculate adjusted means of HbA1c, HOMA%B or HOMA%S according to smoking status. Binary logistic regression analysis was applied to compare the risk estimates of type 2 diabetes based on smoking exposure, and non-smokers were specified as the referent. Prior to the analysis, gender was categorized as a dichotomous variable (men/women). The variable of HBP and alcohol consumption were measured on a dichotomous (yes/no) scale with "no = 0" representing a negative response. The chi-squared test was employed to calculate the population proportion (Normal, i-IIS, i-IR and IIS plus IR population) by smoking status. All statistical analyses were carried out using the PASW statistics v18.0.0 software, a *p*-value of < 0.05 was considered statistically significant.

Results

Characteristics of participants based on smoking status

Table 1 shows the characteristics of subjects categorized by smoking status. Briefly, a total of

Table 2. Univariate analysis: adjusted mean HbA1c levels according to smoking status

HbA1c (%)	Non-smoker	Current light-smoker	Current heavy-smoker	*p*-value
Model 1				
NFG	3345 (5.39 ± 0.01)	680 (5.42 ± 0.01)	765 (5.45 ± 0.01)*	0.016
IFG	795 (5.60 ± 0.01)	154 (5.64 ±0.03)	226 (5.60 ± 0.03)	0.579
FPG < 7 mmol/L	4140 (5.43 ± 0.01)	834 (5.46 ±0.01)	991 (5.48 ± 0.01)*	0.036
Model 2				
NFG	3311 (5.39 ± 0.01)	660 (5.42 ± 0.01)	757 (5.45 ± 0.01)*	0.006
IFG	784 (5.60 ± 0.01)	153 (5.65 ± 0.03)	217 (5.61 ± 0.03)	0.497
FPG < 7 mmol/L	4095 (5.43 ± 0.01)	813 (5.47 ± 0.01)	974 (5.48 ± 0.01)*	0.013
Model 3				
NFG	3344 (5.39 ± 0.01)	680 (5.42 ± 0.01)	765 (5.45 ± 0.01)*	0.007
IFG	795 (5.59 ± 0.01)	154 (5.65 ± 0.03)	226 (5.61 ± 0.03)	0.348
FPG < 7 mmol/L	4139 (5.43 ± 0.01)	834 (5.46 ± 0.01)	991 (5.48 ± 0.01)*	0.009

Data are expressed as Mean ± SE. NFG (normal fasting plasma glucose), FPG < 5.6 mmol/L; IFG (impaired fasting glucose), 5.6 mmol/L ≤ FPG < 7 mmol/L. Age and gender were adjusted in Model 1; Age, gender, glucose, BMI and WC were adjusted in Model 2; Age, gender, BMI, Alcohol consumption and HBP were adjusted in Model 3. *represent p < 0.05 as compared with non-smokers.

5,965 individuals (47.4% male) with a mean age of 49.23 years were included in our analysis, 4,140 of which were non-smokers (69.4%), 834 were current light smokers (13.9%) and 991 were current heavy smokers (16.6%). Compared with non-smokers, current smokers were predominantly males (> 90%), more likely to drink alcohol and more inclined to have a larger waist circumference and a lower BMI. In our analysis, differences in the prevalence of hypertension were marginally significant across groups. No difference in age, medical insurance coverage or education level was detected. Test for blood lipids showed that current smokers displayed higher levels of plasma triglycerides and lower levels of HDL-cholesterol as compared to non-smokers.

Adjusted means of HbA1c according to smoking status

Adjusted means of HbA1c were described in **Table 2** according to smoking status. Participants were stratified into three categories (NFG, IFG and FPG < 7 mmol/L) based on fasting glucose levels. Among participants with normal fasting glucose (NFG), HbA1c levels were increased with the intensity of smoking exposure. Age- and gender-adjusted means of HbA1c for non-smokers, current light smokers and current heavy smokers were 5.39%, 5.42% and 5.45% (Model 1, $p = 0.016$), respectively, which were increased in a dose-responseive manner, and this trend maintained after adjustment for additional confounders (Model 2, $p = 0.006$; Model 3, $p = 0.007$). Similar results were found in both of the IFG and FPG < 7 mmol/L group, but the *p*-value for this trend was not statistically significant among subjects with IFG, which was probably due to the small sample size of current smokers. The above results indicate that the detrimental effects of cigarette smoking on HbA1c were initiated at an early stage and accumulated dose-dependently throughout the course; the higher intensity of exposure to cigarettes, the higher HbA1c was detected.

The association of cigarette smoking and the risk of type 2 diabetes (T2D)

In **Table 3**, the risk estimates for participants with HbA1c ≥ 5.7% were calculated by smoking status to assess the relationship between smoking exposure and the risk of developing T2D. Using non-smokers as the referent, current smokers showed a dose-dependent increase of odds ratio (OR) for T2D, and the ORs were 1.10 for current light smokers (Model 1, $p = 0.317$) and 1.21 for current heavy smokers (Model 1, $p = 0.039$), respectively. This confirmed our findings in the univariate analysis, and further adjustment for potential confounders did not change this relationship (Model 2, OR = 1.27 for heavy smokers, $p = 0.010$; Model 3, OR = 1.26 for heavy smokers, $p = 0.014$).

Table 3. Binary logistic regression analysis for risk of HbA1c ≥ 5.7% according to smoking status

	Non-smoker	Current light-smoker	*p*-value	Current heavy-smoker	*p*-value
Model 1	ref.	1.100 (0.913, 1.326)	0.317	1.211 (1.009, 1.452)	0.039
Model 2		1.130 (0.932, 1.370)	0.215	1.279 (1.061, 1.542)	0.010
Model 3		1.120 (0.921, 1.360)	0.256	1.269 (1.050, 1.534)	0.014

Data are expressed as odds ratios (95% confidence intervals). Age and gender were adjusted in Model 1; Age, gender, glucose, BMI and WC were adjusted in Model 2; Age, gender, glucose, BMI, WC, Alcohol consumption and HBP were adjusted in Model 3.

Table 4. Univariate analysis: adjusted mean HOMA%B according to smoking status

HOMA%B	Non-smoker	Current light-smoker	Current heavy-smoker	*p*-value
Model 1				
NFG	3269 (4.80 ± 0.01)	662 (4.79 ± 0.01)	744 (4.75 ± 0.01)*,#	0.011
IFG	761 (4.60 ± 0.01)	141 (4.55 ± 0.03)	211 (4.53 ± 0.03)*	0.106
FPG < 7 mmol/L	4030 (4.76 ± 0.01)	803 (4.75 ± 0.01)	955 (4.70 ± 0.01)*,#	0.001
Model 2				
NFG	3268 (4.80 ± 0.01)	662 (4.80 ± 0.01)	744 (4.76 ± 0.01)*	0.087
IFG	761 (4.59 ± 0.01)	141 (4.57 ± 0.03)	211 (4.55 ± 0.03)	0.455
FPG < 7 mmol/L	4029 (4.76 ± 0.01)	803 (4.76 ± 0.01)	955 (4.72 ± 0.01)*,#	0.012
Model 3				
NFG	3236 (4.80 ± 0.01)	643 (4.79 ± 0.01)	736 (4.76 ± 0.01)*	0.036
IFG	750 (4.60 ± 0.01)	140 (4.56 ± 0.03)	203 (4.54 ± 0.03)	0.216
FPG < 7 mmol/L	3986 (4.76 ± 0.01)	783 (4.75 ± 0.01)	939 (4.71 ± 0.01)*,#	0.006

Data were log-transformed and expressed as Mean ± SE. NFG (normal fasting plasma glucose), FPG < 5.6 mmol/L; IFG (impaired fasting glucose), 5.6 mmol/L ≤ FPG < 7 mmol/L. Age and gender were adjusted in Model 1; Age, gender, BMI, Alcohol consumption and HBP were adjusted in Model 2; Age, gender, glucose, BMI and WC were adjusted in Model 3. *represent P < 0.05 as compared with non-smokers; #represent P < 0.05 as compared with current light-smokers.

The relationship between cigarette smoking and pancreatic β-cell function and insulin sensitivity

To figure out the mechanisms underlying smoking induced glucose dysregulation, we further examined the relationship between cigarette smoking and β-cell function (**Table 4**). Basically, HOMA%B was dose-responsively decreased with smoking exposure in all three groups, except for that current light smokers shared a similar value of HOMA%B with non-smokers in the age-, gender-, BMI-, alcohol consumption- and HBP- adjusted model (Model 2). Nevertheless, heavy smokers still had a declined β-cell function in relative to non-smokers with the same confounders adjusted, which implied the dose-cumulative effect of cigarette smoking on β-cell dysfunction. Comparison of HOMA%B among IFG population was not statistically significant due to the small sample size of current smokers.

The relationship between cigarette smoking and insulin sensitivity was also explored. As shown in **Table 5**, current smokers manifested slightly higher insulin sensitivity than non-smokers in the NFG group. Age- and gender-adjusted HOMA%S for non-smokers, current light smokers and current heavy smokers was 4.30, 4.39 and 4.42, respectively (Model 1, $p = 0.000$). Adjustment for additional confounders did not change this relationship (Model 2, $p = 0.001$; Model 3, $p = 0.000$). Similar trends were identified in both of the FPG < 7 mmol/L and IFG group, but the result was not statistically significant among participants with IFG due to the small sample size of current smokers.

Comparison of population proportions (Normal, i-IIS, i-IR and IIS plus IR population) by smoking status

β-cell dysfunction and/or insulin resistance play a vital role in the pathogenesis of T2D, different individuals manifest different IIS/IR status in the development of diabetes. To investigate the impact of cigarette smoking on the population composition, subjects were catego-

Table 5. Univariate analysis: adjusted mean HOMA%S according to smoking status

HOMA%S	Non-smoker	Current ight-smoker	Current heavy-smoker	*p*-value
Model 1				
NFG	3269 (4.30 ± 0.01)	662 (4.39 ± 0.02)*	744 (4.42 ± 0.02)*	0.000
IFG	761 (3.97 ± 0.02)	141 (4.04 ± 0.05)	211 (4.06 ± 0.04)	0.237
FPG < 7 mmol/L	4030 (4.24 ± 0.01)	803 (4.33 ± 0.02)*	955 (4.34 ± 0.01)*	0.000
Model 2				
NFG	3268 (4.31 ± 0.01)	662 (4.37 ± 0.02)*	744 (4.40 ± 0.02)*	0.001
IFG	761 (3.98 ± 0.02)	141 (4.01 ± 0.05)	211 (4.03 ± 0.04)	0.699
FPG < 7 mmol/L	4029 (4.25 ± 0.01)	803 (4.31 ± 0.02)*	955 (4.32 ± 0.01)*	0.001
Model 3				
NFG	3236 (4.30 ± 0.01)	643 (4.38 ± 0.02)*	736 (4.40 ± 0.02)*	0.000
IFG	750 (3.97 ± 0.02)	140 (4.03 ± 0.04)	203 (4.05 ± 0.04)	0.241
FPG < 7 mmol/L	3986 (4.24 ± 0.01)	783 (4.32 ± 0.01)*	939 (4.33 ± 0.01)*	0.000

Data were log-transformed and expressed as Mean ± SE. NFG (normal fasting plasma glucose), FPG < 5.6 mmol/L; IFG (impaired fasting glucose), 5.6 mmol/L ≤ FPG < 7 mmol/L. Age and gender were adjusted in Model 1; Age, gender, BMI, Alcohol consumption and HBP were adjusted in Model 2; Age, gender, glucose, BMI and WC were adjusted in Model 3. *represent p < 0.05 as compared with non-smokers.

Table 6. Population proportions (Normal, i-IIS, i-IR and IIS plus IR population) by smoking status

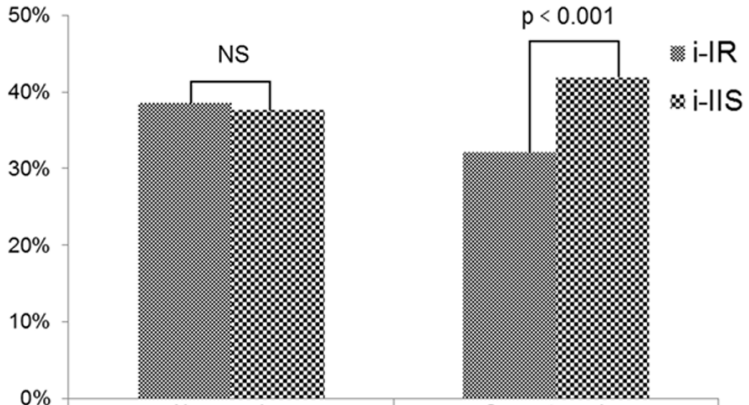
	Normal (n = 1020)	i-IIS (n = 2266)	i-IR (n = 2135)	IIS plus IR (n = 393)
Non-smoker (%)	681 (16.9%)	1519 (37.7%)	1561 (38.7%)	269 (6.7%)
Current smoker (%)	339 (19.0%)	747 (41.9%)	574 (32.2%)	124 (7.0%)

Data are expressed as Number of participants (%). Normal, normal insulin secretion plus normal insulin sensitivity; i-IIS, isolated impaired insulin secretion; i-IR, isolated insulin resistance.

rized into 4 groups (Normal, i-IIS, i-IR, IIS plus IR) based on IIS/IR status. It was found that the proportion of non-smokers with normal, i-IIS, i-IR and IIS plus IR status were 16.9%, 37.7%, 38.7% and 6.7%, respectively (**Table 6**), and no significant difference was detected among non-smokers between the proportion of subjects with i-IIS or i-IR (**Figure 1**). However, the situation is different for current smokers, subjects with i-IIS account for 41.9% of current smokers, which was significantly higher than the proportion of smokers with i-IR (32.2%, *P* = 0.000, **Figure 1**). This is in accordance with what we found in the univariate analysis (**Tables 4**, **5**), and further revealed the role of i-IIS as the main feature of current smoker in metabolic abnormality.

Discussion

Cigarette smoking has been suggested as an independent risk factor for the development of type 2 diabetes, but its exact impact, however, is still remained controversial, which prompted us to conduct the current study. It was reported that Asians and Caucasians differ in basal insulin secretion and insulin sensitivity [18, 22, 23], to avoid the impact of ethnic difference on our study, only Chinese population was included in the present analysis. To rule out the influence of anti-diabetic medications in insulin secretion, participants with known diabetes or those being on anti-diabetic medications were also excluded from our analysis. The technique of hyperinsulinemic-euglycemic glucose clamp (HEGC) was usually used as the gold standard for evaluating insulin resistance and pancreatic β-cell function [24, 25], but the labor-intensive and time-consuming nature of this technique has limited its application in large-scale epidemiology studies [26]. Alternatively, the method of iHOMA was an updated version of HOMA1 for assessing β-cell function and insulin sensitivity in large-scale studies [27], which was reported to correlate well with estimations of obtained from HEGC [28]. Using the iHOMA software, we found that pancreatic β-cell function was dose-dependently declined with smoking exposure, which is consistent with many previous findings [10, 12] and supported by the mechanistic studies conducted in animal



	Non-smoker	Current smoker
i-IR	38.70%	32.20%
i-IIS	37.70%	41.90%

Figure 1. Proportions of i-IIS and i-IR population according to smoking status.

models [16, 17, 29, 30]. However, Daniel et al reported that current smoking is associated with higher β-cell function in normal-glycemic Canadians [11]. In this study, participants were predominately females (68.3% for current smokers) with relatively young age (38.3 years for current smokers). It has been known that age and gender are factors to impact basal insulin secretion [31-33]. According to Tata et al, aging is associated with deteriorated β-cell function [34]. Indeed, studies reported negative impact of cigarette smoking on insulin response were commonly seen among participants with a mean age of 45 years or above [10, 12], which is in line with the average age of 48.5 years in our analysis.

It is speculated that the effect of cigarette smoking on β-cell function was dose-cumulative and at some extent time-dependent [35], and thus, smoking may serve as a second strike on the deterioration of β-cell function among middle-aged or elderly smokers. Gender-differences in the association between smoking exposure and basal insulin secretion were also observed in previous reports [12, 31]. Östgren et al demonstrated that cigarette smoking is closely related to β-cell dysfunction in non-diabetic male smokers, whereas no such effect was detected among females [12]. The rationale behind this phenomenon may include the female sexual hormone estrogen which exerts a protective effect against β-cell dysfunction by interacting with the estrogen receptor-mediated signaling pathways [36-38]. Alternative explanations for the gender-differences in β-cell dysfunction may also include differences in smoking intensity and smoking duration between the two genders. Moreover, according to Ko et al, no relationship was detected between cigarette smoking and basal insulin secretion in a non-diabetic population [13]. However, participants with IGT were excluded from this study, which may introduce selection bias and leading to the underestimation of smoking related β-cell deterioration, because the impaired insulin secretion upon glucose stimulation occurs earlier in smokers with IGT than those with IFG or NFG [39].

In addition, ethnic difference might be another factor that leading to disparities in β-cell function [18, 19]. The prevalence of diabetes susceptibility genes and their SNP variants vary among different ethnic groups [40-42]. It was reported that smoking has synergistic effects with certain functional SNP on β-cell dysfunction by means of gene-environment interaction. Thus, smokers who carry a specific diabetes-related SNP are more likely to develop β-cell dysfunction than those who do not [43], which could partially explain the disparities among different racial groups. Overall, discrepancies among previous studies may be attributed to variations in age, gender, ethnic origin and sample size of candidates, or differences in methods used for assessing smoking status, etc. Our study included a large sample size of 5,965 participants from the same ethnic origin, thus it has, to some extent, eliminated the impact of ethnic difference and sample size on the outcomes studied.

The relationship between cigarette smoking and insulin resistance was another focus of our study. Using the CHNS data, we found that current smokers showed slightly increased insulin sensitivity than non-smokers in healthy Chinese adults. However, our result differs from some previous studies which stated that smokers are insulin resistant [5, 8, 11, 44, 45]. Further analysis revealed that the subjects of

these studies were relatively young and with larger measurements of waist circumference (WC), BMI or waist-hip ratio (WHR). In another word, younger smokers with obesity were more prone to develop insulin resistance in these studies. This indicates that the impact of cigarette smoking on insulin sensitivity varied according to age and body fat [46-48]. In addition, gender and glucose status have also been proposed as factors that have impacts on whether or not cigarette smoking affects insulin sensitivity [11, 14]. However, so far relevant studies were rare and even contradictive results were reported in the past literatures [49-51]. Therefore, more studies are warranted to get a further insight into the role of age, gender, body fat etc. in the association of cigarette smoking and insulin sensitivity.

In summary, even though current smokers manifested slightly increased insulin sensitivity in relative to non-smokers in our study, its implication was obscure. The present study revealed that cigarette smoking was associated with impaired β-cell function and i-IIS was the primary metabolic abnormality detected in current smokers. It has been known that impaired insulin secretion and insulin resistance are two main features of type 2 diabetes. The relative contribution of IIS and IR to diabetes varied among different ethnic groups [52-54]. It was reported that East Asians with IIS were more susceptible to developing diabetes than those with IR [22]. Correspondingly, in a cohort study conducted in Japanese healthy adults [55], Morimoto et al demonstrated that 50.6% newly diagnosed T2D could be attributed to i-IIS, which confirmed the critical role of IIS in the onset of T2D in Asians. We have up to 41.90% of current smokers with i-IIS in our study; given the importance of IIS in the development of T2D, evaluation of insulin secretion among current smokers is imperative so that participants at high risk of developing T2D could be identified at an early stage.

The strength of our study is that it is population based and has a large sample size of 5,965 participants, and therefore, the results can be generalized to the entire Chinese population. Furthermore, the updated version of the HOMA Calculator (iHOMA2) was employed in our study, which provides a better estimation of pancreatic β-cell function and insulin sensitivity. To our knowledge, this is the first cross-sectional study that simultaneously examined the effects of cigarette smoking on both HbA1c levels and β-cell function in a Chinese population, which comprehensively elucidated the influence of smoking in glucose metabolism from phenomenon to mechanism. Several limitations for our study are necessary to point out. Due to the disadvantages of the cross-sectional study design, it is difficult to draw a causal inference from our data. Cotinine is a biomarker for smoking exposure, but the concentration of which was not measured in the CHNS survey; as an alternative, the self-reported questionnaire was used to assess smoking status in the present study, which might lead to inaccurate estimation of cigarette exposure. Even though we have adjusted for several important potential confounders in our study, the possibility of residual confounding cannot be completely eliminated, and a more comprehensive adjustment was needed in the future.

In conclusion, our findings demonstrated that cigarette smoking is dose-dependently associated with impaired β-cell function in a non-diabetic Chinese population, and current smokers are more potent to have a higher risk of diabetes with elevated HbA1c.

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Disclosure of conflict of interest

None.

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