Original Article

Cigarette Smoking Increases Risk for Incident Metabolic Syndrome in Chinese Men—Shanghai Diabetes Study*

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Abstract

Objective To determine whether smoking increases the risk for developing metabolic syndrome (MetS) in Chinese men.

Methods A total of 693 men with no MetS at baseline were followed for 2.9-5.5 years. Subjects were divided into nonsmokers, ex-smokers, and current smokers according to baseline smoking status.

Results After adjusting for age, education level, alcohol intake, fasting plasma insulin, HOMA-IR index, and BMI at baseline and weight change, current smokers were dose-dependently associated with increased risk for developing new MetS compared with nonsmokers. The odds ratio (OR) was 2.131 (95% CI, 1.264, 3.592; $P<0.01$) for the NCEPIII definition or 3.083 (95% CI, 1.807, 5.295; $P<0.01$) for the JCDCG definition of MetS. Ex-smokers who had quit for $\geqslant$13 years significantly decreased the risk for developing new MetS defined by the JCDCG definition. Compared with nonsmokers, current smokers were significantly associated with increased incidence of hypertriglyceridemia and low HDL-C.

Conclusion Smoking is a risk factor for developing MetS in Chinese men after adjusting for age, education level, alcohol intake, fasting plasma insulin, HOMA-IR, BMI, and weight change. This could be due to an increased incidence of dyslipidemia. Smoking cessation for >13 years decreased the risk for developing MetS defined by the JCDCG definition.

Key words: Smoking; Metabolic syndrome; Dyslipidemia

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INTRODUCTION

Metabolic syndrome (MetS), a constellation of metabolic abnormalities including central obesity, glucose intolerance, dyslipidemia, and hypertension, is well documented to increase the risk for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), and is correlated with all-cause mortality[1]. MetS is becoming an epidemic worldwide and is considered

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one of the most important health challenges in China owing to rapid socioeconomic development and nutrition transitions[2]. In Shanghai, the most cosmopolitan city in China, the prevalence of MetS in men was around 10%-26%[3-4].

Smoking, in addition to other modifiable risk factors including physical inactivity, excessive weight gain, and high alcohol intake, is considered a strong risk factor for atherosclerosis and cardiovascular diseases[5]. According to the latest survey results, in 2002, the total number of smokers was about 350 million (almost one third of all smokers worldwide) in mainland China. Men account for the majority and the average cigarette consumption per person per day was 14.8 cigarettes[6]. It is estimated that tobacco-related deaths will reach 7 million worldwide in 2025. As the world's largest producer and consumer of tobacco products, 2 million of these deaths are predicted to occur in China[7]. The association of cigarette smoking and MetS has been studied in cross-sectional and longitudinal populations[8-11]. However, available data on this issue are controversial[8-11]. Studies from Japan and Korea linked smoking with development of MetS, whereas a study conducted in Turkey showed an inverse effect of smoking on predicting MetS in women[9-11]. Moreover, cohort studies on smoking and risk for developing new MetS in the Chinese population has not yet been demonstrated.

Because of high prevalence of MetS and large number of male smokers in China, evaluation of the relation between smoking and MetS in Chinese individuals has major public health relevance. As such, the aims of this study were to examine the role of smoking in prediction of MetS in Chinese men with a 3-year follow-up and to investigate associations between smoking status and development of MetS components.

MATERIALS AND METHODS

Survey and Study Population

The present analysis was based on data from Shanghai Diabetes Study (SHDS)[12]. The population of SHDS has been described in detail elsewhere[3,12-13]. Briefly, baseline data from SHDS were collected in Huayang and Caoyang communities in Shanghai between September 1998 and November 2001. Between December 2003 and February 2004, a follow-up (face-to-face) survey was conducted after a median of 3 (range, 2.9-5.5) years. A total of 1 275 men aged 20-95 years who had complete data obtained for identification of MetS and cigarette smoking status during the baseline survey and enrolled in the follow-up visit were chosen as present study cohort. Subjects with following conditions were excluded: presence of cancer, severe disability, or severe psychiatric disturbance (n=22); and refusal to provide individual smoking status or incomplete MetS-associated examinations at follow-up survey (n=308). The remaining 945 men were included in the present study; data on 693 of them who had no MetS at baseline were evaluated to determine incidence risk for developing MetS. Informed consent was obtained from each participant. The Shanghai Diabetes Institute served as coordinating and data center of the study. The investigation staff consisted of physicians, epidemiologists, and nurses who were trained before the survey. The protocol was followed in accordance with Helsinki Declaration and approved by local ethics committee.

Physical Examination

Height and weight were measured with subjects standing without shoes and in light clothing. Waist circumference (WC) was measured at the horizontal plane between the inferior costal margin and the iliac crest on midaxillary line with the subjects standing relaxed and in underwear. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Blood pressure measurements were taken three times (with a 1-minute rest interval) using a sphygmomanometer then averaged.

Laboratory Assays

Each participant was asked to arrive at the community healthcare center at 6-7 AM following an overnight fast. Venous blood samples were collected and each participant received a 75-g oral glucose tolerance test (OGTT). Those with a validated history of DM were exempted from the OGTT. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated based on fasting insulin (FINS) and fasting plasma glucose (FPG) according to the equation: HOMA-IR = FINS [μU/mL] × FPG [mmol/L]/22.5[14]. FPG was measured by glucose oxidase method. Serum insulin was determined by radioimmunoassay (RIA) (Linco, St Louis, MO). Total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and triglyceride

(TG) were measured by automated biochemical instrument (DPC, Los Angeles, CA).

Questionnaires

A standardized questionnaire was used in face-to-face interviews by trained staff at the baseline and follow-up survey. Data on smoking habits, alcohol intake behavior, education levels, and disease history were collected. Two questions were designed to evaluate current cigarette smoking habits (mean daily cigarette consumption in the past 1 year and duration of smoking) and three questions related to quitting behaviors (duration of smoking cessation, mean daily cigarette consumption, and duration of smoking before smoking cessation). Subjects were divided into three groups by smoking status at baseline survey: nonsmokers were defined as those who had never smoked, or smoked only occasionally; current smokers were those who smoked ⩾1 cigarette/day for ⩾ 1 year; and ex-smokers were those who had regularly smoked in the past but had quit for ⩾1 year. Current smokers were subdivided into two groups by daily cigarette amount at baseline: 1-20 cigarettes/day, and ⩾21 cigarettes/day. Ex-smokers were categorized as three groups by years of smoking cessation: 1-4 years; 5-12 years, and ⩾13 years. Education level was categorized into: low education (illiteracy, primary and secondary education, <8-9 years schooling), medium education (high school education, 9-12 years schooling), and high education (college or university education, >14 years schooling). Subjects were divided into three groups according to alcohol intake behavior at baseline: nondrinkers (those who never or only occasionally drank), current drinkers (those who drank ⩾6 g alcohol per day for ⩾1 year), and ex-drinkers (those who had been a drinker but quit for ⩾6 months).

Metabolic Syndrome Definition

MetS was defined according to the National Cholesterol Education Program's Adult Treatment Panel III criteria in 2005 (NCEPIII) (USA) with waist circumference cutoff points for Asians[15] and the Chinese Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults definition (JCDCG)[16] (Table 1). Medication to control hyperlipidemia was not considered when diagnosing MetS and low HDL-C in this study.

Table 1. Definitions for MetS

	NCEPIII Definition at Least Three of the Following Criteria	JCDCG Definition at Least Three of the Following Criteria
Impaired Glucose Metabolism	FPG⩾5.6 mmol/L or with DM history	FPG⩾6.1 mmol/L and/or 2-h PG ⩾7.8 mmol/L or with DM history
Hypertension	Blood pressure ⩾130/85 mmHg or medication	Blood pressure ⩾130/85 mmHg or medication
Hypertriglyceridemia	TG⩾1.7 mmol/L	TG ⩾1.7 mmol/L
Low HDL-C	HDL-C＜1.03 mmol/L (men); ＜1.29 mmol/L (women)	HDL-C＜1.04 mmol/L
Central Obesity	Waist circumference ⩾90 cm (men); ⩾80 cm (women)	Waist circumference ＞90 cm (men); ＞85 cm (women)

Note. DM, diabetes mellitus; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; JCDCG, Chinese Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults; MetS, metabolic syndrome; NCEPIII, National Cholesterol Education Program's Adult Treatment Panel III; PG, plasma glucose; TG, triglyceride.

Statistical Analyses

Statistical analyses were performed with SPSS 15.0 for Windows. Data are expressed as mean±SD or median (interquartiles range) according to the distribution. Categorical variables are expressed as frequency or proportion. The distribution of continuous variables was assessed for normality by tests of normality. Insulin and TG, skew-distributed, were logarithmically transformed for statistical analyses and back-transformed to natural units for presentation in the text and tables. Statistical differences between subjects with and without MetS were analyzed by Mann-Whitney *U* test or *t*-test for median or means and chi-square test for proportions. Odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were obtained with binary logistic regression. Linear trends in ORs across increasing categories of smoking for current smokers and ex-smokers were evaluated by trend test. All reported *P* values are two-tailed and the level of significance was defined as $P<0.05$.

RESULTS

Among 945 men in the present study, 693 were

free of MetS at baseline. Of these, 222 subjects (32.0%) were nonsmokers, 95 (13.7%) ex-smokers, and 376 (54.3%) current smokers. Subjects without MetS at baseline were followed for a total of 2 357 person-years. Table 2 shows the baseline characteristics of the study population grouped by MetS status at follow-up. Subjects with MetS had higher BMI, WC, systolic blood pressure (SBP), diastolic blood pressure (DBP), TG, TC, HDL-C, LDL-C, FPG, and FINS levels compared with non-MetS participants at follow-up according to both the NCEPIII and the JCDCG definitions. Current smokers tended to develop new MetS, although nonsignificantly by the NCEPIII definition.

Table 2. Baseline Clinical Characteristics of Study Subjects with or without Metabolic Syndrome

	NCEPIII Definition		JCDCG Definition	
Variable	**Non-MetS**	**MetS**	**Non-MetS**	**MetS**
n	542	150	539	151
Age (years)	54 (43-71)	60 (44-71)	55 (43-71)	55 (43-68)
BMI (kg/m^2)	22.4±2.9	24.9±2.7**	22.4±2.8	24.8±2.8**
Waist Circumference (cm)	79±8	87±8**	79±8	87±8**
SP (mmHg)	124±18	131±20**	124±18	128±19**
DP (mmHg)	78±10	82±11**	78±10	81±10**
TG (mmol/L)	1.20 (0.91-1.63)	1.60 (1.32-2.38)**	1.19 (0.91-1.64)	1.56 (1.33-2.30)**
TC (mmol/L)	4.63±0.98	4.95±1.12**	4.65±1.00	5.00±1.11**
HDL-C (mmol/L)	1.32±0.22	1.29±0.22*	1.32±0.22	1.27±0.22**
LDL-C (mmol/L)	3.21±0.83	3.44±0.95**	3.22±0.84	3.49±1.01**
FPG (mmol/L)	4.8 (4.5-5.2)	5.1 (4.7-5.4)**	4.9 (4.5-5.2)	5.1 (4.7-5.5)**
FINS (mU/L)	5.27 (3.36-7.86)	6.97 (4.88-10.62)**	5.18 (3.34-7.74)	7.11 (4.88-10.13)**
Smoking Status, % (*n*)				
Nonsmoker	33.4 (181)	27.3 (41)	34.1 (184)	23.2 (35)*
Ex-Smoker	13.3 (72)	15.3 (23)	13.7 (74)	11.9 (18)
Current Smoker	53.3 (289)	57.3 (86)	52.1 (281)	64.9 (98)*
Education Level, % (*n*)				
Low Education Level	43.2 (233)	52.0 (78)	43.3 (232)	49.7 (75)
Middle Education Level	36.4 (196)	22.7 (34)**	35.6 (191)	27.2 (41)
High Education Level	20.4 (110)	25.3 (38)	21.1 (113)	23.2 (35)
Alcohol Consumption, % (*n*)				
Nondrinker	71.4 (387)	66.7 (100)	71.1 (383)	68.2 (103)
Ex-Drinker	0 (0)	0 (0)	0 (0)	0 (0)
Current Drinker	28.6 (155)	33.3 (50)	28.9 (156)	31.8 (48)

Note. Data represent means ± SD, median (interquartile range 25%-75%), or % (*n*). Statistical significance of differences between groups was analyzed by Mann-Whitney *U* test or *t*-test for median or means and chi-square test for proportions. $^{*}P<0.05$; $^{**}P<0.01$, *vs* non-MetS. BMI, body mass index; DBP, diastolic blood pressure; FINS, fasting insulin; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; JCDCG, Chinese Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults; LDL-C, low-density lipoprotein cholesterol; NCEPIII, National Cholesterol Education Program's Adult Treatment Panel III; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

After a median follow-up period of 3 years, the number of new-onset MetS according to the NCEPIII definition and the JCDCG definition was 150 (21.7%) and 151 (21.9%), respectively. Multivariable binary regression analysis revealed that current smokers had a strong association with developing new MetS defined by both the NCEPIII and JCDCG definitions compared with nonsmokers. ORs reached 2.131 (NCEPIII definition; $P<0.01$) and 3.083 (JCDCG definition; $P<0.01$) after adjustment for age, alcohol intake, education level, FINS, HOMA-IR index, BMI, and weight change (Figure 1A). Smoking status is a

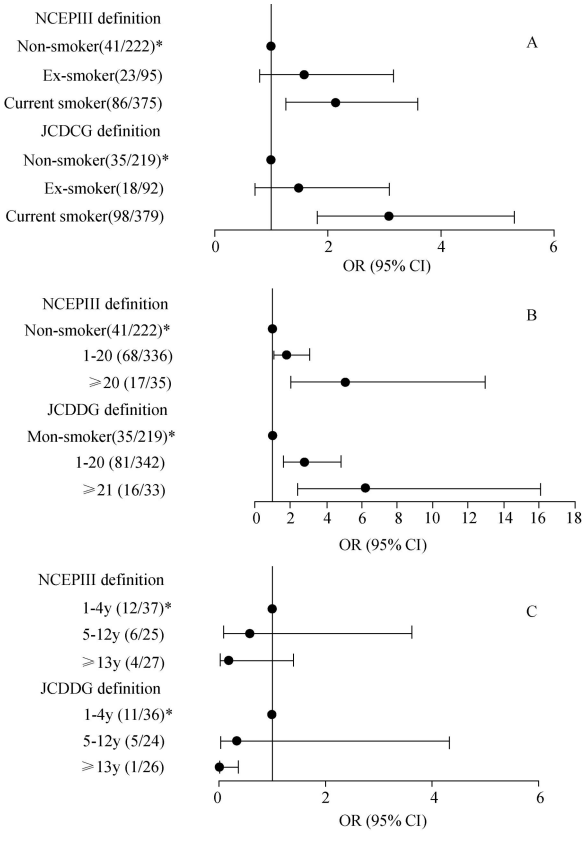

Figure 1. ORs of smokers for incidence of MetS defined by the NCEPIII or JCDCG criteria. A: Subjects were divided by smoking habit at baseline with cases/total subjects shown in brackets. B: Current smokers were grouped by daily cigarette amount at baseline. C: Ex-smokers were grouped by smoking cessation years (y) at baseline. CI, confidence interval (shown by error bars). *Reference group.

modifiable risk factor, and 17 (1.3%) nonsmokers started smoking, 57 (10.3%) current smokers quit, and 23 (15.5%) ex-smokers started smoking again at follow-up in the present study. We further evaluated the association between smoking and risk for MetS in subjects who did not change smoking status and found that it remained the same (data not shown). Moreover, smoking amount increased the risk for developing MetS defined by both definitions in a dose-dependent fashion (all $P<0.01$ for trend, Figure 1B). OR for developing MetS according to NCEPIII and JCDCG definitions, compared with non-smokers, was 1.801 (95% CI, 1.049, 3.091) and 2.801 (95% CI, 1.617, 4.852), respectively for those who smoked 1-20 cigarettes/day and 5.108 (95% CI, 2.012, 12.972) and 6.207 (95% CI, 2.397, 16.074), respectively, for those who smoked ⩾ 21 cigarettes/day after controlling for age, education level, alcohol intake, FINS, HOMA-IR index, BMI, and body weight change (Figure 1B). As for ex-smokers, smoking cessation had a year-dependent trend ($P<0.01$ for trend) to lower the risk for developing MetS defined by JCDCG criteria but not by NCEPIII criteria (Figure 1C). After stratification by smoking cessation years in ex-smokers, subjects who had stopped smoking for ⩾13 years had a lower risk for developing MetS defined by the JCDCG definition (Figure 1C).

To investigate the mechanisms of smoking and occurrence of new MetS during the follow-up period, we compared the risk for developing different MetS components in subjects without MetS at baseline stratified by smoking status (Table 3). For example, we conducted logistic regression analysis to evaluate risk for follow-up new-onset high blood pressure grouped by smoking habits in participants who were free of both MetS and high blood pressure at baseline. After adjusting for age, education level, alcohol intake, FINS, HOMA-IR index, BMI, and weight change, current smokers had a significantly higher risk for developing hypertriglyceridemia and low HDL-C compared with nonsmokers by JCDCG definition (Table 3) and higher risk for low HDL-C by NCEPIII definition (data not shown).

DISCUSSION

The present study was designed to evaluate the effect of smoking on MetS incidence in Chinese men after a 3-year follow-up. Our results demonstrate that current smokers had a significantly higher risk for developing MetS than nonsmokers by both the NCEPIII and the JCDCG definition after adjusting for several cofactors including age, education level, alcohol intake, FINS, HOMA-IR index, and BMI at baseline and weight change. There was a dose-dependent association between the amount smoked and development of MetS by both definitions. Our finding that smoking was positively associated with the occurrence of MetS is in agreement with two previous cohort studies conducted in Japan and Korea, in which ORs for current smokers who smoked >20 cigarettes per day were 1.50 (95% CI, 1.18, 1.90) in Japanese[10] and 2.16 (95% CI, 1.39, 3.37) in Korean subjects[9]. However, a study from Turkey showed an inverse association between smoking and incidence of MetS[11]. They reported that heavy smoking (⩾11 cigarettes daily) was significantly “protective” (RR,

Table 3. Incident MetS Components Based on JCDCG Definition among Subjects without MetS at Baseline According to Smoking Status

Smoking Status	High Blood Pressure		Hyperglycemia	Hypertriglyceridemia	Low HDL-C	Central Obesity
Nonsmokers	Cases, *n*	17 (97)	31 (176)	38 (178)	39 (210)	16 (186)
	Proportion, %	17.5	17.6	21.3	18.6	8.6
	OR (95% CI)	1.000 (reference)	1.000 (reference)	1.000 (reference)	1.000 (reference)	1.000 (reference)
Ex-Smokers	Cases, *n*	13 (41)	19 (83)	16 (72)	13 (81)	3 (72)
	Proportion, %	31.7	22.9	22.2	16.0	4.2
	OR (95% CI)	2.266 (0.900, 5.704)	1.088 (0.537, 2.200)	1.287 (0.601, 2.753)	0.955 (0.451, 2.018)	0.908 (0.219, 3.757)
Current Smokers	Cases, *n*	53 (236)	44 (327)	81 (266)	92 (336)	30 (332)
	Proportion, %	22.5	13.5	30.5	27.4	9.0
	OR (95% CI)	1.726 (0.858, 3.469)	0.928 (0.527, 1.636)	1.689 (1.005, 2.839)*	1.742 (1.086, 2.794)*	2.142 (0.912, 5.029)

Note. Odds ratios (ORs) were determined by binary logistic regression and adjusted for age, education level, alcohol intake, fasting plasma insulin, HOMA-IR index, and BMI at study entry and weight change. *$P<0.05$ *vs*. nonsmoker. CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; JCDCG, Chinese Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults; MetS, metabolic syndrome.

0.50; 95% CI, 0.26, 0.94) for MetS in women after adjustment for multiple risk factors including age, physical activity grade, and family income bracket. Since significantly lower waist circumference was observed in heavy smokers compared with those who never smoked, they speculated that the "protective" effect was mediated by the effect of smoking on lowering abdominal obesity. However, studies reported either in cross-sectional or longitudinal populations have indicated that abdominal obesity was more prevalent in smokers than in nonsmokers not only in men but also in women, although body weight, or BMI, was lower in smokers than in nonsmokers[17-18]. In our study, a positive relationship (data not shown), even though statistically nonsignificant, was observed between smoking and WC, a simple indicator of central obesity. Nicotine is a potent activator of the hypothalamic-pituitary-adrenal (HPA) axis[19]. Cortisol level was reported elevated in smokers versus nonsmokers[19]. Thus hyperactivity of HPA axis and higher cortisol secretion observed in smokers may be the link between nicotine and central obesity.

We did not find a positive, independent association between ex-smokers and risk for developing MetS compared with nonsmokers or current smokers. However, the study from Korea found that ex-smokers had a higher risk for incidence of MetS compared with nonsmokers (OR, 2.43; 95% CI, 1.80, 3.29) or with sustained smokers (OR, 1.45; 95% CI, 1.06, 1.98)[9]. Smaller sample size and a longer period of smoking cessation of ex-smokers in our study may contribute to our negative results. In our population, ex-smokers were those who had stopped smoking at baseline, while ex-smokers in the Korean study were those who smoked at baseline but quit by follow-up. This might be true, since we found in our study that ex-smokers who had abstained for >13 years had a significantly lower risk for developing MetS by the JCDCG definition.

To determine associations between smoking status and occurrence of each component of MetS after 3 years' follow-up, we performed logistical regression analysis in subjects free of both MetS and one of five MetS components at baseline. We found that current smokers were associated with a higher risk for abnormalities in serum TG and HDL-C levels, but not for incidence of high blood pressure, abnormal FPG, or increased WC. Epidemiologic studies conducted in cross-sectional populations have demonstrated a positive association between smoking and dyslipidemia (mainly high TG and low HDL-C)[5,20-21]. Similar results could also be viewed in the present baseline population, in which prevalence

of hypertriglyceridemia or low HDL-C was higher in current smokers than in nonsmokers (45.1% vs. 36.2%; *P*=0.006 and 17.7% vs. 11.1%; *P*=0.036, respectively). Craig et al.[22] reported in a meta-analysis that plasma TG increased by 9% and HDL-C reduced by 6% in smokers as compared with nonsmokers. Smokers who had been smoking for >20 years exhibited impaired elimination of TG from a mixed meal, even when they had normal fasting triglyceride levels[21]. Nicotine has been proposed to stimulate release of catecholamines by increasing sympathetic nerve activity. This leads to lipolysis and increased plasma concentration of TG[23], in which enzymes were considered involved in alterations of TG and HDL-C metabolism. Previous research has demonstrated that smokers, compared with nonsmokers, exhibited elevated hepatic lipase activity, which led to a reduction of HDL-C and increased TG[24]. In addition, increased hepatic re-esterification of free fatty acids through enhanced lipolysis by smoking tended to increase hepatic very low-density lipoprotein (VLDL)-TG production and resulted in increased TG[23].

Previous studies reported associations between smoking and other MetS components including impaired glucose metabolism and hypertension (central obesity has been discussed above)[11,25-26]. The relation between long-term smoking and hypertension is still unclear and controversial[27]. It is established that smoking could cause acute increase in blood pressure due to release of catecholamines induced by nicotine[19]. However, several epidemiologic studies including ours failed to confirm an independent link between long-term smoking and hypertension[11,20]. Thus smoking might not be a strong risk factor for hypertension[27]. Prospective, population-based studies have demonstrated that smoking increases the risk for developing diabetes[25-26], although cross-sectional studies failed to show any positive association[20,28]. Insulin resistance was widely thought a link between smoking and risk for diabetes, and dysfunction of insulin secretion proposed as an alternate explanation[21,29-30]. Attvall et al.[29] reported that, compared with nonsmokers, smokers had reduced insulin sensitivity presenting as a lower peripheral glucose uptake detected by euglycemic clamp technique. In addition, smoking could impair peripheral vascular endothelium function[31-32], which may result in insulin resistance[33]. Compared with nonsmoking patients, smokers with chronic pancreatitis showed significant impairment of insulin secretion and lower beta-cell mass in pancreas[34].

There are some limitations in the present study. First, baseline smoking status was self-reported by participants and was not confirmed using biologic markers such as cotinine levels; thus misclassification may have occurred in some cases. However, any misclassification should be uniform among the three groups and not more common in current smokers. Second, the amount of cigarette smoking was defined by daily cigarette consumption in the past 1 year and was provided by smokers themselves, which might not reflect the precise number of cigarettes at that time. Third, we could not use data on physical activity as adjustment factor in the analysis because a portion of relevant data was missing. Lastly, the data we obtained from the present study could only be analyzed with binary logistical regression since the subjects were only followed once with an average time of 3 years. Further study with a longer period of follow-up will be conducted in the future.

In conclusion, in our community-based population smoking was associated with higher risk for developing MetS in men independent of age, education level, alcohol intake, fasting plasma insulin, HOMA-IR index, and BMI at study entry and weight change. Dyslipidemia induced by smoking may be particularly important in this process. Smoking cessation for >13 years decreased risk for developing MetS defined by JCDCG criteria. Giving up smoking would reduce the incidence of MetS in China.

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