

ORIGINAL

Association of alcohol consumption with the impaired β -cell function independent of body mass index among Chinese men

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Abstract. Alcohol consumption is associated with type 2 diabetes. However, the relationship between alcohol consumption and β -cell function is still unclear. The aim of this study is to investigate the association between them. 675 Chinese men aged 20-75 years were recruited. The subjects were first classified into never drinkers, abstainers, light drinkers (0.1-19.9 g/day), moderate drinkers (20.0-39.9 g/day) and heavy drinkers (≥ 40.0 g/day) and then, were further divided into two subgroups according to body mass index (BMI) (BMI $<25\text{kg/m}^2$ and BMI $\geq 25\text{kg/m}^2$). Analysis procedure was adjusted by the confounders including age, smoking status, BMI, waist circumference (WC), blood pressure, lipids and blood uric acid. Compared with never drinkers, alcohol consumption was associated with decreased homeostasis model assessment of β -cell function (HOMA- β) independent of BMI. The homeostasis model assessment of insulin resistance (HOMA-IR) was significantly correlated with alcohol consumption history in the group of BMI $<25\text{kg/m}^2$ and was significantly correlated with alcohol consumption in the group of BMI $\geq 25\text{kg/m}^2$. The results suggest that alcohol consumption is associated with the β -cell dysfunction independent of BMI in Chinese community dwelling men.

Key words: Alcohol consumption, β -cell function, Body mass index, Chinese men

WITH ECONOMIC DEVELOPMENT in China, the alcohol consumption increases sharply [1] and the prevalence of diabetes also increases greatly. Yang's study [2] showed that the age-standardized prevalence of total diabetes and prediabetes in China were 9.7% and 15.5%, respectively. The β -cell function of type 2 diabetic patients in Chinese-American is impaired earlier and more prominent performance [3]. Previous studies have shown alcohol intake was associated with insulin resistance (IR) and obesity [4-7], however, it is not clear the effect of alcohol consumption on β -cell secretion.

The aim of this study was to evaluate whether alcohol consumption was associated with β -cell function, and the association may be further confounded by an

increase in obesity among community-dwelling men in urban area of China.

Methods

Subject

The study sample was drawn from the central population register (≥ 5 years) aged 20-75 years living in Shungen, Shunya and Shunyu communities of Jinan City, China. We randomly recruited 1865 individuals attending face to face investigation. Study purpose and procedures were explained to participants. All subjects signed a written informed consent. The project was approved by the Ethics Committee of Provincial Hospital Affiliated to Shandong University.

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Abbreviations: BMI, body mass index; WC, waist circumference; IR, insulin resistance; FBG, fasting blood glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; Fins, fasting insulin; HOMA-IR, the homeostasis model assessment of insulin resistance; HOMA- β , homeostasis model assessment of β -cell function; SBP, systolic blood pressure; DBP, diastolic blood pressure

Exclusion criteria were self-reported history of diabetes, cardiovascular disease, pancreatitis, liver or kidney disease and because the prevalence of alcohol drinkers among women was low, we only selected the men into our study. A total of 675 men were finally successfully recruited in this study.

Assessments of alcohol consumption

The information of alcohol consumption was obtained using a standardized questionnaire including drinking history (years), drinking frequency of each day or month, average intake of each type of beverage (beer, wine, hard liquor ($>38\%$ v/v) and light liquor ($\leq 38\%$ v/v)). Daily alcohol intake was calculated in grams by summing up monthly ethanol intake of each type of beverage and then divided by 30.5 with the following content: 50mL of hard liquor, 21.85g; 50mL of light liquor, 15.75g; one 640mL-bottle of beer, 31.36g and 50 mL of wine, 5.2g according to the Chinese Food Composition Table 2004 [8].

All subjects were divided into five groups: never, abstain (>0.5 year) [9], light (0.1-19.9 g/day) [10], moderate (20.0-39.9 g/day) and heavy drinkers (≥ 40.0 g/day) [10] and then further divided into overweight ($\text{BMI} \geq 25 \text{ kg/m}^2$) and non-overweight ($\text{BMI} < 25 \text{ kg/m}^2$) groups [11].

Evaluation of risk factors

Information on demographic characteristics and risk factors were gained using clinical questionnaires. All subjects were informed to be fasting for an overnight of at least 12 h and avoid drinking and smoking and heavy physical activity before the examination. Anthropometric data and fasting blood samples were collected by trained medical professional using a standardized protocol. Body weight, height, waist circumference (WC) and blood pressure were measured, respectively. BMI was calculated as weight (kg)/height² (m²). The plasma levels of fasting blood glucose (FBG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and blood uric acid were detected by automatic biochemical analyzer (Olympus AU5400), respectively. The fasting insulin (Fins) was assessed by radioimmunoassay. The β -cell function (HOMA- β) and insulin resistance (HOMA-IR) were calculated by the homeostasis model using Levy's computer model [12] ($\text{HOMA-IR} = \text{FBG} \times \text{FIns} / 22.5$; $\text{HOMA-}\beta = 20 \times \text{FIns} / \text{FBG} - 3.5$).

Statistic analysis

Statistic analysis was performed using SPSS17.0. All values were expressed as mean \pm standard deviation. Study characteristics were compared between categories of alcohol intake using variance, chi-square and covariance. Multiple regression analysis was used to evaluate the contribution of each confounding factors for FBG, HOMA- β and HOMA-IR of subjects categorized by BMI. A value of $p < 0.05$ was considered significant. Bonferroni correction was used to correct for multiple testing.

Results

The characteristics of the participants were shown in Table 1. Among the subjects, current drinkers were 58.8% and 15.4% of them consumed alcohol more than 40 g/day. Most of the heavy drinkers were young men (average age 37 years). Non-smokers were reported by 48.7%, former smokers by 12.9% and still smokers by 38.4%. The percent of current smokers were 46.5%, 53.7% and 36.1% in light, moderate and heavy groups, respectively. There were significant differences among groups. Adjusting for both age and smoke, the levels of FBG were higher in moderate-to-heavy drinkers. TG and TC were observed higher in moderate drinkers. HOMA- β was lower in moderate-to-heavy drinkers.

The proportion of $\text{FBG} \geq 6.1 \text{ mmol/L}$ [13] was highest in the abstainers (22.9%) and lowest in the light drinkers (8.9%). More than half of the subjects (58.1%) were overweight and there were more overweight subjects in moderate drinkers than never drinkers (69.1% vs. 53.1%).

Figs. 1-3 showed the association between alcohol and FBG, HOMA-IR or HOMA- β categorized by BMI excluding the abstainers. Adjusting for age and smoke, the FBG was found higher in moderate-to-heavy drinkers for total and $\text{BMI} \geq 25 \text{ kg/m}^2$ subjects. HOMA-IR was found lower in drinkers than never drinkers but no significant difference was observed. HOMA- β was found decreased in any dose of alcohol consumption groups independent of BMI. Significant difference still existed for most comparisons especially between never and heavy drinkers when adjusted for multiple testing ($p < 0.0083$).

Tables 2-4 showed the multiple stepwise regression analysis using FBG, HOMA-IR and HOMA- β as objective variables and various confounding factors as explanatory variables. TG and TC were significantly

Table 1 Characteristics of study participants according to alcohol consumption

	Never drinkers	Abstainers	Current drinkers			p , p'
			Light	Moderate	Heavy	
N	243	35	213	123	61	
Age (year)	45 \pm 17	53 \pm 14	49 \pm 14	45 \pm 12	37 \pm 13	<0.001
Smoke (n) (never/past/current)	162/20/61	20/4/11	79/35/99	42/15/66	26/13/22	<0.001
FBG (mmol/L)	5.30 \pm 0.9	5.57 \pm 0.97	5.25 \pm 0.72	5.90 \pm 1.94	5.57 \pm 1.66	<0.001 <0.001
TG (mmol/L)	1.61 \pm 1.13	1.64 \pm 0.69	1.77 \pm 1.76	2.32 \pm 1.86	1.88 \pm 1.49	0.006 0.035
TC (mmol/L)	5.11 \pm 0.88	5.40 \pm 1.0	5.27 \pm 0.96	5.66 \pm 0.94	5.11 \pm 1.09	<0.001 0.018
HDL-C (mmol/L)	1.37 \pm 0.27	1.34 \pm 0.27	1.42 \pm 0.31	1.47 \pm 0.34	1.42 \pm 0.30	0.033 0.049
LDL-C (mmol/L)	3.24 \pm 0.74	3.51 \pm 0.90	3.27 \pm 0.74	3.51 \pm 0.81	3.17 \pm 0.87	0.013 0.168
Uric (μ mol/L)	331.94 \pm 67.91	348.11 \pm 89.74	343.01 \pm 74.52	354.06 \pm 88.43	338.44 \pm 63.77	0.155 0.387
Fins (mmol/L)	10.76 \pm 15.21	9.20 \pm 5.60	8.77 \pm 5.10	8.89 \pm 5.65	8.37 \pm 4.66	0.159 0.316
HOMA-IR	2.66 \pm 4.61	2.28 \pm 1.43	2.08 \pm 1.35	2.31 \pm 1.50	2.14 \pm 1.58	0.343 0.584
HOMA- β	126.66 \pm 128.20	98.29 \pm 58.05	110.61 \pm 71.06	90.93 \pm 67.54	94.08 \pm 58.0	<0.001 0.001
BMI (kg/m ²)	25.50 \pm 3.90	26.35 \pm 4.30	25.64 \pm 3.21	26.48 \pm 3.08	25.43 \pm 3.15	0.164 0.205
SBP (mmHg)	122.37 \pm 14.65	128.89 \pm 20.00	125.86 \pm 16.00	124.67 \pm 17.62	120.12 \pm 15.83	0.005 0.206
DBP (mmHg)	80.12 \pm 10.20	83.09 \pm 11.38	82.58 \pm 10.71	83.15 \pm 10.01	79.06 \pm 10.76	0.006 0.136
WC (cm)	87.54 \pm 9.75	91.60 \pm 9.69	88.46 \pm 8.56	90.08 \pm 8.85	87.80 \pm 11.37	0.069 0.180

Data are mean \pm SD. p' were adjusted for age and smoke.

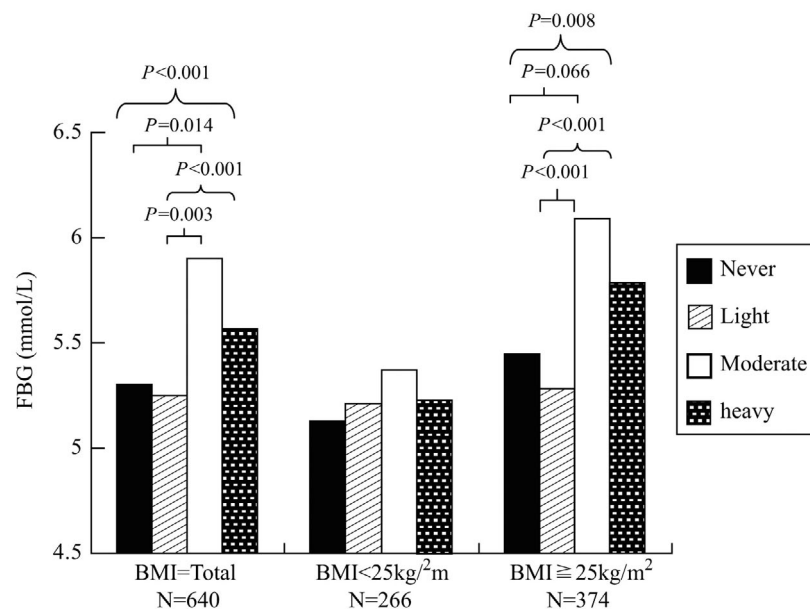


Fig. 1 The association between alcohol consumption and FBG excluding the abstainers
The differences between groups were analyzed by analysis of covariance adjusted for age and smoke.

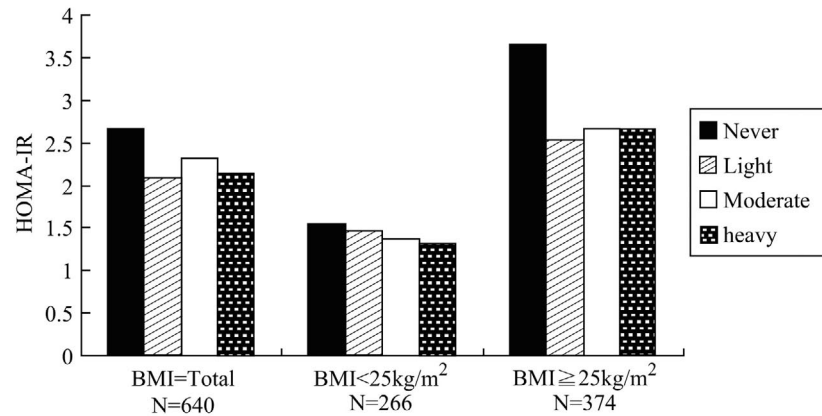


Fig. 2 The association between alcohol and HOMA-IR excluding the the abstainers
The differences between groups were analyzed by analysis of covariance adjusted for age and smoke.

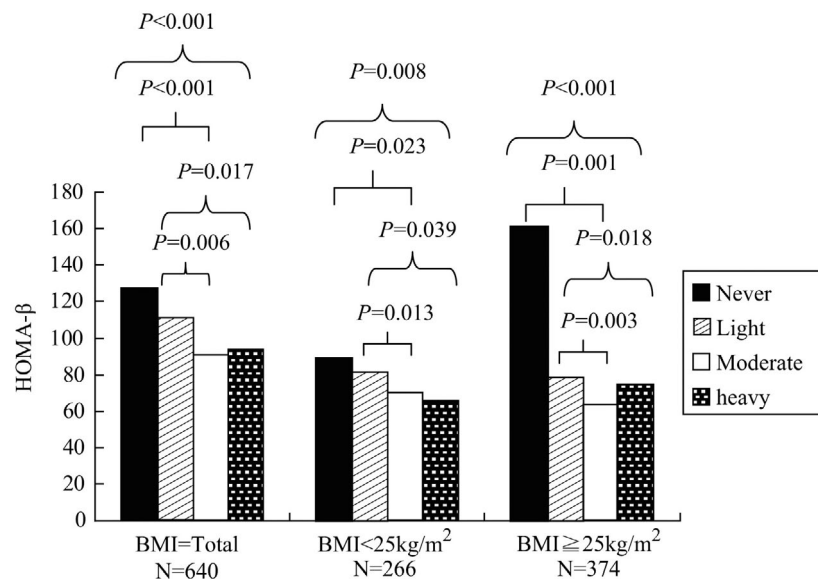


Fig. 3 The association between alcohol and HOMA-β excluding the the abstainers
The differences between groups were analyzed by analysis of covariance adjusted for age and smoke.

and independently associated with increased FBG in all and BMI≥25 kg/m² subjects. Age and TC were associated with increased FBG in subjects with BMI<25 kg/m². Alcohol history was significantly and independently associated with decreased HOMA-IR in all and BMI<25 kg/m² subjects, whereas, alcohol consumption was significantly and independently associated with decreased HOMA-IR in the subjects with BMI≥25 kg/m². WC was significantly and independently associated with increased HOMA-IR in all and BMI≥25 kg/m² subjects. Uric was significantly and independently associated with

HOMA-IR. Alcohol consumption and age were correlated with decreased HOMA-β and WC was correlated with increased HOMA-β independent of BMI.

Table 5 showed the multiple stepwise regression analysis using HOMA-IR and HOMA-β as objective variables and various confounding factors as explanatory variables categorized by FBG. In the subject with FBG≥6.1mmol/L, alcohol consumption and age were significantly and independently associated with decreased HOMA-IR and HOMA-β, whereas, BMI was significantly and independently associated

Table 2 Multiple regression analysis of various confounding factors for FBG by BMI

factors	BMI=Total (N=675)		BMI<25(kg/m ²) (N=283)		BMI \geq 25(kg/m ²) (N=392)	
	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>
Age (year)	0.075	0.052	0.008	0.006	0.038	0.443
Alcohol consumption (never/abstainer/light/moderate/heavy)	0.059	0.050	0.099	0.084	0.064	0.187
Alcohol history (year)	0.032	0.465	0.096	0.116	0.034	0.484
TG (mmol/L)	0.153	<0.001	0.098	0.096	0.168	<0.001
TC (mmol/L)	0.245	<0.001	0.133	0.010	0.276	<0.001
Smoke (never/past/current)	-0.054	0.149	0.023	0.685	-0.048	0.329
Uric (μ mol/L)	-0.064	0.087	0.028	0.631	-0.090	0.063
WC (cm)	0.047	0.221	0.044	0.467	0.020	0.329
Constant	3.760	<0.001	4.193	<0.001	3.709	<0.001
R ²	0.109	<0.001	0.085	<0.001	0.097	<0.001

Table 3 Multiple regression analysis of various confounding factors for HOMA-IR by BMI

factors	BMI=Total (N=675)		BMI<25(kg/m ²) (N=283)		BMI \geq 25(kg/m ²) (N=392)	
	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>
Age (year)	-0.061	0.123	0.047	0.402	-0.030	0.026
Alcohol consumption (never/abstainer/light/moderate/heavy)	-0.044	0.309	-0.049	0.398	-0.312	0.015
Alcohol history (year)	-0.116	0.010	-0.021	0.004	-0.094	0.952
TG (mmol/L)	0.063	0.105	0.248	<0.001	0.048	0.340
TC (mmol/L)	0.022	0.575	-0.055	0.340	0.052	0.307
Smoke (never/past/current)	-0.066	0.082	-0.183	0.001	-0.067	0.188
Uric (μ mol/L)	0.004	0.006	0.002	0.024	0.005	0.040
WC (cm)	0.079	<0.001	0.060	0.324	0.073	0.002
Constant	-5.837	<0.001	0.888	0.001	-3.709	0.143
R ²	0.091	<0.001	0.135	<0.001	0.062	<0.001

Table 4 Multiple regression analysis of various confounding factors for HOMA- β categorized by BMI

factors	BMI=Total (N=675)		BMI<25(kg/m ²) (N=283)		BMI \geq 25(kg/m ²) (N=392)	
	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>
Age (year)	-1.602	<0.001	-0.757	<0.001	-2.203	<0.001
Alcohol consumption (never/abstainer/light/moderate/heavy)	-11.566	<0.001	-6.671	<0.001	-16.091	<0.001
Alcohol history (year)	-0.015	0.754	0.021	0.790	0.008	0.901
TG (mmol/L)	0.010	0.791	0.116	0.051	0.001	0.997
TC (mmol/L)	-0.050	0.190	-6.826	0.042	-0.036	0.455
Smoke (never/past/current)	-0.017	0.631	-0.096	0.100	0.019	0.703
Uric (μ mol/L)	0.109	0.020	1.041	0.062	0.081	0.089
WC (cm)	2.802	<0.001	1.050	0.010	2.212	0.001
Constant	-81.841	0.012	73.508	0.025	55.979	0.414
R ²	0.169	0.020	0.133	<0.001	0.136	<0.001

Table 5 Multiple regression analysis of various confounding factors for HOMA-IR and HOMA- β by FBG

factors	HOMA-IR				HOMA- β			
	FBG ≥ 6.1 mmol/L (N=77)		FBG <6.1mmol/L (N=598)		FBG ≥ 6.1 mmol/L (N=77)		FBG <6.1mmol/L (N=598)	
	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>
Age (year)	-0.209	0.002	-0.047	0.219	-1.278	<0.001	-1.366	<0.001
Alcohol consumption (never/abstainer/light/moderate/heavy)	-1.193	0.039	-0.032	0.448	-8.885	<0.001	-9.248	<0.001
Alcohol history (year)	-0.019	0.881	-0.084	0.001	-0.006	0.911	-0.006	0.909
TG (mmol/L)	0.018	0.873	0.072	0.055	0.065	0.086	0.075	0.052
TC (mmol/L)	-0.045	0.689	0.017	0.648	-0.019	0.838	-0.019	0.646
Smoke (never/past/current)	-0.145	0.211	-0.035	0.343	0.025	0.506	0.006	0.870
Uric (μ mol/L)	0.129	0.234	0.003	<0.001	0.051	0.187	0.065	0.094
BMI (kg/m^2)	0.204	0.059	0.197	<0.001	9.297	<0.001	0.104	0.782
WC (cm)	0.162	0.137	0.098	0.115	0.116	0.071	3.126	<0.001
Constant	17.384	<0.001	-3.786	<0.001	-51.013	0.040	-83.808	0.006
R ²	0.139	0.004	0.252	<0.001	0.202	<0.001	0.178	<0.001

with increased HOMA- β . In the subject with FBG <6.1mmol/L, alcohol history (year) and alcohol consumption were associated with decreased HOMA-IR and HOMA- β , respectively, whereas, BMI and WC were associated with increased HOMA-IR and HOMA- β , respectively.

Discussion

The β -cell dysfunction plays a key role in the development of type 2 diabetes [14]. In the study, our main finding is that at any levels of alcohol consumption, the HOMA- β levels decreased and the relationship between them was independent of body mass index. A U-shaped relationship was observed for the HOMA-IR and alcohol intake, with a low mark in the light drinkers.

The current methods for the assessment and evaluation of β -cell function are pulsatile insulin secretion, hyperglycemic clamp, intravenous glucosetolerance test, oral glucose tolerance test (OGTT) and so on. However, these methods operate more complicated and subjects suffering from large, so it is not conducive to large-scale clinical trial use [15].

FBG is much more convenience to be tested and it is closely associated with β -cell functions [16]. Piche's [17] study has shown that adjusting for age, sex, BMI, and WC, subjects were characterized by impaired insulin secretion and decreased insulin sensitivity with ele-

vated fasting glucose levels. In China, studies also showed that the increased fasting plasma glucose level reflected progressive decomposition of β -cell functions [18], and could be used to guide the strategy of clinical treatments. This supports that FBG is a valuable indicator for the evaluation of β -cell function.

This study showed that 11.4% of the subjects had high FBG levels (≥ 6.1 mmol/L) and over half of them was current drinkers. The proportion of the individuals with FBG ≥ 6.1 mmol/L was lowest in light drinkers. The multiple regression analysis indicated that alcohol consumption, TG and TC were the most important risk factors for impaired FBG, but the R² was only 0.109, which may suggest that the other risk factors such as genetic, environmental and lifestyle may have more impacts on FBG. Similarly, a study from Korean also showed that not only moderate but also heavy drinking had higher incidence of impaired fasting glucose or type 2 diabetes in Korean men [15]. In this study, the FBG level of heavy drinkers was decreased compared with that of moderate drinkers, but no statistical difference was observed. The reason may be the numbers of the heavy drinkers was small and most of the heavy drinkers were young.

Meanwhile, the light drinkers associated with lower FBG, TG, TC, HOMA-IR levels and higher HOMA- β levels, while the moderate-to-heavy drinkers had converse characteristics. This indicated that light drinking

may ameliorate the metabolic indicators.

Currently there were few studies about the relationship between alcohol consumption and β -cell dysfunction. This study showed that the HOMA- β level was lower in the four levels of drinkers than never drinkers independent of BMI, which indicated that alcohol consumption may associate with β -cell secretion impact. The multiple regression analysis also showed that alcohol consumption was a major factor of β -cell dysfunction independent of BMI. Crandall's study [19] had shown that higher alcohol consumption was associated with lower insulin secretion at any levels of insulin sensitivity after adjusting age, sex, race, diet, body weight and sports. These data supported our study. When categorized by FBG, the alcohol consumption was also strongly associated with β -cell dysfunction in subjects with FBG < 6.1 mmol/L. This suggests that alcohol consumption may play a role over the pre-diabetes to diabetes. The possible mechanism of alcohol consumption leads to the β -cell dysfunction may include the following: 1) Chronic alcohol consumption is a risk factor for chronic pancreatitis and is reported to be associated with chronic pancreatitis in 50 to 70% of patients [20]; 2) Chronic alcohol consumption accelerates pancreas fibrosis [21]; 3) Chronic alcohol consumption may lead to some optical and structural abnormalities of β -cells [22], that may contribute, at least in part, to the β -cell functional disturbance. Of course, further studies are needed on human.

The relationship between alcohol consumption and IR, type 2 diabetes has been widely concerned. Some studies showed there was a "U" or "J" relationship between them [23-25]. But other studies [26-28] did not observe the "U" or "J" curve. Alcohol consumption, and the resulting health effects, are more complex. Our earlier experiments had found that chronic excess alcohol consumption degraded insulin-stimulated glucose uptake and increased insulin resistance by up-regulating the Gs α in isolated rat skeletal muscle [29] and down-regulating the GLUT4 expression in rat cardiac muscle [30] and affected, in a dose-response manner, adipokine contents in both VAT and sera [31]. The mechanism by which alcohol may ameliorate insulin resistance is unclear. A proposed hypothesis to explain it suggests that alcohol may inhibit gluconeogenesis in the liver by increasing the NADH (reduced-form of nicotinamide adenine dinucleotide)/NAD (nicotinamide adenine dinucleotide) ratio and the lactate/pyruvate ratio [32].

In this study, the HOMA-IR level was lowest in light drinkers shown a "U" curve but statistical difference was not observed. Our multiple regression analysis showed that HOMA-IR was negatively associated with the alcohol dose in overweight men while alcohol history played a greater role in non-overweight men. Previous studies only account of the effect of alcohol dose on HOMA-IR but ignored the effect of alcohol history (length). We think all of them were important factors for HOMA-IR. Increased BMI was an important determinant of insulin resistance [33]. We also observed the level of HOMA-IR was higher in subjects with BMI ≥ 25 kg/m² (Fig. 2) and there was more heavy drinkers in subjects with BMI ≥ 25 kg/m² than subjects with BMI < 25 kg/m² (16.6% vs. 14.1%). So the effect of drinking dose on HOMA-IR is more significant while the change of HOMA-IR in subjects with BMI < 25 kg/m² needs more time to be observed.

In addition, obesity is an independent risk factor for IR [33]. This study also confirmed WC remained significantly associated with increased IR adjusting for alcohol consumption, smoking, blood lipids, and uric acid. Over half of the subjects were overweight and especially in the moderate-to-heavy drinkers. This may indicate that alcohol consumption had a significant impact on obesity in Chinese men. Taking into account WC [34] was considered a better indicator of visceral fat, this result promoted that alcohol may increase insulin resistance by increasing visceral fat in overweight people.

In conclusion, an approximately U-shaped association was observed between alcohol consumption and HOMA-IR among Chinese men. Adjusting for age, smoke, lipids and blood uric acid, alcohol consumption and obesity were important risk factors of β -cell dysfunction. In the development of type 2 diabetes, β -cell dysfunction plays a decisive role [35], and so it may be more meaningful to pay more attention to the association of alcohol consumption and insulin secretion.

Obviously, there were some limitations in this study. First, this study relies on self-report of alcohol consumption, history of disease, and so on, which may result in error and bias. Second, there are many other confounders including type of binge, the diet, family history of diabetes, and so on, remain to be explored. Third, the number of heavy drinkers was small. Fourth, the cross-sectional study design, as well as other studies, limited in its ability to explore causal relationship between alcohol and β -cell function. Prospective pop-

ulation-based studies are needed to be done.

Conflict of Interest

The authors declare no conflicts of interest.

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