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Original Article

Long-Term Adverse Effects of Cigarette Smoking on the Incidence Risk of Metabolic Syndrome With a Dose-Response Relationship: Longitudinal Findings of the Korean Genome and Epidemiology Study Over 12 Years

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ABSTRACT

Objective: To investigate the association between the intensity and cumulative dose of cigarette smoking and incidence risk of metabolic syndrome (MetS) in a longitudinal prospective study over 12 years of follow-up.

Methods: This study included 3151 men aged 40 to 69 years from the Korean Genome and Epidemiology Study. MetS was defined as proposed by the Joint Interim Statement of the *Circulation* 2009 report. The hazard ratios (HRs) and 95% confidence intervals (95% CIs) for incidence risk of MetS were calculated from 2 separate perspectives: (1) number of cigarettes smoked per day (intensity) and (2) total number of cigarettes smoked over a person's lifetime (cumulative dose) using multiple logistic regression analyses.

Results: In comparison with never smokers, the HRs (95% CIs) were 0.97 (0.78-1.21) for former smokers and 1.50 (1.07-2.01) with 0 to 9 cigarettes per day, 1.66 (1.34-2.06) with 10 to 19 cigarettes per day, and 1.75 (1.34-2.29) with ≥20 cigarettes per day for current smokers after adjusting for confounding variables. Similar positive dose-response relationships were also observed when the cumulative dose of cigarette smoking was categorized into former and current smokers, with subcategories of <20 and >20 pack-years (PYs). The HRs (95% CIs) were 0.99 (0.77-1.23) for <20 PYs and 0.99 (0.77-1.28) for ≥20 PYs for former smokers and 1.63 (1.32-2.02) for <20 PYs and 1.67 (1.30-2.14) for ≥20 PYs for current smokers after adjusting for the same covariables.

Conclusion: Cigarette smoking intensity and cumulative dose were both found to be positively associated with the incidence risk of MetS in men.

Introduction

Metabolic syndrome (MetS) is a cluster of cardiometabolic abnormalities, including abdominal obesity, glucose intolerance, hypertension, and atherogenic dyslipidemia. Although the definition of MetS varies among organizations, there is a general consensus that the global prevalence of MetS has been increasing during recent decades. This upward trend is becoming a significant threat to public health due to the increased incidence risk of type 2 diabetes and cardiovascular disease (CVD).[1,2] According to a meta-analysis, MetS is associated with a twofold increased risk of CVD and stroke and a 1.5-fold increased risk of all-cause mortality.[2] As further increases in the prevalence of MetS are anticipated in the future,[3] early identification of modifiable risk factors for MetS is important from a preventive perspective.

The detrimental effects of cigarette smoking on atherosclerotic CVD and cancers are widely established. Moreover, several previous

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; HR, hazard ratio; KoGES, Korean Genome and Epidemiology Study; MetS, metabolic syndrome; PY, pack-year.

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studies have suggested that smoking is associated with MetS.[4] In 2012, a meta-analysis on smoking and the risk of MetS was conducted by Sun et al.[5] Although their study demonstrated a positive association between smoking and MetS in some cross-sectional studies, it failed to reveal significance or a cause-effect relationship in long-term prospective studies. Even among those that did show some significance, there were limitations such as smoking and MetS being merely a secondary dataset or the study involving only a limited number of confounding variables. Thus, the longitudinal relationship between smoking and the risk of MetS remains inconsistent and controversial. Moreover, there has yet to be a longitudinal prospective study that includes a long-term follow-up period with the inclusion criteria of intensity, duration, and cumulative dose of smoking along with a sufficient number of confounding variables. Therefore, we investigated the association between the intensity and cumulative dose of cigarette smoking and incidence risk of MetS in a large-sample, community-based, longitudinal prospective study over 12 years of follow-up.

Methods

Study Population

We utilized data obtained from the Korean Genome and Epidemiology Study (KoGES) Ansan-Ansung cohort. This database was provided by the Korea Centers for Disease Control and Prevention after a thorough review and evaluation of our research plan (http://www.cdc.go.kr/CDC/eng/main.jsp). The KoGES consists of 6 large prospective cohort studies governed by the Korea National Institute of Health for investigating factors associated with chronic diseases in Korea. The Ansan-Ansung study involved community dwellers of both sexes aged 40 to 69 years who live in Ansan (an urban region) or Ansung (a rural region). The participants of this cohort were assessed biennially from 2001 until 2014. Participation in the study was voluntary, and informed consent was obtained from all participants. The Declaration of Helsinki was followed, and the Ethics Committee of Korea National Institute of Health approved the study protocol. More information on the KoGES has been published in previous reports.[6] A baseline survey was conducted from 2001 to 2002, and 4758 men were recruited (Fig. 1). Participants who satisfied 1 or more of the following criteria were excluded: (1) previously diagnosed with MetS (n = 1257), (2) missing data (n = 26), or (3) lost to follow-up (n = 324). Finally, 3151 participants were selected to take part in the study.

Definition of MetS

We defined MetS as proposed by the 2009 Joint Interim Statement of *Circulation*.[1] According to this definition, MetS included any 3 of the following 5 conditions: (1) waist circumference of >90 cm in men and >80 cm in women, (2) triglyceride level of ≥150 mg/dL or current triglyceride-lowering drug treatment, (3) high-density lipoprotein cholesterol (HDL-C) level of <40 mg/dL in men and <50 mg/dL in women, (4) systolic blood pressure (BP) of ≥130 mm Hg and/or diastolic BP of ≥85 mm Hg or drug treatment, and (5) fasting glucose level of ≥100 mg/dL or current glucose-lowering drug treatment.

Measurement of Anthropometric and Biochemical Parameters

Trained medical staff obtained anthropometric measurements following a standardized procedure. Height was measured to the nearest 0.1 cm with a measuring rod attached to a balanced beam scale (Seca 225; Seca) using a Frankfurt horizontal plane while the participants stood as straight as possible and inhaled deeply. Body weight was measured to the nearest 0.1 kg using a digital electronic scale while the participants wore light indoor clothing without shoes; the scale had been set to 0 prior to obtaining measurements (GL-6000-20; G-tech). Waist circumference was measured by a trained technician to the nearest 0.1 cm in a horizontal plane at a level midway between the lower rib margin and iliac crest following normal expiration. Body mass index (BMI, kg/m^2) was calculated as the ratio of weight (kg) divided by height squared (m^2). We analyzed the baseline characteristics of our study population according to both smoking intensity (expressed as the number of cigarettes smoked per day) and cumulative dose of smoking (expressed as the total pack-years [PYs]). Smoking status was divided as never smokers, former smokers, and current smokers, with further subdivision according to intensity and amount. We approached the quantity of cigarette exposure in 2

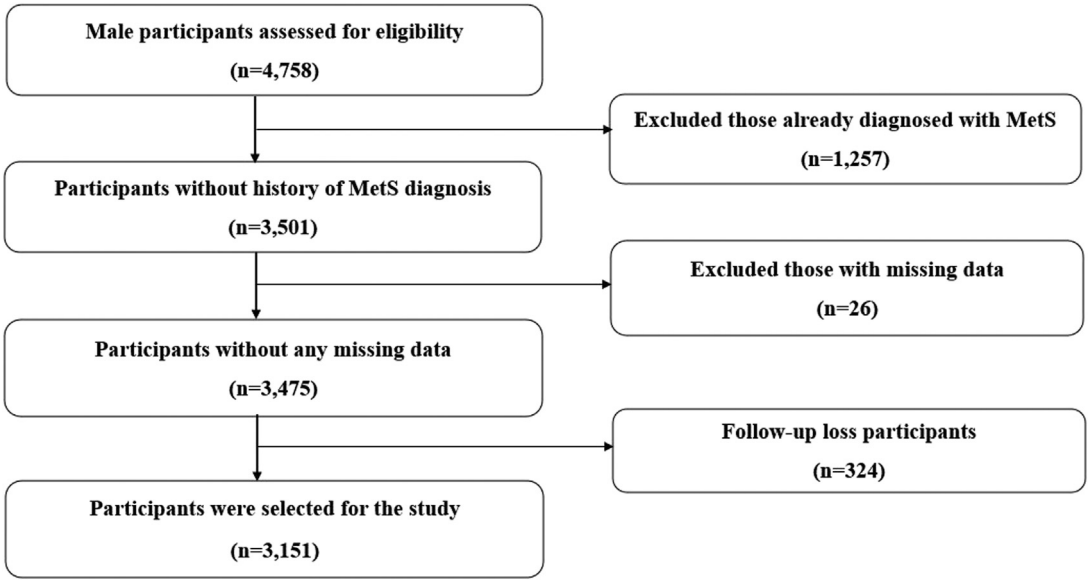

Fig. 1. Flowchart of the study population selection from the baseline survey conducted from 2001 to 2002. *MetS* = metabolic syndrome.

separate perspectives: (1) number of cigarettes smoked per day (intensity) and (2) total number of cigarettes smoked over a person's lifetime (cumulative dose). The smoking intensity was categorized by 0 to 9, 10 to 19, and >20 cigarettes per day, and the cumulative dose of cigarette smoking was categorized into former and current smokers, with subcategories of <20 and ≥20 PYs, respectively. Alcohol drinking status was categorized into 2 groups as either current drinkers or nondrinkers. Physical activity was divided into 3 groups: (1) no exercise, (2) irregular exercise (1-2 times/week), and (3) regular exercise (≥3 times/week). Monthly income was classified into 3 categories: (1) <1 million Korean Won, (2) 1 to 2 million Korean Won, and (3) >2 million Korean Won. We divided the participant education level into 3 categories: (1) elementary school or lower, (2) middle to high school, and (3) high school graduate. Systolic and diastolic BP measurements were assessed 3 times in the right upper arm using a standard mercury sphygmomanometer (Baumanometer; Baum), and the mean of the second and third BP readings was used for analysis. The mean arterial BP was calculated as follows: [systolic BP + (2 × diastolic BP)]/3. After fasting overnight for at least 8 hours, the fasting plasma glucose, total cholesterol, triglyceride, and HDL-C levels were measured enzymatically using a 747 Chemistry Analyzer (Hitachi 7600). The plasma insulin concentration level was assessed using radioimmunoassay (LINCO kit). The formula for calculating the homeostasis model assessment-insulin resistance (HOMA-IR) score was as follows: [fasting insulin (μIU/mL) × fasting glucose (mg/dL)/405].

Statistical Analysis

All data are presented as mean and standard deviation, median with interquartile range, or number with percentage. The analysis of variance test was used to compare continuous variables, while the χ^2 test was used to assess categorical variables. To demonstrate the cumulative incidence of MetS, the Kaplan-Meier curves were used. The HR and 95% (CI) for incident MetS were calculated using a multivariate Cox proportional-hazards regression model after adjusting for potential confounding variables and setting never smokers as the reference group for the intensity and duration of smoking. We conducted log-rank tests to determine the differences in the cumulative incidence of MetS among the groups. All analyses were conducted using SAS version 9.4 statistical software (SAS Institute Inc.). All statistical tests were two-sided, and statistical significance was set at $P < .05$.

Results

The mean age of the 1257 participants who had already been diagnosed with MetS at baseline was 52.8 (8.5) years; similarly, the mean age of the 3151 participants without MetS at baseline was 51.5 (8.9) years ($P < .001$). Table 1 shows the baseline characteristics of 3151 male participants without MetS at baseline, according to cigarette smoking intensity expressed as the number of cigarettes smoked per day. As the smoking intensity increased, the following parameters proportionally decreased with significance: (1) systolic BP, (2) diastolic BP, (3) mean BP, (4) fasting plasma glucose level, (5) total cholesterol level, (6) HDL-C level, and (7) serum insulin level. Alcohol drinking significantly increased proportionally with smoking intensity. The proportions of participants with a monthly income of >2 million Korean Won and a high school graduate education level were lowest in the group with the highest cigarette smoking intensity.

Table 2 shows the baseline characteristics of the same participants according to the cumulative dose of cigarette smoking (expressed as PYs). Former and current smokers were further divided into <20 and >20 PYs of the total cumulative dose. In both subgroups <20 and >20 PYs, the BMI, waist circumference, systolic BP, diastolic BP, mean BP, fasting plasma glucose level, and total

Table 1
Baseline Characteristics of the Study Population According to Daily Cigarette Exposure Expressed as the Number of Cigarettes per Day

Baseline characteristics	Never smokers	Former smokers	Current smokers (cigarettes/d)			*P* value[a]
			0-9	10-19	≥20	
n	628	943	234	409	937	
Age (y)	52.0 ± 8.9	52.0 ± 9.1	52.0 ± 9.0	51.3 ± 9.0	50.8 ± 8.5	0.026
Body mass index (kg/m^2)	23.8 ± 2.5	23.8 ± 2.6	23.5 ± 2.8	22.9 ± 2.6	23.1 ± 2.7	<.001
Waist circumference (cm)	81.6 ± 6.8	82.1 ± 6.6	81.5 ± 7.1	80.3 ± 6.7	81.0 ± 6.6	<.001
Systolic blood pressure (mm Hg)	120.8 ± 16.1	119.8 ± 16.4	118.9 ± 15.1	117.5 ± 16.0	117.2 ± 16.2	<.001
Diastolic blood pressure (mm Hg)	81.2 ± 11.1	80.4 ± 10.4	79.8 ± 9.1	78.8 ± 10.3	78.8 ± 10.1	<.001
Mean arterial pressure (mm Hg)	94.4 ± 12.2	93.5 ± 11.7	92.8 ± 10.5	91.7 ± 11.6	91.6 ± 11.5	<.001
Fasting plasma glucose (mg/dL)	86.0 ± 16.1	88.0 ± 16.8	86.2 ± 12.5	85.4 ± 18.9	85.1 ± 16.0	0.002
Total cholesterol (mg/dL)	188.1 ± 33.3	193.4 ± 34.2	189.0 ± 34.3	187.6 ± 35.2	187.2 ± 37.2	0.001
Triglyceride (mg/dL)	118 (93-169)	129 (97-168)	126 (96-169)	123 (100-171)	134 (105-188)	<.001
HDL-C (mg/dL)	45.4 ± 10.0	46.0 ± 9.5	47.1 ± 10.6	45.3 ± 9.9	45.2 ± 10.2	0.008
Serum insulin (mg/L)	6.2 (4.7-6.5)	6.2 (4.8-6.4)	6.2 (4.6-6.3)	6.0 (4.4-6.1)	6.0 (4.6-6.0)	0.019
HOMA-IR (mU/L)	1.28 (0.97-1.74)	1.33 (1.00-1.78)	1.33 (0.94-1.84)	1.23 (0.92-1.76)	1.26 (0.87-1.64)	0.006
Alcohol drinking (%)[b]	58.5	58.8	69.1	78.3	79.8	<.001
Regular exercise (%)[c]	27.5	29.1	29.1	25.5	27.4	0.246
Monthly household income (%)						0.011
<1 million Korean Won	27.7	24.6	33.6	31.7	31.9	
1-2 million Korean Won	32.4	31.8	26.6	30.0	31.3	
>2 million Korean Won	39.9	43.6	39.8	38.3	36.8	
Education levels (%)					68.7	0.030
Elementary school or lower	25.3	21.0	26.4	22.9	23.5	
Middle to high school	61.8	68.8	62.2	68.3	68.7	
>High school graduate	12.9	10.2	11.4	8.8	7.8	
Family history of diabetes (%)	8.9	12.5	6.0	9.1	9.9	0.017

Abbreviations: HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance.
Data are expressed as the mean ± standard deviation or percentage.
[a] *P* values were calculated using the analysis of variance or χ^2 test.
[b] Alcohol intake of 2 or more times per week.
[c] Moderate-intensity physical exercise of 3 or more times per week.

Table 2
Baseline Characteristics of the Study Population According to the Cumulative Dose of Cigarette Smoking in Pack-Years

Baseline characteristics	Never smokers	Former smokers	Former smokers	Current smokers	Current smokers	*P* value[a]
		<20 PYs	≥20 PYs	<20 PYs	≥20 PYs	
n	628	491	452	525	1055	0.026
Age (y)	52.0 ± 8.9	52.0 ± 9.1	52.0 ± 9.0	51.3 ± 9.0	50.8 ± 8.5	0.026
Body mass index (kg/m^2)	23.8 ± 2.6	23.8 ± 2.4	24.1 ± 2.5	23.7 ± 2.6	23.1 ± 2.7	<.001
Waist circumference (cm)	81.6 ± 6.8	82.1 ± 6.6	81.5 ± 7.1	80.3 ± 6.7	81.0 ± 6.6	<.001
Systolic blood pressure (mm Hg)	120.8 ± 16.1	118.1 ± 14.9	121.7 ± 17.6	115.9 ± 14.8	118.4 ± 16.5	<.001
Diastolic blood pressure (mm Hg)	81.2 ± 11.1	79.6 ± 10.1	81.1 ± 10.7	79.4 ± 9.7	79.2 ± 10.2	<.001
Mean arterial pressure (mm Hg)	94.4 ± 12.2	92.4 ± 11.1	94.7 ± 12.3	90.9 ± 10.7	92.3 ± 11.7	<.001
Fasting plasma glucose (mg/dL)	86.0 ± 16.1	87.6 ± 16.0	88.5 ± 17.6	86.2 ± 17.3	84.9 ± 15.8	0.001
Total cholesterol (mg/dL)	188.1 ± 33.3	192.1 ± 34.4	194.8 ± 34.0	191.4 ± 34.4	185.7 ± 37.0	<.001
Triglyceride (mg/dL)	118 (93-169)	127 (95-165)	134 (101-170)	127 (100-171)	132 (103-187)	<.001
HDL-C (mg/dL)	45.4 ± 10.0	46.3 ± 9.3	45.6 ± 9.8	45.3 ± 9.7	45.7 ± 10.4	0.523
Serum insulin (mg/L)	6.2 (4.7-8.3)	6.0 (4.7-8.1)	6.4 (5.1-8.6)	6.2 (4.6-8.3)	6.0 (4.4-8.1)	0.008
HOMA-IR (mU/L)	1.28 (0.97-1.74)	1.29 (0.97-1.74)	1.36 (1.04-1.93)	1.30 (0.94-1.78)	1.22 (0.89-1.73)	<.001
Alcohol drinking (%)[b]	58.8	74.1	63.7	80.3	77.3	<.001
Regular exercise (%)[c]	27.5	28.2	30.1	26.5	27.5	0.015
Monthly household income (%)						<.001
<1 million Korean Won	27.7	17.6	32.3	25.4	35.5	
1-2 million Korean Won	32.4	31.5	32.0	29.5	30.6	
>2 million Korean Won	39.9	50.9	35.7	45.1	33.9	
Education levels (%)						
Elementary school or lower	25.3	16.2	26.0	18.2	26/4	
Middle to high school	61.8	68.6	68.9	70.7	66.2	
> High school graduate	12.9	15.2	5.1	11.1	7.4	
Family history of diabetes (%)	8.9	12.8	12.2	8.0	9.7	0.042

Abbreviations: HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; PYs = pack-years.
Data are expressed as the mean ± standard deviation or percentage.
[a] *P* values were calculated using the analysis of variance or χ^2 test.
[b] Alcohol intake of 2 or more times per week.
[c] Moderate-intensity physical exercise of 3 or more times per week.

cholesterol level were significantly lower in current smokers than in former smokers. The proportions of participants with a monthly income of >2 million Korean Won and a high school graduate education level were lowest in the group with the highest cumulative dose of cigarette smoking.

Table 3 shows the biennial incidence of MetS during follow-up. In total, 1218 (38.6%) of 3151 individuals developed MetS during the 12-year follow-up period, with an incidence rate ranging from 4.7 to 13.4 per 2 years.

The cumulative probabilities of being diagnosed with MetS according to the intensity and cumulative dose of cigarette smoking are presented in Figure 2 *A* and *B*. The longer and heavier smokers showed significantly higher cumulative incidences of MetS over 12 years after the baseline survey (log-rank test, $P < .001$).

Table 4 presents the HRs and 95% CIs for incident MetS according to smoking intensity categorized by 0 to 9, 10 to 19, and >20 cigarettes per day. Compared with the reference group of never smokers, the HRs (95% CIs) for incident MetS increased in a dose-response manner. In comparison with never smokers, the HRs (95% CIs) were 0.97 (0.78-1.21) for former smokers and 1.50 (1.07-2.01) with 0 to 9 cigarettes per day, 1.66 (1.34-2.06) with 10 to 19 cigarettes per day, and 1.75 (1.34-2.29) with ≥20 cigarettes per day for current smokers after adjusting for age, alcohol drinking, physical activity, household income, education level, mean arterial pressure, triglyceride, HDL-C, and HOMA-IR.

Similar positive dose-response relationships were also observed, when the cumulative dose of cigarette smoking was categorized into former and current smokers, with subcategories of <20 and >20 PYs (Table 5). In comparison with never smokers, the HRs (95% CIs) were 0.99 (0.77-1.23) for <20 PYs and 0.99 (0.77-1.28) for ≥20 PYs for former smokers and 1.63 (1.32-2.02) for <20 PYs and 1.67 (1.30-2.14) for ≥20 PYs for current smokers after adjusting for the same covariables.

Table 3
Incidence of Metabolic Syndrome During the Study Follow-up Years

Year range	Follow-up	n	Incidence cases (n)	Incidence rate over 2 y
2001-2002	Baseline	3151	-	-
2003-2004	2 y	2996	125	4.2
2005-2006	4 y	2662	356	13.4
2007-2008	6 y	2333	262	11.2
2009-2010	8 y	2315	244	10.5
2011-2012	10 y	2124	101	4.7
2013-2014	12 y	2013	130	6.5

Discussion

In this large-scale prospective study of community-dwelling Korean men during 12 years of follow-up, the intensity and cumulative dose of cigarette smoking were both positively and independently associated with an increased incidence risk of MetS after adjusting for potential confounding variables. The positive association between cigarette smoking and MetS is compatible with the findings of previous studies. Although a recent meta-analysis showed positive associations between smoking and MetS in cross-sectional studies, it failed to reveal statistical significance and cause-effect relationships in long-term prospective studies with a limited number of confounding variables.[5] When stratified into the mean follow-up period, the pooled relative risk of MetS for current smokers was 1.44 (95% CI, 1.18-1.75) for 5 prospective studies with a mean follow-up of <5 years;[7–12] however, the positive associations were not observed in the subgroup analysis for 2 prospective studies with a mean follow-up of ≥5 years.[13,14] Moreover, most previous studies were adjusted using an insufficient number of confounding variables; therefore, the longitudinal relationship between smoking and the risk of MetS remains controversial. We determined the dose-response effects of active

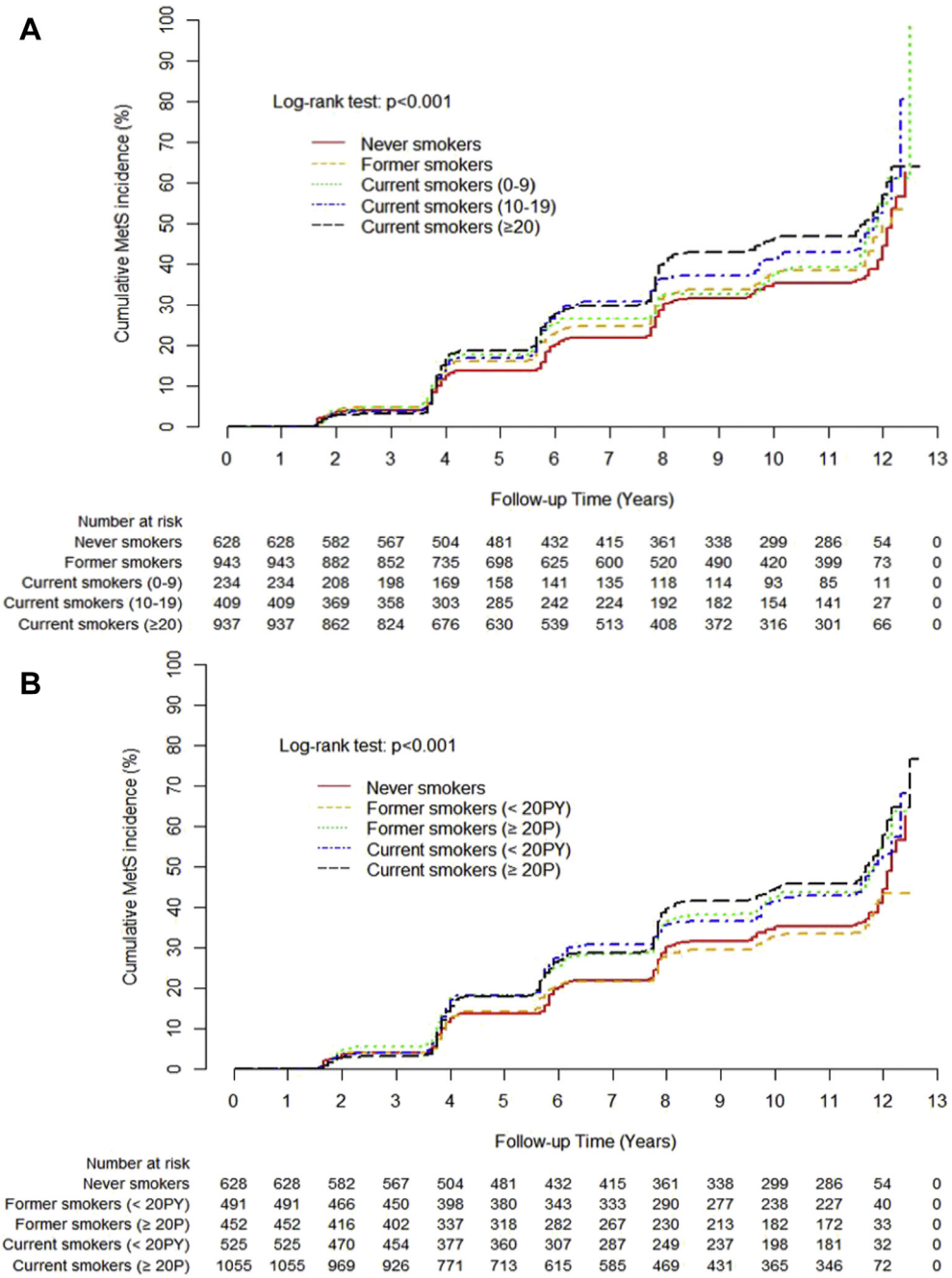

Fig. 2. Cumulative incidence of MetS according to, *A*, smoking intensity expressed as the number of cigarettes per day and, *B*, cumulative dose of smoking expressed as the number of pack-years. *MetS* = metabolic syndrome; *PY*= pack-year.

cigarette smoking on the incidence of MetS after adjusting for comprehensive confounding variables, including age, alcohol drinking, physical activity, household income, education level, mean arterial pressure, triglyceride, HDL-C, and HOMA-IR. To the best of our knowledge, no study has analyzed the risk associated with both smoking intensity (in the number of cigarettes per day) and total lifetime cumulative dose of smoking (in the number of PYs) in a long-term follow-up cohort study with a large-sample population. From our results, we have found a cause-effect relationship of the total cumulative effect of cigarette smoking; the number of cigarettes a person smokes in a day and the cumulative dose of lifetime smoking are both positively associated with the incidence risk of MetS.

Although the underlying biologic mechanisms that explain smoking-induced increases in the development of MetS are not fully understood, several lines of evidence suggest that cigarette smoking evokes insulin resistance and chronic low-grade inflammation through direct and/or indirect pathways. It is widely reported that cigarette smoking contributes to insulin resistance, a core feature in the pathophysiology of MetS.[15] Attvall et al[16] showed that habitual smoking acutely impaired insulin action and led to insulin resistance using the euglycemic clamp technique. Insulin resistance, also known as hyperinsulinemia, leads to hyperglycemia, peripheral vasoconstriction, and sodium retention, which produce systemic hypertension and glucose intolerance.[17] Insulin resistance also triggers hepatic production of very-low-

Table 4
Hazard Ratios and 95% Confidence Intervals for Incident MetS According to Daily Cigarette Exposure Expressed as the Number of Cigarettes per Day

Variables	Never smokers	Former smokers	Current smokers (cigarettes/d)		
			0-9	10-19	≥20
n	628	943	234	409	937
New cases of MetS, n	217	303	89	164	395
Mean follow-up, y	8.5 ± 3.6	8.3 ± 3.6	7.7 ± 3.8	7.7 ± 3.7	7.5 ± 3.6
Person-years of follow-up	5315	7797	1807	3132	7005
Incidence rate/1000 person-years	40.8	38.9	49.3	52.4	56.4
Model 1	1.00 (reference)	1.03 (0.83-1.28)	1.50 (1.10-2.05)	1.68 (1.35-2.09)	1.74 (1.33-2.26)
Model 2	1.00 (reference)	0.98 (0.78-1.12)	1.52 (1.11-2.07)	1.65 (1.33-2.05)	1.73 (1.33-2.26)
Model 3	1.00 (reference)	0.97 (0.78-1.21)	1.50 (1.07-2.01)	1.66 (1.34-2.06)	1.75 (1.34-2.29)

Abbreviation: MetS = metabolic syndrome.
Model 1: adjusted for age, alcohol drinking, physical activity, household income, education level, and mean arterial pressure.
Model 2: adjusted for age, alcohol drinking, physical activity, household income, education level, mean arterial pressure, triglyceride, and high-density lipoprotein cholesterol.
Model 3: adjusted for age, alcohol drinking, physical activity, household income, education education level, mean arterial pressure, triglyceride, high-density lipoprotein cholesterol-cholesterol, and homeostasis model assessment-insulin resistance.

density lipoproteins, which leads to atherogenic dyslipidemia, including hypertriglyceridemia and low HDL-C level.[18]

Moreover, visceral fat accumulation has been identified as a key factor in initiation of MetS through insulin resistance and chronic low-grade inflammation. Cigarette smoking has unfavorable effects on body composition, such as visceral obesity as well as osteoporosis and sarcopenia. Yun et al[19] reported that the odds ratios (95% CIs) of central adiposity assessed by visceral fat thickness using ultrasonography in ex-smokers and current smokers were 1.70 (1.21-2.39) and 1.86 (1.27-2.73), respectively. In addition, cigarette smoking chronically stimulates the airway tract and subsequently can increase inflammatory markers. Several toxins, such as carbon monoxide, benzene, benzopyrene, and other reactive oxidant substances in cigarettes, activate respiratory tract inflammation in a direct manner, resulting in the production of potent inflammatory mediators, such as tumor necrosis factor-α and interleukins. Moreover, the proinflammatory cytokines induced by chronic exposure to cigarette smoking indirectly lead to systemic low-grade inflammation beyond the respiratory system, contributing to the initiation and progression of insulin resistance and MetS. Another key substance in tobacco smoke is cyanide, a potent oxidant, which results in high thiocyanate levels in renal failure.[20–22] Analysis on the interaction between renal function and the effect of smoking on MetS will be another focus of future studies.

According to our data, the prevalence of MetS at baseline was 26% (1257/4758), and the cumulative incidence during the follow-up period was 39% (1218/3151). The sum of these 2 prevalence rates is 65%, which represents a total prevalence at a given timepoint. MetS appears to have a relatively high prevalence rate. According to a meta-analysis, MetS is associated with a twofold increased risk of CVD and stroke and a 1.5-fold increased risk of all-cause mortality.[2] In another study, patients with MetS and smoking ($P = .004$) had a significant association with CVD risk.[23] Thus, it is crucial to identify the risk factors for the development of MetS and take preventive measures.

Our study has some limitations that must be acknowledged. First, our results may have a limited application to other populations because Koreans are ethnically highly homogeneous and have lower BMIs than other ethnicities, especially Caucasians. Second, there is a potential for selection bias between study participants and nonparticipants, as cohort participation was completely voluntary. Third, women were excluded from our study; due to a cultural tendency to hide their smoking status, a reported number only account for a relatively small portion of the total female smoker population. However, excluding women from our study could be considered a strength since we excluded a potential selection bias. We have not quantified alcohol consumption and physical activity, which may have a dose-dependent impact on HDL-C. Furthermore, we may have overlooked nutrition and unhealthy eating habits as additional confounding factors since the group with the highest smoking intensity had the lowest education level. Despite these limitations, our findings have established cigarette smoking as a risk factor for MetS, which was supported by our longitudinal study that assessed both the intensity and cumulative dose of smoking.

Conclusions

In conclusion, both cigarette smoking intensity and cumulative dose were positively associated with MetS among community-dwelling Korean men in this large-scale, longitudinal,

Table 5
Hazard Ratios and 95% Confidence Intervals for Incident MetS According to the Cumulative Dose of Cigarette Smoking in Pack-Years

Variables	Never smokers	Former smokers	Former smokers	Current smokers	Current smokers
		<20 PYs	≥20 PYs	<20 PYs	≥20 PYs
n	628	491	452	525	1055
New cases of MetS, n	217	162	191	207	441
Mean follow-up, y	8.6 ± 3.5	8.5 ± 3.6	7.9 ± 3.7	7.6 ± 3.7	7.5 ± 3.7
Person-years of follow-up	5315	4226	3571	4002	7943
Incidence rate/1000 person-years	40.8	38.3	53.5	51.7	55.5
Model 1	1.00 (reference)	0.95 (0.72-1.23)	1.11 (0.86-1.43)	1.65 (1.34-2.04)	1.68 (1.31-2.15)
Model 2	1.00 (reference)	0.94 (0.72-1.22)	1.01 (1.78-1.30)	1.63 (1.32-2.01)	1.70 (1.32-2.17)
Model 3	1.00 (reference)	0.99 (0.77-1.23)	0.99 (0.77-1.28)	1.63 (1.32-2.02)	1.67 (1.30-2.14)

Abbreviations: MetS = metabolic syndrome; PYs = pack-years.
Model 1: adjusted for age, alcohol drinking, physical activity, household income, education level, and mean arterial pressure.
Model 2: adjusted for age, alcohol drinking, physical activity, household income, education level, mean arterial pressure, triglyceride, and high-density lipoprotein cholesterol.
education level, mean arterial pressure, triglyceride, high-density lipoprotein cholesterol, and homeostasis model assessment-insulin resistance.

prospective, 12-year follow-up study. Our findings support the possible beneficial role of smoking prevention and cessation on the future incidence risk of MetS.

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Disclosure

The authors have no multiplicity of interest to disclose.

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