Research Highlight

The Impact of Cigarette Smoking on Metabolic Syndrome

JIA Wei Ping

Metabolic syndrome (MetS) is a constellation of interconnected cardiometabolic disorders, including obesity, hyperglycemia, dyslipidemia, and elevated blood pressure. MetS is a precursor to type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD); it increases the risk of T2DM by 3-4 times[1] and the risk of CVD by 1.4-fold[2], and is more prevalent in obese individuals. As the obesity rates increase, the prevalence of MetS in the population is increased. In 2006, the global prevalence of MetS in adults was estimated to be 20%-25%[3], and in China, in 2007-2008, using the criteria of the Chinese Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults (JCDCG), it reached 21.9% among the adult population aged ≥20 years old[4].

Smoking is a significantand modifiablerisk factor for many of the common chronic diseases, such as cancer, lung disease, and CVD, and is a potential MetS risk factor. Many people are active or passive smokers; globally, 1.1 billion people are smokers, which is approximately one third of the adult population[5]. In 2002, the Chinese National Survey described 350 million active smokers, and 540 million passive smokers, aged between 15 and 69 years of age[6]. Consequently, the impact of smoking on MetSand other diseasesis of great interest.

The association between active smoking and MetS risk, or the risk of one of its associated disorders, is not fully understood. Among more than 1 000 components, nicotine is the best-known of the major harmful components released from cigarette smoke. Nicotinic acetylcholine receptors (nAChRs) are widely expressed in the central and peripheral nervous system. As ligand-gated ion channels, nicotine mediates a fast synaptic transmission of the neurotransmitter at the neuromuscular junction and ganglia through binding to nAChRs. This directly or indirectly augments the release of several important neurotransmitters and hormone, mainly including arginine vasopressin (AVP), corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), growth hormone (GH), dopamine (DA), serotonin, glutamate, and γ-aminobutyric acid in the central nervous system, acetylcholine (ACh) in the central and peripheral nervous system, epinephrine and norepinephrine by the adrenal medulla, cortisol by the adrenal cortex[7-8]. Note that the hypothalamic-pituitary-adrenal axis (HPA)[9] and the renin-angiotensin-aldosterone system (RAAS)[10] have been implicated in those processes. So it is obvious that there are associations between smoking and some metabolic disorders. Here, we review the associations between smoking and MetS, and smoking and its associated disorders, and present the available evidence of the risk of MetS associated with smoking.

Association between Smoking and MetS

There are sex-specific differences in the association between cigarette smoking and MetS development. In men, most research supports the view that there is a positive association between smoking and MetS risk. Two cross-sectional population surveys in men have observed a higher MetS risk for active smokers than for those who have never smoked, even for water-pipe smoker[11], and the risk of MetS in smokers is dose-dependent, i.e., the risk of MetS increases in men with the number of cigarettes smoked each day[12-13] and total pack-years of cigarettes smoked during the lifetime of an individual[13]. Recently, a meta-analysis, carried out on the association between smoking and MetS using data from 13 prospective cohort studies (56 691 participants and 8 688 MetS cases) from Asia (South Korea, Taiwan, China, Japan and Turkey), Europe (Norway, Britain and Finland), and North America, concluded that active smoking is significantly associated with an increased MetS risk [relative risk (RR) 1.26, 95% CI: 1.10-1.44][14] and heavy smokers have a higher risk than light smokers [RR (95% CI): 1.42 (1.27-1.59) *vs.* 1.10 (0.90-1.35)].

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Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai Clinical Center for Diabetes, Shanghai Diabetes Institute, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Key Clinical Center for Metabolic Disease, Shanghai, China

Furthermore, this positive association existed among these subgroups, which were grouped according to the different definitions of MetS or different geographical areas (Asia and Europe). However, this positive association between smoking and MetS only existed in men: the RR of MetS in active male smokers reached 1.34 (95% CI: 1.20-1.50), which was higher than that for former male smokers [RR: 1.19 (1.00-1.42)]. But it is paradoxical that the positive association between smoking and MetS existed only in studies with a follow-up duration of <5 years, but not in studies with longer follow-up durations.

In this meta-analysis, MetS is not associated with smoking for women. Note that some studies have even shown a negative association between smoking and MetS risk[15]. This could be due to lower smoking amount in women or misclassification of their exposure status; alternatively these results could be confounded by other factors, such as changes in menopausal status.

Association between smoking status and the development of metabolic syndrome evaluated by the prospective studies are shown in Supplement Table.

Association between Smoking and the Individual Disorder Associated with MetS

Smoking is involved in the development of MetS components. An exploration of the link between smoking and the individual MetS components could explain the connection between smoking and MetS.

Association between Smoking and Obesity

Smoking is viewed as helpful in controlling obesity, and it is thought that smoking cessation leads to weight gain and that the resumption of smoking will result in weight loss[7]. The World Health Organization Monitoring Cardiac Disease (WHO MONICA) surveys have shown that, in the 42 populations studied, regular smokers had significantly lower BMIs than individuals who had never smoked[16]. However, one cross-sectional study has shown that smokers have a higher waist-to-hip ratio (WHR) than non-smokers, and demonstrated a dose-dependent relationship between WHR and the number of cigarettes smoked each day[17]. Another 5-year follow-up study indicated that smoking independently increased the risk of obesity (BMI≥26.4 kg/m^2)[18]. However, the effect of smoking on obesity may be due to the poorer lifestyle habits of heavy smokers.

The mechanisms by which smoking affects weight are not clear. Nicotine has complicated effects on the central nervous system regulation of eating and energy expenditure. It promotes the release of various neurotransmitters and hormone (norepinephrine, DA, serotonin andγ-aminobutyric acid) which influences brain chemicals to suppress eating and increase or decrease metabolic rate. The release of norepinephrine and epinephrine elevates thermogenesis in adipose tissue, partly by increasing lipolysis and the subsequent recycling of fatty acids into triglycerides. The acute responses decrease appetite and increase body metabolism, whereas the chronic changes increase appetite and decrease metabolic rate[7]. In addition, nicotine also increases the likelihood of insulin resistance and excess cortisol which may be involved in the relationship of smoking with abdominal obesity[7].

Association between Smoking and Dyslipidemia

Smoking is known to alter lipid metabolism. It is associated with an increase in plasma triglyceride (TG) levels and a decrease in serum high density lipoprotein cholesterol (HDL-C) levels; lipid changes that are often found in insulin resistant patients[18]. A dose-response relationship of daily smoking levels with high serum triglyceride levels and low HDL-C levels has been observed[19]. This dose-response effect of smoking on serum cholesterol concentrations suggests that there should be a gradient of increased CVD risk from non-smokers, with a low CVD risk, through light, moderate, and heavy smokers, who are at increased risk of CVD[20].

The link between cigarette smoking and dyslipidemia can be explained by the elevated plasma free fatty acids (FFAs) which is caused by decreased lipoprotein lipase activity[20], increased 3-hydroxy-3-methylglutaryl-CoA reductase activity, and increased glucose-6-phosphatase dehydrogenase activity[21]. These FFAs stimulate the hepatic synthesis and secretion of cholesterol, which increases the production of VLDL and then increases serum triglyceride concentrations and decreases HDL concentrations[7,19].

Association between Smoking and Glucose Metabolism

Long-term cigarette smokers have been reported to have increased risk of hyperinsulinemia, which is a marker of insulin resistance[22-23]. This association has also been demonstrated in a study

that looked at the long-term use of nicotine gum[24]. Prospective studies, carried out in several different geographical areas, have shown that smoking increases the risk of T2DM in a dose-dependent manner in both men and women[25-28].

One trial, using the euglycemic clamp technique, showed that smoking one cigarette every hour for 6 h could impair the effect of insulin and lead to insulin resistanceby lowering peripheral glucose uptake[29].

Cigarette smoking may directly reduce insulin sensitivity by increasing the plasma levels of insulin-antagonistic hormones, such as catecholamines, cortisol, and growth hormones, and increasing plasma FFAs levels, which increase the risk of development of T2DM[21,30].

Association between Smoking and Blood Pressure

A case-control study showed that the daytime ambulatory BP was significantly higher in hypertensive smokers than in non-smokers (150/97 *vs*. 143/93 mmHg), whereas night-time BP was not significantly different between the two groups (129/79 *vs.* 126/78 mmHg)[34]. Light smokers were reported to have comparable or even slightly lower BPs than non-smokers, although heavy smoking is associated with a persistent rise in blood pressure[32-33]. However, two perspective cohort studies showed that smoking is a predictor of the development of hypertension in middle-aged normotensive men[35-36]. Furthermore, smoking is associated with hypertension in a dose-response manner: compared to nonsmokers, men who smoked 1-19 cigarettes per day and men who smoked more than 20 cigarettes per day have a 1.5-fold and 2.4-fold increased likelihood of developing hypertension, respectively[36].

Obesity is a potential confounder of this link, as are age and concomitant alcohol usage, and the interaction of smoking and these factors on hypertension should be considered. The link between smoking and hypertension should be evaluated with the stratification of subjects according to the different levels of these confounding factors.

Nicotine induces an acute pressor effect, due to increasing the release of AVP, sympathetic excitatory catecholamines (epinephrine and norepinephrine)[8] and activate the renin-angiotensin-aldosterone system (RAAS) by increasing activities of aldosterone and angiotensin-converting enzyme (ACE)[10]. Blood pressure increases with continuous smoking, but starts to decrease after stopping smoking for 30 min. In addition, smoking, and nicotine, can increase the risk of atherosclerosis[31]. However smoking is not known as a hypertension risk factor, as the link between chronic smoking and the development of hypertension is inconsistent[32-33].

Association of Environmental Tobacco Smoke with MetS and its Associated Disorders

Passive smoke exposure (PSE) and secondhand smoke (SHS), collectively known as environmental tobacco smoke (ETS), have adverse health outcomes, and are also MetS risk factors[37-39]. Nicotine is released while cigarettes burn and is contained in expired air after puff inhalations. The amount of nicotine obtained from ETS depends on the concentration, duration and frequency of exposure. One population study that examined 304 randomly selected Chinese households showed that, in adults, compared to those exposed to ETS ≤4 days per week, the individuals exposed to ETS >5-7 days per week was significantly associated with a higher risk of MetS, elevated TG, reduced HDL-C and central obesity, and the corresponding adjusted ORs (95% CIs) were 2.8 (1.2-6.6), 2.1 (1.1-3.9), 1.9 (1.1-3.1), and 2.7 (1.6-4.5), respectively[37]. In the US, the National Health and Nutrition Examination Survey (NHANES III, 1988 to 1994) examined 2 273 young adults and found that there was a significant dose-response relationship between levels of exposure to ETS (as categorized by the tertiles of serum cotinine levels) and the prevalence of MetS, and the adjusted ORs ranged from 2.5 for the lowest tertile to 6.7 for the highest tertile compared to individuals that were not exposed to ETS[38]. A 15-year prospective cohort study of young adults showed that showed that a graded association between smoking exposure and the development of impaired fasting glucose (IFG) existed: compared to never smokers without PSE, the adjusted hazard ratios (HRs) (95% CIs) for the incidence of IFG were 1.35 (1.06-1.71) for never smokers with PSE and 1.65 (1.27-2.13) for smokers[39].

Association Between Smoking Cessation and the Associated Disorders of MetS

Although cessation of smoking is associated with a small number of adverse health consequences, such as weight gain[40], and even an increased risk of impaired glucose metabolism and Met [28,41-43], those

adverse effects are preventable and the effects are likely to be reduced after several years of non-smoking[28,42-43]. An increased smoking cession period is linked to decreased visceral fat area and decreased risk MetS development[44]. Our cohort study showed that male ex-smokers, who had quit for 13 years or more, had a significantly decreased risk of developing MetS compared with individuals who had quit for between one and four year[45].

Conclusions

This review has demonstrated that, in men at least, smoking increases the risk of MetS, and with the exception of increased body weight, smoking increases the likelihood of possessing the disorders associated with MetS. There is no clear evidence for an increased risk of MetS in women who smoke. Furthermore, passive smoking is associated with an increased risk of MetS. Any adverse effects of smoking cessation are preventable and temporary. Thus, the long-term benefits of the reduced risks of MetS, CVD and other common health problems mean that it is never too late to stop smoking.

Correspondence and Reprints: JIA Wei Ping, MD, PhD, E-mail: wpjia@sjtu.edu.cn

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Supplement Table. Association between Smoking and the Development of Metabolic Syndrome Evaluated by the Prospective Studies

Active Smoking						
Source	Participants	Age Range (yrs)	Follow-up period (yrs)	Definition of MetS	Adjusted RR (95% CI or *P* value) (Smokers vs nonsmokers)	*P* value for positive dose-response relationship of smoking amount with MetS
Nakanishi 2005 Japan[S1]	Men: 2 994	35-59	>7	Modified NCEP-ATP III (2005)	—	0.001[a]
Wannamethee 2006 Britain[S2]	Men: 3 051	40-59	20	NCEP-ATP III (2001)	1.36 (1.00-1.83)[b]	—
Onat 2007 Turkey[15]	Overall: 1 961	Mean, 48	Mean, 5.9	Modified NCEP-ATP III (2005)	≥11 cigarettes smoked daily: 0.69 (0.56-0.93)[c]	—
	Men: 947				≥11 cigarettes smoked daily: 0.84 (NS)[c]	—
	Women: 1 014				≥11 cigarettes smoked daily: 0.50 (0.26-0.94)[c]	—
Wilsgaard 2007 Norway[S3]	Men: 7 328	20-56	Mean, 13.8	Modified NCEP-ATP III (2001)	≥20 cigarettes smoked daily: 1.25 (1.02-1.53)[d]	NS[d]
	Women: 7 273	20-56	Mean, 13.8	Modified NCEP-ATP III (2001)	≥20 cigarettes smoked per day: 1.41 (1.02-1.94)[d]	NS[d]
Kim 2009 Korea[41]	Men: 4 542	Median, 42	Mean, 2.9	WHO (2000)	1.54 (1.21-1.95)[e]	*P* <0.05[e]
Zhu 2011 China[45]	Men: 693	20-95	Median, 3	NCEP-ATP III (2005)	2.13 (1.26-3.59)[f]	<0.01[f]
				JCDCG (2007)	3.08 (1.81-5.30)[f]	<0.01[f]
Smoking cessation						
Source	Study participants	Age Range (yrs)	Follow-up period (yrs)	Definition of MetS	Adjusted RR (95% CI or *P* value) (ex-smokers vs nonsmokers)	
Nakanishi 2005 Japan[S1]	Men: 2 994	35-59	>7	Modified NCEP-ATP III (2005)	1.43 (1.14-1.79)[a]	
Onat 2007 Turkey[15]	Overall: 1 961	Mean, 48	5.9	Modified NCEP-ATP III (2005)	Overall: 0.96 (NS)[c]	
	men: 947				Men: 1.18 (NS)[c]	
	Women: 1 014				Women: 1.10 (NS)[c]	

Abbreviations: MetS: metabolic syndrome; NCEP: the National Cholesterol Education Program; ATP III: Adult Treatment Panel III; WHO: World health organization; JCDCG: the Chinese Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults; NS: nonsignificant.

Supplement References

S1. Nakanishi, N, Takatorige, T, Suzuki, K. Cigarette smoking and the risk of the metabolic syndrome in middle-aged Japanese male office workers. Ind Health, 2005; 43:295-301.

S2. Wannamethee, SG, Shaper, AG, Whincup, PH. Modifiable lifestyle factors and the metabolic syndrome in older men: Effects of lifestyle changes. J Am Geriatr Soc, 2006; 54:1909-14.

S3. Wilsgaard, T, Jacobsen, BK. Lifestyle factors and incident metabolic syndrome. The Tromso Study 1979-2001. Diabetes Res Clin Pract, 2007;78:217-24.

Notes:

a. Adjusted for age, family history of diabetes, alcohol intake, and regular physical activity at study entry.

b. Adjusted for age, body mass index, physical activity, alcohol intake, total fat, carbohydrate, and dietary pattern.

c. Adjusted for age, baseline family income bracket, and physical activity grade.

d. Adjusted for age, alcohol intake, coffee consumption, years of education, and leisure-time physical activity.

e. Adjusted for age, baseline weight, lifestyle, status (alcohol and exercise), and the number of components of the metabolic syndrome, and weight change

f. Adjusted for age, alcohol intake, education level, fasting plasma insulin, homeostasis model assessment-estimated insulin resistance (HOMA-IR) index, body mass index at baseline, and weight change