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

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Original investigation

Keywords: Smoking, metabolic syndrome, inflammation, insulin resistance

Posted Date: June 8th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-535722/v1>

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Abstract

Background

Previous studies have demonstrated positive associations between smoking and metabolic syndrome (MetS) in several cross-sectional studies. However, the association was not consistent in long-term studies, which makes longitudinal effects remain controversial. Thus, we investigated the association between cigarette smoking and incidence risk of MetS in a large-sample, community-based, longitudinal prospective study in both intensity and cumulative dose of cigarette smoking over 12 years of follow-up.

Methods

Among 10,038 participants, a total of 5568 men ages 40-69 years old without MetS at baseline were selected from the Korean Genome and Epidemiology Study (KoGES). The hazard ratios (HRs) and 95% confidence interval (CIs) 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 intensity (expressed as number of cigarettes per day) and duration of smoking (expressed as number of pack-years).

Results

Compared to the referent never smokers, the HRs (95% CIs) for incident MetS increased as the intensity of smoking in current smokers also increased: 1.50 (1.07-2.01) for 0-9 cigarettes/day, 1.66 (1.34-2.06) for 10-19 cigarettes/day, and 1.75 (1.34-2.29) for ≥ 20 cigarettes/day, after adjusting for age, alcohol drinking, physical activity, household income, educational level, mean arterial pressure, triglyceride, HDL-cholesterol level, and homeostasis model assessment insulin resistance. These positive relationships were similar when the cumulative dose of smoking was used in current smokers. Compared to the referent never smokers, the HRs (95% CIs) for incident MetS increased as the cumulative dose also increased: 1.63 (1.32-2.02) for <20 PYs and 1.67 (1.30-2.14) for $20 \geq$ PYs after adjusting for the same co-variables.

Conclusions

Both cigarette smoking intensity and cumulative dose were positively associated with MetS among community-dwelling Korean men in the large-scale, longitudinal, prospective, 12-year follow-up study.

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 two-fold increased risk of CVD and stroke and a 1.5-fold increase in 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 of MetS is important from a preventive perspective.

Emerging evidence suggests that cigarette smoking is a risk factor of MetS. The detrimental effects of cigarette smoking on atherosclerotic CVD and cancers are established widely; several previous studies have suggested that smoking is associated with development of MetS [4]. In 2012, a meta-analysis on smoking and risk of MetS was conducted by Sun et al. [5]. Although their study demonstrated 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 risk of MetS remains both inconsistent and controversial. Moreover, there has yet to be a longitudinal prospective study that includes a long-term follow-up period with inclusion criteria of intensity, duration, and cumulative dose of smoking along with a sufficient number of confounding variables. Therefore, we investigated the association between cigarette smoking and risk of MetS in a large-sample, community-based, longitudinal prospective study to examine both the intensity and cumulative dose of cigarette smoking over a 12-year period.

Methods

Study population

We utilized data solely 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 six large prospective cohort studies governed by the Korea National Institute of Health (KNIH) for investigating factors associated with chronic diseases in Korea. The Ansan-Ansung study involved community dwellers of both sexes from 40–69 years of age 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 KNIH approved the study protocol. More information on the KoGES has been published in previous reports [6]. A baseline survey was conducted from 2001–2002, and 4758 men were recruited (Fig. 1). Participants who satisfied one or more of the following criteria were excluded: previously diagnosed with MetS ($n = 1257$), missing data ($n = 26$), or 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 [7]. According to this definition, MetS included any three of the following five conditions: a) waist circumference > 90 cm in men and > 80 cm in women; b) triglyceride level $\geq$ 150 mg/dL or current triglyceride-lowering drug treatment; c) high-density lipoprotein cholesterol (HDL-C) HDL-C level < 40 mg/dL in men and < 50 mg/dL in women or current cholesterol-lowering drug treatment; d) systolic blood pressure $\geq$ 130 mmHg and/or diastolic $\geq$ 85 mmHg or drug treatment; and e) fasting glucose level $\geq$ 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, Hamburg, Germany) 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 zero prior to obtaining measurements (GL-6000-20; G-tech, Pyeongtaek, Korea). 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 the iliac crest following normal expiration. Body mass index (BMI, kg/m²) was calculated as the ratio of weight (kg) divided by height squared (m²). We analyzed the baseline characteristics of our study population according to both intensity of smoking (expressed as number of cigarettes smoked per day) and cumulative dose of smoking (expressed as total pack-years [PYs]). Smoking status was divided as never smokers, former smokers, and current smokers, with further subdivision according to intensity and amount. Alcohol drinking status was categorized into two groups as either current drinkers or non-drinkers. Physical activity was divided into three groups: no exercise, irregular exercise (1–2 times/week), and regular exercise (> 3 times/week). Monthly income was classified into three categories: < 1 million Korean Won, 1–2 million Korean Won, and > 2 million Korean Won. We divided the participant education level into three categories: elementary school or lower, middle to high school, and high school graduates. Systolic and diastolic blood pressure (BP) measurements were assessed three times in the right upper arm using a standard mercury sphygmomanometer (Baumanometer; Baum, Copiague, NY, USA), and the mean of the second and third blood pressure readings was used for analysis. Mean arterial BP was calculated as follows: [systolic BP + (2 x diastolic BP)]/3. After fasting overnight for at least eight hours, the fasting plasma glucose, total cholesterol, triglyceride, and HDL-C levels were measured enzymatically using a 747 Chemistry Analyzer (Hitachi 7600, Tokyo, Japan). The plasma insulin concentration level was assessed using radioimmunoassay (LINCO kit, St. Charles, MO, USA). The formula for calculating the homeostasis model assessment-insulin resistance (HOMA-IR) score was as follows: [fasting insulin (μ IU/mL) * fasting glucose (mg/dL)/405].

Statistical analysis

All data were represented as mean and standard deviation, median with interquartile range, or as number with percentage. An analysis of variance test was used to compare the continuous variables, while a chi-

square test was carried out to assess categorical variables. To demonstrate the cumulative incidence of MetS, Kaplan-Meier curves were used. We conducted log-rank tests to determine the differences in cumulative incidence of MetS among the groups. The hazard ratios (HRs) and 95% confidence interval (CIs) 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 intensity (expressed as number of cigarettes per day) and duration of smoking (expressed as number of pack-years). All analyses were conducted using SAS version 9.4 statistical software (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided, and statistical significance was set at $P < 0.05$.

Results

Table 1 shows the baseline characteristics of 3151 male participants without MetS at baseline, according to intensity of cigarette smoking expressed as number of cigarettes smoked per day. As the intensity of smoking increased, the following parameters proportionally decreased with significance: systolic BP, diastolic BP, mean BP, fasting plasma glucose, total cholesterol, HDL-C, and serum insulin level. Alcohol drinking significantly increased proportionally with smoking intensity. The proportion of participants with a monthly income > 2 million Korean Won and a high-school graduate education were lowest in the group with the highest intensity of cigarette smoking.

Table 2 shows the baseline characteristics of the same participants according to cumulative dose of cigarette smoking (expressed as PYs). Former smokers and current smokers were further divided into <20 PYs and >20 PYs of total cumulative dose. In both subgroups <20 PYs and >20 PYs, the BMI, waist circumference, systolic BP, diastolic BP, mean BP, fasting plasma glucose, and total cholesterol levels significantly decreased in current smokers compared to former smokers. The proportions of monthly income > 2 million Korean Won and education level of high school graduates 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 individuals (38.6%, 1218/3151) developed MetS during the 12-year follow-up period, with an incidence rate ranging from 4.7–13.4 per 2 years.

The cumulative probabilities of being diagnosed with MetS according to intensity of smoking and cumulative dose of cigarette smoking are presented in Figures 2A and 2B. The longer and heavier smokers showed significantly higher cumulative incidences of MetS over 12 years after the baseline survey (log-rank test, $P < 0.001$).

Table 4 presents the HRs and 95% CIs for incident MetS according to intensity of smoking. In comparison to the control group of never smokers, the HRs (95% CIs) of the incidence of MetS increased in a dose-response manner in all three models. In Model 1, the HRs were calculated after adjusting for age, alcohol drinking, physical activity, household income, educational level, and mean arterial pressure. In Model 2, additional potential confounding variables of serum triglyceride and HDL-cholesterol levels were adjusted. In Model 3, we made further adjustments by analyzing the HOMA-IR levels. Compared to the

referent never smokers, the HRs (95% CIs) for incident MetS increased as the intensity of smoking in current smokers also increased: 1.50 (1.07-2.01) for 0-9 cigarettes/day, 1.66 (1.34-2.06) for 10-19 cigarettes/day, and 1.75 (1.34-2.29) for ≥ 20 cigarettes/day, after adjusting for age, alcohol drinking, physical activity, household income, educational level, mean arterial pressure, triglyceride, HDL-cholesterol level, and HOMA-IR.

These positive relationships were similar when the cumulative dose of smoking was used in current smokers. Compared to the referent never smokers, the HRs (95% CIs) for incident MetS increased as the cumulative dose also increased: 1.63 (1.32-2.02) for <20 PYs and 1.67 (1.30-2.14) for $20 \geq$ PYs, after adjusting for the same co-variables (Table 5).

Discussion

In this large-scale prospective study of community-dwelling Koreans during 12 years of follow-up, the intensity and cumulative dose of cigarette smoking were both positively and independently associated with 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]. In the studies with a mean follow-up period < 5 years [8–13], the average relative risk (RR) was 1.44 (95% CI: 1.18–1.75), whereas in studies with a mean follow-up duration > 5 years, the RR was only 1.16 (95% CI: 0.99–1.35), without statistical significance [14, 15]. Moreover, most studies were adjusted using an insufficient number of confounding variables, thus the longitudinal relationship between smoking and risk of MetS remains controversial. To the best of our knowledge, no study has analyzed the risk associated with both intensity of smoking (in number of cigarettes per day) and total lifetime cumulative dose of smoking (in number of PYs) in a long-term follow-up cohort study with a large sample population. We determined the dose-response effects of active cigarette smoking on the incidence of MetS after adjusting for comprehensive confounding variables including age, alcohol drinking, physical activity, household income, educational level, mean arterial BP, triglycerides, HDL-cholesterol, and HOMA-IR.

The most plausible hypothesis for the pathophysiology of MetS is insulin resistance (aided by fatty-acid excess) as a consequence of inappropriate lipolysis. Obesity is a state in which there is increased storage of fatty acids in the form of triglycerides in adipose tissue [16]. Continuous release of fatty acids from stored triglycerides causes dyslipidemia and drives gluconeogenesis in the liver [17–19]. Abdominal obesity, therefore, can be considered an important causal link that connects cardiovascular risk factors with white blood cell (WBC) count. In this regard, we explored the possible interactive effects of cigarette smoking as a representation of lifestyle factors and BMI as an indicator of metabolic factors; however, cigarette smoking and BMI were independently associated with WBC count, and no interaction was found between these two factors in the current study. Therefore, cigarette smoking and BMI might have had an

additive combined effect on high WBC count, but no synergistic interaction was observed between the two.

Although the underlying biological mechanisms that explain smoking-induced increases in 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 established that cigarette smoking contributes to insulin resistance, a core feature in the pathophysiology of MetS [20]. Atvall et al. 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 [21]. Insulin resistance also triggers hepatic production of very low-density lipoproteins, which leads to atherogenic dyslipidemia, including hypertriglyceridemia and low HDL-C level [22].

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 detrimental effects on body composition such as visceral obesity as well as osteoporosis and sarcopenia. Yun et al. [23] 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. Many 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 pro-inflammatory cytokines induced by chronic exposure to cigarette smoking indirectly lead to systemic low-grade inflammation beyond the respiratory system, contributing to initiation and progression of insulin resistance and MetS.

Our study had some limitations that must be acknowledged. First, our results might have a limited application to other populations because Koreans are ethnically highly homogeneous and have lower BMIs compared to other ethnicities, especially Caucasians. Second, there is potential for selection bias between study participants and non-participants, 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 accounts for a relatively small portion of the total smoker population. However, excluding women from our study could be considered a strength since we excluded a potential selection bias. Nevertheless, 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 intensity and cumulative dose of smoking.

Conclusion

Both cigarette smoking intensity and cumulative dose were positively associated with MetS among community-dwelling Korean men in the large-scale, longitudinal, prospective, 12-year follow-up study. Thus, smoking prevention and cessation could be important for prevention of MetS.

Abbreviations

MetS: metabolic syndrome

CVD: cardiovascular disease

KoGES: Korean Genome and Epidemiology Study

KNIH: Korea National Institute of Health

BP: blood pressure

HDL: high density lipoprotein

HOMA-IR: homeostasis model assessment-insulin resistance

HR: hazard ratio

CI: confidence interval

PYs: pack-years

RR: relative risk

WBC: white blood cell

BMI: body-mass-index

Declarations

Ethics approval and consent to participate

The Ansan–Ansung study protocol was reviewed and approved by the Institutional Review Board of the Korea Centres for Disease Control and Prevention, and all study participants gave their written informed consent. The study was approved by the Institutional Review Board of Gangnam Severance Hospital.

Consent for publication

Not applicable.

Availability of data and materials

The dataset used in this study (Ansan-Ansung cohort) were made available after review and evaluation of the research plan by the Korea Centers for Disease Control and Prevention (<http://www.cdc.go.kr/CDC/eng/main.jsp>).

Competing interests

The authors declare no competing interests.

Funding

This study did not receive any specific grant from funding agencies in the public, commercial, and not-for-profit sectors.

Authors' contributions

Kim AH, Seo IH, and Lee YJ conceived and designed the study, collected, analyzed, and interpreted the data, wrote the first draft and revised later drafts of the article. Kim AH, Seo IH, and Lee HS analyzed and interpreted the study data, and performed the statistical analysis. Lee YJ revised the article, and all authors approved the final manuscript.

Acknowledgements

The authors thank all the participants and survey staff of the KoGES for their contributions to our study.

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Tables

Table 1. Baseline characteristics of the study population according to daily cigarette exposure expressed as number of cigarettes per day

	Never smokers	Former smokers	Current smokers (cigarettes/day)			P value*
			0-9	10-19	≥20	
n	628	943	234	409	937	
Age (years)	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	<0.001
Waist circumference (cm)	81.6 ± 6.8	82.1 ± 6.6	81.5 ± 7.1	80.3 ± 6.7	81.0 ± 6.6	<0.001
Systolic blood pressure (mmHg)	120.8 ± 16.1	119.8 ± 16.4	118.9 ± 15.1	117.5 ± 16.0	117.2 ± 16.2	<0.001
Diastolic blood pressure (mmHg)	81.2 ± 11.1	80.4 ± 10.4	79.8 ± 9.1	78.8 ± 10.3	78.8 ± 10.1	<0.001
Mean arterial pressure (mmHg)	94.4 ± 12.2	93.5 ± 11.7	92.8 ± 10.5	91.7 ± 11.6	91.6 ± 11.5	<0.001
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)	<0.001
HDL-cholesterol (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 (%) [†]	58.5	58.8	69.1	78.3	79.8	<0.001
Regular exercise (%) [‡]	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

Data are expressed as the mean $\pm$ SD or percentage. *P-values were calculated using ANOVA or the chi-squared test. [†]Alcohol intake $\geq$ twice/week. [‡]Moderate intensity physical exercise $\geq$ three times/week.

Table 2. Baseline characteristics of the study population according to cumulative dose of cigarette smoking in pack-years

	Never smokers	Former smokers	Former smokers	Current smokers	Current smokers	P value*
		< 20PY	≥ 20P	< 20PY	≥ 20PY	
n	628	491	452	525	1055	0.026
Age (years)	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	<0.001
Waist circumference (cm)	81.6 ± 6.8	82.1 ± 6.6	81.5 ± 7.1	80.3 ± 6.7	81.0 ± 6.6	<0.001
Systolic blood pressure (mmHg)	120.8 ± 16.1	118.1 ± 14.9	121.7 ± 17.6	115.9 ± 14.8	118.4 ± 16.5	<0.001
Diastolic blood pressure (mmHg)	81.2 ± 11.1	79.6 ± 10.1	81.1 ± 10.7	79.4 ± 9.7	79.2 ± 10.2	<0.001
Mean arterial pressure (mmHg)	94.4 ± 12.2	92.4 ± 11.1	94.7 ± 12.3	90.9 ± 10.7	92.3 ± 11.7	<0.001
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	<0.001
Triglyceride (mg/dL)	118 (93- 169)	127 (95- 165)	134 (101- 170)	127 (100- 171)	132 (103- 187)	<0.001
HDL-cholesterol (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)	<0.001
Alcohol drinking (%) [†]	58.8	74.1	63.7	80.3	77.3	<0.001
Regular exercise (%) [‡]	27.5	28.2	30.1	26.5	27.5	0.015
Monthly household income (%)						<0.001
<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	39.9	50.9	35.7	45.1	33.9	

Won						
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

Data are expressed as the mean $\pm$ SD or percentage. *P-values were calculated using ANOVA or the chi-squared test. [†]Alcohol intake $\geq$ twice/week. [‡]Moderate intensity physical exercise $\geq$ three times/week.

Table 3. Incidence of MetS during the study follow-up years

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

Table 4. Hazard ratios and 95% CIs for incident MetS according to daily cigarette exposure expressed as number of cigarettes per day.

	Never smokers	Former smokers	Current smokers (cigarettes/day)		
			0-9	10-19	≥20
n	628	943	234	409	937
New cases of MetS, n	217	303	89	164	395
Mean follow-up, years	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)

Model 1: adjusted for after adjusting for age, alcohol drinking, physical activity, household income, educational level, and mean arterial pressure.

Model 2: adjusted for after adjusting for age, alcohol drinking, physical activity, household income, educational level, mean arterial pressure, triglyceride, and HDL-cholesterol.

Model 3: adjusted for after adjusting for age, alcohol drinking, physical activity, household income, educational level, mean arterial pressure, triglyceride, HDL-cholesterol, and HOMA-IR.

Table 5. Hazard ratios and 95% CIs for incident MetS according to cumulative dose of cigarette smoking in pack-years.

		Former smokers	Former smokers	Current smokers	Current smokers
		< 20PY	≥ 20P	< 20PY	≥ 20PY
n	628	491	452	525	1055
New cases of MetS, n	217	162	191	207	441
Mean follow-up, years	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)

Model 1: adjusted for after adjusting for age, alcohol drinking, physical activity, household income, educational level, and mean arterial pressure.

Model 2: adjusted for after adjusting for age, alcohol drinking, physical activity, household income, educational level, mean arterial pressure, triglyceride, and HDL-cholesterol.

Model 3: adjusted for after adjusting for age, alcohol drinking, physical activity, household income, educational level, mean arterial pressure, triglyceride, HDL-cholesterol, and HOMA-IR.

Figures

Figure 1

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 KNIH approved the study protocol. More information on the KoGES has been published in previous reports [6]. A baseline survey was conducted from 2001–2002, and 4758 men were recruited

Panel A

Number at risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Never smokers	628	628	582	567	504	481	432	415	361	338	299	286	54	0
Former smokers	943	943	882	852	735	698	625	600	520	490	420	399	73	0
Current smokers (0-9)	234	234	208	198	169	158	141	135	118	114	93	85	11	0
Current smokers (10-19)	409	409	369	358	303	285	242	224	192	182	154	141	27	0
Current smokers (≥ 20)	937	937	862	824	676	630	539	513	408	372	316	301	66	0

Panel B

Number at risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Never smokers	628	628	582	567	504	481	432	415	361	338	299	286	54	0
Former smokers (< 20PY)	491	491	466	450	398	380	343	333	290	277	238	227	40	0
Former smokers (≥ 20 PY)	452	452	416	402	337	318	282	267	230	213	182	172	33	0
Current smokers (< 20PY)	525	525	470	454	377	360	307	287	249	237	198	181	32	0
Current smokers (≥ 20 PY)	1055	1055	969	926	771	713	615	585	469	431	365	346	72	0

Figure 2

The cumulative probabilities of being diagnosed with MetS according to intensity of smoking and cumulative dose of cigarette smoking are presented in Figures 2A and 2B