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Complete List of Authors:	Jee, Yongho; Seoul National University, Department of Public Health Jung, Keum Ji; Yonsei University Graduate School Institute for Health Promotion, Dept. of Public Health Lee, Sunmi; National Health Insurance Service, Health Insurance Policy Research Institute Back, Joung Hwan; Health Insurance Policy Research Institute Jee, Sun Ha; Graduate School of Public Health, Yonsei University, Epidemiology Cho, Sung-il ; Seoul National University, Department of Public Health
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Smoking is the first leading cause of Cardiovascular Disease in Young Men: The Korean Life Course Health Study

Yongho Jee, MPH[1,2], Keum Ji Jung, PhD[2,4], Sunmi Lee, PhD[3], Joung Hwan Back, PhD[3], Sun Ha Jee, PhD[2,4*], Sung-il Cho, MD, PhD[1*]

[1] Department of Public Health, Seoul National University, Seoul, Republic of Korea

[2] Institute for Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Republic of Korea

[3] Health Insurance Policy Research Institute, Wonju, Republic of Korea

[4] Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Republic of Korea

Running title: Smoking is the first leading cause of Cardiovascular Disease

*These last authors contributed equally to this work

*Corresponding authors. Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Republic of Korea.

E-mail address: jsunha@yuhs.ac (S.H. Jee).

Department of Public Health, Seoul National University, Seoul, Republic of Korea

E-mail address: scho@snu.ac.kr (S.I. Cho).

These two authors equally contributed as corresponding author.

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Table 3, Figure 4

Abstract

Objective: To examine the effect of smoking on risk of atherosclerotic cardiovascular disease (ASCVD) in Korean young adults and to examine whether serum total cholesterol levels could modify the effect of smoking on ASCVD.

Design: A prospective cohort study within a national insurance system.

Setting: Health screenings provided by national insurance in 1992 and 1994.

Participants: 118,531 young men between 20 and 29 years of age and were followed up for 23 years.

Outcome measure: To assess the independent effects of smoking on the risk of Ischemic Heart Disease (IHD), stroke, and ASCVD, Cox proportional hazards regression models were used, controlling for age, hypertension, diabetes, hypercholesterolemia, and alcohol drinking.

Results: The total number of current smokers was 78,455 (66.2%), and 94,113 (79.7%) of the sample recorded a total cholesterol level < 200 mg/dl measured at baseline. Between 1993 and 2015, 2,786 cases of IHD (53/100,000 person year), 2,368 cases of stroke (45.4/100,000 person year), and 6,368 ASCVD (122.7/100,000 person year) occurred. The risk of IHD, stroke, and total ASCVD events was found to increase for current smokers, with a hazard ratios (HR) with 95% Confidence Interval (CI) of 1.5 (95% CI: 1.3,1.6), 1.4 (95% CI: 1.2,1.6), and 1.4 (95% CI: 1.3,1.5), respectively. Further, the risks above were also found throughout the range of serum levels of cholesterol.

Conclusions: Smoking among Korean young adult men was independently associated with increased risk of IHD, stroke and ASCVD. The concentration of cholesterol in Korean men did not modify the effect of smoking on ASCVD.

Keywords: Smoking, Cardiovascular Disease, Young adults

Strengths and limitations of this study

- Novel result from Korean young adults is that smoking is the first leading cause of Cardiovascular Disease (CVD) while smoking is the second leading cause of CVD in middle aged adults.
- The large sample size of cohort with 118,531 young men between 20 and 29 years of age and were followed up for 23 years.
- The limitations of this study include possible measurement errors and the non-random sample used.

INTRODUCTION

Atherosclerotic cardiovascular diseases (ASCVD) are the leading cause of death globally, with more people dying from ASCVD than any other causes of death annually. A total of 17.7 million people died as a result of ASCVDs in 2015 globally, comprising 31% of all deaths. Of these deaths, 7.4 million are estimated to have been the result of coronary heart disease, whilst 6.7 million were due to stroke (WHO). According to previous studies published in the western countries, tobacco use has been reported to be a major risk factor for ASCVD following hypertension.[1]

A growing concern is that for young adults, cigarette smoking may be the first leading cause of ASCVD, owing to the high prevalence of cigarette smoking in comparison to lower levels of alternate risk factors, including hypertension, diabetes, and high cholesterol levels. However, despite these observations, there remain only a small number of studies considering the relationship between smoking and ASCVD in Korea and other countries in East Asia. [2-5]

Further, comparisons with Western populations may be less informative owing to the relatively lower levels of cholesterol commonly present in Asian countries. Biological studies have explored the interaction between smoking and serum cholesterol levels.[6-9] Nevertheless, very few studies have analyzed the interaction effects of smoking and serum cholesterol on ASCVD in young adults

'World No Tobacco Day 2018' is a campaign, with the primary objective of raising awareness of the link between tobacco use and negative health outcomes, predominantly heart and other cardiovascular diseases (CVD) including stroke. It will

also seek to expand the range of potential strategies key public actors such as governmental and public bodies can take to reduce the health risks of tobacco use. If there is an established link between tobacco smoking in young adults and CVD, the campaign will further increase awareness on smoking in young adults. The government and the public can then subsequently take actions to reduce risks of smoking at earlier stage. Unfortunately, however, the association between smoking and CVD in young adults has not received much attention because at least a long term (over 20 years) follow-up study is needed. This serves as motivation for this study, in which we aimed to examine the effect of smoking on risk of ASCVD in Korean young adults with relatively low serum cholesterol levels. We also investigated whether the effect of smoking can be modified by serum levels of cholesterol.

METHOD

Study participants

In Korea, the Korean Medical Insurance Corporation (KMIC) provided health insurance for private school staff and civil servants prior to the current insurance system, under which it was integrated as National Health Insurance.[2] A total of 4,862,438 (10.7%) of the Korean population were covered by KMIC insurance, of which 1,297,833 were employees, and 3,364,605 were dependents. All insured participants are required to participate in a biennial health checkup.[2] Approximately 94% of the insured participants in 1992 and 1994 were examined biennially. We established a prospective cohort for participants (aged 20-29) who routinely responded to the questionnaire on disease risk

factors and chronic diseases, naming this study the Korean Life Course Health Study (KLCHS). The KLCHS cohort included 307,041 Koreans (142,461 males, 164,580 females) who were screened by KMIC in 1992 and 1994. Of these participants, 205,840 (67.0%) were registered in 1992 and 101,201 (33.0%) were registered in 1994.

Of these 307,041 participants, 71,760 (23.4%) who had incomplete data height, blood pressure, fasting glucose, total cholesterol, or body mass index were excluded. We also excluded 6,170 people from our analysis who reported a past history of cancer and ASCVD, as well as 2,091 people who had missing information on smoking, exercise, or alcohol drinking, and 65 people who died before start of follow-up. Female participants were excluded, because of the low prevalence of smoking for females in Korea, resulting in a total of 118,531 eligible participants for the analysis (Figure 1). The study proposal obtained an approval by the Institutional Review Board of Human Research, Yonsei University (4-2001-0029). This study was a retrospective cohort using past routine laboratory data and did not receive consent.

Data collection

The biennial KMIC screening was provided at local hospitals by medical practitioners according to standard protocols. During the two-year interval examination from 1992 to 2008, we examined the variables related to the lifestyle of participants, such as daily smoking amount, duration of smoking, and variables related to drinking. From data collected at baseline, participants were defined as ‘current smokers’ if they were smoking currently, ‘never smokers’ if they had no prior history of smoking, and ‘ex-

smokers' if they had previously smoked but at the time of measurement did not smoke. Current smokers were further categorized by amount of cigarettes consumed on average per day (1–9, 10–19, and 20 or greater) as well as duration of smoking (1–9, 10–19, and 20 or more years) following the example of previous studies.[2,10,11]

The definition of hypertension was a systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg.[12] Body mass index (BMI) was measured as weight (kg) / height $(m)^2$. Serum total cholesterol was grouped as desirable (<200 mg/dl), borderline-high (200-239 mg/dl), and high (≥240 mg/dl).[13] Definition of diabetes was fasting blood glucose ≥ 126 mg / dl.[14]

Follow-up and outcomes

The main outcome variables used in the analysis were morbidity and mortality categorized by IHD, stroke, and ASCVD. For IHD, alone (ICD 10 codes, I20–I25), acute myocardial infarction (AMI) alone (I21), and angina pectoris (AP) alone (ICD 10 codes, I20) are used. For stroke, stroke alone (I60-I69) was used. Finally, with regard to ASCVD, we used total ASCVD, including disease of hypertensive (I10–I15), ischemic heart disease (I20–I25), all stroke (I60–I69), other heart disease (I44–I51), sudden death (R96), and other vascular disease (I70–I74).

The study outcomes were identified through diagnosis information recorded in hospital admission, and from causes of death using death certificates. The study follow-up was nearly 100% complete, as we were able to search ASCVD event data electronically by

KMIC registrants regarding the morbidity information of ASCVD. The period of follow-up was 23 years from January 1st, 1993 to December 31st, 2015. Data on causes of death were available during years 1993–2015, and incidence could be tracked during years 1995–2015.

A validation study was conducted by 20 internists from the Korean Society of Cardiology in 2009.[15] For the participants who provided written permission for the use of their personal information, 673 CHD events between 1994 and 2007 were confirmed with individual hospital medical records, showing that 73% of designated myocardial infarctions were valid. The validation study was updated in 2013 with a value of 93%.[16] The validation study on mortality data has not been conducted.

Statistical analysis

First, we examined relationships between smoking status and established ASCVD risk factors at baseline. In considering continuous ASCVD risk factors, we used ordinary least squares regression and coded smoking quantity as an ordinal variable. In this study, the Mantel Haenszel method was applied for dichotomous variables.[17]

To assess the independent effects of smoking on the risk of IHD, stroke, and ASCVD, Cox proportional hazards models were used, controlling for age and the confounding variables such as hypertension, diabetes, high cholesterol, and alcohol drinking. The proportional assumption was also tested utilizing Schoenfeld residuals, and the survival curve according to smoking status was plotted using the life-table method. We used Levins formula for calculating population attributable risk (PAR).[18] In additional

analyses, we excluded all events that had occurred in the first 4 years of follow-up. These analyses ensured sensitivity in our results. In all analyses, a two-sided significance level of 0.05 was used.

Patient and Public Involvement

Patients and or public were not involved.

RESULTS

The average age of the study participants was 26.7 ± 2.0 (SD) years. Among the 118,531 men, 78,455 (66.2%) were current smokers, 15,126 (12.8%) were ex-smokers, and 92,403 (78%) had hypertension. For total cholesterol, 94,413 (79.7%) had a total serum cholesterol level < 200 mg/dL, 19,764 (16.6%) had a borderline level of 200-240 mg/dL, and 4,444 (3.8%) had a level of 240 mg/dL or higher. In terms of amount of smoking, 28.9% smoked more than 20 cigarettes per day while 45.5% and 25.6% of current smokers smoked 1 to 9 and 10 to 19 cigarettes per day, respectively. Among current smokers, 92.0% smoked for less than 10 years while 7.6% and 0.4% of current smokers smoked for 10 to 19 years and more than 20 years, respectively.

Population characteristics by smoking status are presented in Table 1. After adjusting for age, current smokers had a significantly higher body mass index (P for trend = 0.0056), higher consumption of alcohol drinking (P for trend <.0001), and higher prevalence of diabetes (P for trend = 0.0060) than nonsmokers.

During 23 years of follow up (5,191,823 person-years), 2,786 (90 fatal) IHD cases (53/100,000 person year), stroke cases 2,368 (126 fatal) (45.4/100,000 person year), and 6,368 ASCVD cases (306 fatal) (122.7/100,000 person year) occurred

The independent effects of smoking on IHD, stroke, and ASCVD were analyzed controlling for confounding factors through Cox proportional hazards models, as shown in Table 2. The hazard ratios (HR) relating to IHD for current smokers were 1.5 (P <.0001), and those of ex-smokers were 1.0 (P <.0001). The HR of stroke was 1.4 (P <.0001) for current smokers and 1.1 (P = 0.5008) on ex-smokers.

Compared to nonsmokers, the HR for any ASCVD event was 1.4 (P < 0.0001) in current smokers and 1.1 in ex-smokers (P = 0.1406). Figure 2 shows the survival probability by smoking history (never, former, 1-9, 10-19, ≥20 cigarette per day among current smokers) and the corresponding unadjusted association with ASCVD. The overall results demonstrated that smoking among young men increased the risk for ASCVD relative to nonsmokers. After adjusting for age and traditional ASCVD risk factors, the HRs for IHD and stroke were estimated for groups classified by amount of smoking (A and B in Figure 3) and duration of smoking (C and D in Figure 3). For IHD and stroke, the risk of events increased linearly with higher amount of cigarette per day (P for trend, <.0001 and <.0001, respectively) and longer duration of smoking (P for trend, <.0001 and <.0001, respectively).

To examine whether serum total cholesterol levels could modify the effect of smoking on ASCVD, we divided the cohort participants into quartile of total cholesterol. The risks above were also found throughout the range of serum levels of cholesterol

demonstrating that serum total cholesterol levels did not modify the effect of smoking on ASCVD (Figure 4).

Estimated risk factor prevalence in current studies of smoking and other additional risk factors were used to estimate the PARs for IHD alone, stroke alone and total ASVCD (Table 3). For IHD, current smoking accounts for about 24.9% of events, and hypertension accounts for 8.1% of events. In the case of stroke, smoking was estimated to account for 20.9%, whilst hypertension was estimated to be responsible for 13.3% of stroke cases.

DISCUSSION

Our study investigated the association between smoking and risk of ASCVD among Korean young men within a cohort study with a 23 year of follow-up. To our knowledge, this is the first study focusing on Korean young adults. In our study, smoking was the most crucial risk factor attributing to 20% of ASCVD mortality in middle age.

Diabetes, hypertension, and hyperlipidemia are well known risk factors for ASCVD[10]. However, for young adults with relatively low incidence of diabetes, hypertension and hyperlipidemia, smoking is the most important and an independent risk factor for predicting ASCVD in the present study. Furthermore, the high smoking rate among young people is important with respect to the development of middle-aged hypertension and transition to ASCVD.[19-20] Thus, middle-aged ASCVD morbidity is likely predominantly predicted by smoking in young adulthood.

The body of research centered upon the health effects of smoking is steadily increasing, with findings reported from many countries around the world. However, few studies have examined the effect of smoking on ASCVD in young adults.[21] Here, we present evidence that current smoking is an independent risk factor affecting the incidence of IHD, stroke and ASCVD.

These risk associations have been estimated across total serum cholesterol groups. A cohort study in Hasayama Japan found that smoking showed positive association with coronary heart disease in people with high levels of serum cholesterol above 180 mg / dl, but not with people with low level of cholesterol less than 180 mg / dl].[22-23] Afterward, six epidemiological studies were conducted. Among them, one study from Puerto Rico Heart Health Program[24] showed similar results, but not all.[7-11] Of course, all studies were conducted among adult populations. To the best of our knowledge, no study has been done on young adults with much lower levels of serum cholesterol. In addition, the high smoking rate among young adults is likely to be, even directly, linked to high blood pressure among the adult population who developed ASCVD as a major health problem.

In our analysis, there was no observed increase in risk of IHD or stroke among ex-smokers. That is, the risk of ASCVD in ex-smokers was similar with that of nonsmokers. These findings suggest that the risk of IHD lasts for an unknown period, while the high risk for ASCVD decreases after smoking cessation.

There are several studies regarding cardiovascular risk among young people. According to a study conducted by Bernaards et al.,[25] blood pressure and waist circumference were

decreased by lowering weekly tobacco consumption in younger participants. However, they did not report the risk of developing cardiovascular disease events due to changes in smoking. This seems to be another significant topic relating to the health of young adults. Another study conducted by Morotti et al.[21] on young women with polycystic ovary syndrome (PCOS) reported an association between smoking habitude in lean PCOS patients, and the increase of soft markers of cardiovascular risk. For young adult African Americans, the association between cigarette smoking and carotid intima assuming the genetic variation of smokers was reported and the -930$^{A/G}$ polymorphism modified the association among young healthy adults.[26] The study on association between second hand smoking among childhood and cardiovascular event in adulthood was conducted and found that the carotid plaque risk in adulthood is increased in children whose parents had smoked.[27-28]

This LCHS study has several strengths, such as high follow-up rates and a large, national sample. The large sample size of cohort allowed us to investigate the association of smoking with various levels of serum cholesterol. However, selection bias may be a potential issue, since the final sample contains a subset of over 118,531 young male adults (38.6%) out of 307,041 subjects initially selected for our study. We therefore urge conservative interpretations of our study results with regard to the general population.

In conclusion, smoking is a leading cause of ASCVD among young adults in Korea, a country with a low total cholesterol level and a high smoking rate. And the association was not modified by total cholesterol level. Smoking among Korean young adult men was independently associated with increased risk of IHD, stroke and ASCVD. The

concentration of cholesterol in Korean men did not modify the effect of smoking on ASCVD. Therefore, smoking cessation on young adult smokers is essential to prevent CVD later in adult life. Moreover, clinical practice guidelines and policies should emphasize to treat nicotine addiction in young smokers.

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Conflict of interests: We declare that we have non conflicts of interest.

Ethics approval: The study proposal obtained an approval by the Institutional Review Board of Human Research, Yonsei University (4-2001-0029).

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Data sharing statement: No additional data are available.

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Figure legends

Figure 1. Defining the study population

Figure 2. Survival of atherosclerotic cardiovascular disease event by smoking history in Korean young adult men, 1992-2015

Figure 3. Hazard ratios with 95% confidence intervals for from ischemic heart disease, and stroke by cigarette per day and duration of smoking

Figure 4. Hazard ratios with 95% confidence intervals for ischemic heart disease and stroke by total cholesterol groups of smokers compared with nonsmokers: Each group of total cholesterol levels are as follows: first, 149 mg/dl; second, 150-169 mg/dL; third, 170-194 mg/dL; fourth, ≥195 mg/dL. The reference group is non-smokers in each quartile of total cholesterol.

Table 1. Baseline Characteristics of the Korean Life Course Health Study, 1992-1994, According to Smoking Status*

Characteristic	Nonsmokers (n=24,950)	Ex-smokers (n=15,126)	No. of cigarettes per day among current smokers			
			1-9 (n=22,642)	10-19 (n=35,690)	≥20 (n=20,123)	*P* for Trend¶
Age, year	26.6 (2.1)	26.9 (1.9)	26.6 (2.0)	26.8 (1.9)	26.8 (1.9)	0.1622
Systolic Blood Pressure, mmHg	120.4 (11.6)	120.0 (11.8)	119.8 (11.6)	120.1 (11.6)	120.3 (11.6)	0.2558
Diastolic Blood Pressure mmHg	78.0 (9.0)	77.7 (9.1)	77.5 (9.0)	77.8 (9.0)	78.0 (9.0)	0.1122
Total cholesterol, mg/dL	173.4 (32.9)	173.4 (32.6)	172.9 (33.1)	174.5 (33.4)	177.2 (34.4)	0.9543
Body mass index, kg/m^2	22.3 (2.4)	22.4 (2.4)	22.3 (2.4)	22.5 (2.5)	22.9 (2.6)	0.0056
Fasting serum glucose, mg/dL	86.7 (13.3)	86.6 (13.5)	86.2 (14.1)	86.4 (14.1)	86.6 (15.3)	0.4821
Alcohol consumption, g per day	7.3 (17.7)	9.7 (19.7)	12.2 (22.6)	14.5 (25.1)	20.4 (36.1)	<.0001
Conditions, %						
Hypertension†	22.7	21.8	20.7	22.1	23.0	0.7987
Hypercholesterolemia‡	3.4	3.3	3.3	3.9	4.7	0.0743
Diabetes§	0.7	0.8	0.9	0.9	1.0	0.0060
Alcohol use‖	61.2	81.3	88.2	88.3	86.9	0.1035
Physical activity						

*Data are expressed as means (SD) unless otherwise indicated; †Systolic blood pressure of at least 140 mmHg and/or diastolic blood pressure of at least

90 mmHg; ‡Total cholesterol level of at least 6.21 mmol/L (240 mg/dL); § Fasting serum glucose value of at least 6.99 mmol/L (126 mg/L); ‖Consumption of Soju which is a colorless distilled beverage of Korean origin; ¶Testing for trend across nonsmokers and current smokers; ex-smokers were excluded.

Table 2. Risk of Morbidity from Ischemic Heart Disease, Cerebrovascular Disease, and Atherosclerotic Cardiovascular Disease in Korean Men in the Korean Life Course Health Study, 1992-2015*

	Ischemic Heart Disease		Cerebrovascular Disease		Atherosclerotic Cardiovascular Disease	
Variables and Categories	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (5-year age group)	1.4 (1.2 – 1.6)	<.0001	1.4 (1.3 – 1.6)	<.0001	1.3 (1.2 – 1.4)	<.0001
Cigarette smoking						
Ex-smoker	1.0 (0.9 – 1.2)	0.8567	1.1 (0.9 – 1.3)	0.5008	1.1 (1.0 – 1.2)	0.1406
Current smoker	1.5 (1.3 – 1.6)	<.0001	1.4 (1.2 – 1.6)	<.0001	1.4 (1.3 – 1.5)	<.0001
Blood Pressure†						
High normal	1.2 (1.1 – 1.4)	<.0001	1.2 (1.0 – 1.3)	0.0152	1.2 (1.1 – 1.3)	<.0001
Stage 1 hypertension	1.6 (1.4 – 1.8)	<.0001	1.7 (1.5 – 2.0)	<.0001	1.7 (1.5 – 1.8)	<.0001
Stage 2 hypertension	2.0 (1.6 – 2.5)	<.0001	3.2 (2.5 – 4.0)	<.0001	2.9 (2.5 – 3.3)	<.0001
Total cholesterol‡						
Borderline-high cholesterol	1.4 (1.3 – 1.6)	<.0001	1.4 (1.3 – 1.6)	<.0001	1.4 (1.3 – 1.5)	<.0001
High cholesterol	2.5 (2.1 – 2.8)	<.0001	1.7 (1.4 – 2.1)	<.0001	2.1 (1.8 – 2.3)	<.0001
Fasting blood sugar§						
Diabetes	1.3 (0.9 – 1.9)	0.1375	1.6 (1.1 – 2.3)	0.0222	1.5 (1.2 – 1.9)	0.0008
Physical activity						
No exercise	1.1 (1.0 – 1.3)	0.0122	1.1 (1.0 – 1.3)	0.2156	1.1 (1.0 – 1.3)	0.0075

*Hazard ratio (HRs) and 95% confidence intervals (CIs) from multivariable Cox proportional hazards models. †The reference category is normal (systolic

blood pressure<140 mmHg and diastolic blood pressure<90mm Hg). ‡ The reference category is desirable (serum cholesterol level, < 5.17 mmol/L [200 mg/dL]). §The reference category is a fasting serum glucose level of less than 6.99 mmol/L (126 mg/dL).

Table 3. Population Attributable Risks (PARs) and 95% Confidence Intervals (CIs) From Smoking and Other Risk Factors of Ischemic Heart Disease, Cerebrovascular Disease, and Atherosclerotic Cardiovascular Disease in Korean Men: The Korean Life Course Health Study

Variables and Categories	Prevalence	Ischemic Heart Disease	Cerebrovascular Disease	Atherosclerotic Cardiovascular Disease
	%	PAR (95% CI)	PAR (95% CI)	PAR (95% CI)
Smoking				
Current smoker	66.2	24.9 (16.6 – 28.4)	20.9 (11.7 -28.4)	20.9 (16.5 – 24.9)
Blood Pressure*				
Hypertension	22.0	8.1 (6.2 – 9.9)	13.3 (9.9 – 14.9)	9.9 (9.9 – 11.7)
Total cholesterol†				
Borderline	16.6	6.2 (4.7 – 9.1)	6.2 (4.7 – 7.7)	6.2 (4.7 – 7.6)
High	3.8	5.4 (4.0 – 6.4)	4.0 (2.9 – 4.7)	4.0 (2.9 – 4.7)
Fasting blood sugar‡				
Diabetes	0.9	0.3 (-0.9 – 0.8)	0.5 (0.08 – 1.1)	0.4 (0.2 – 0.8)
Physical activity				
No exercise	??			

*The reference category is normal (systolic blood pressure < 140 mmHg and diastolic blood pressure < 90mm Hg). †The reference category is desirable (serum cholesterol level < 5.17 mmol/L [200 mg/dL]). ‡ The reference category is a fasting serum glucose level of less than 6.99 mmol/L (126 mg/dL).

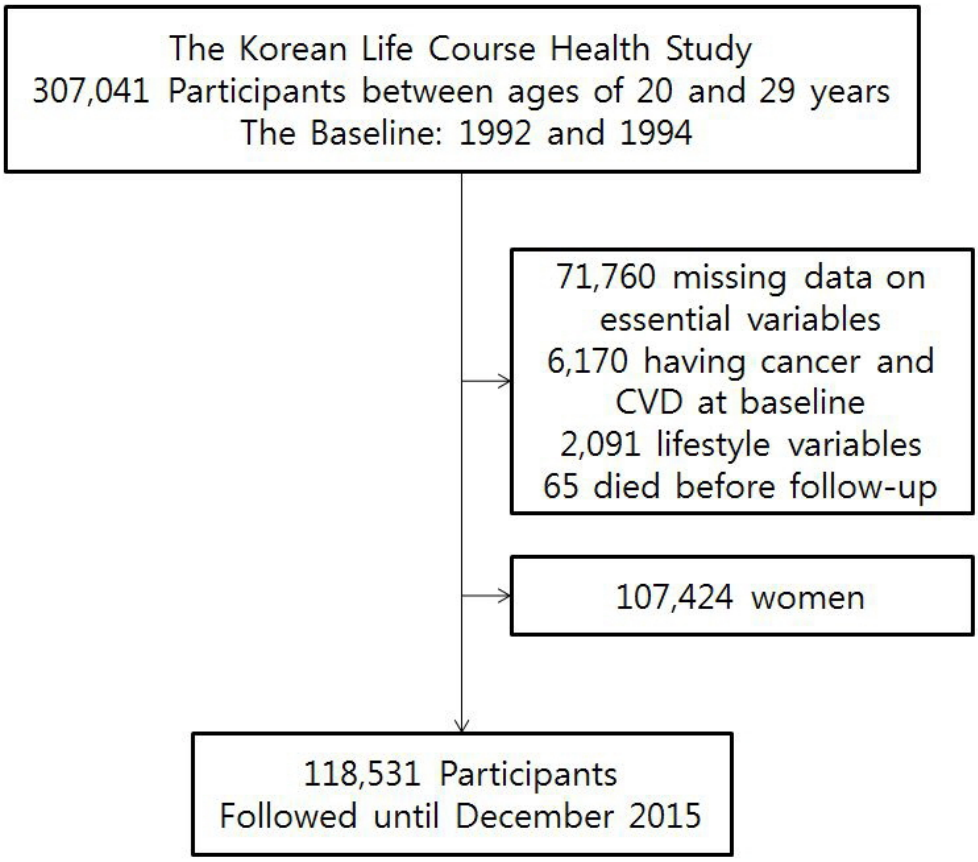

Figure 1

64x56mm (300 x 300 DPI)

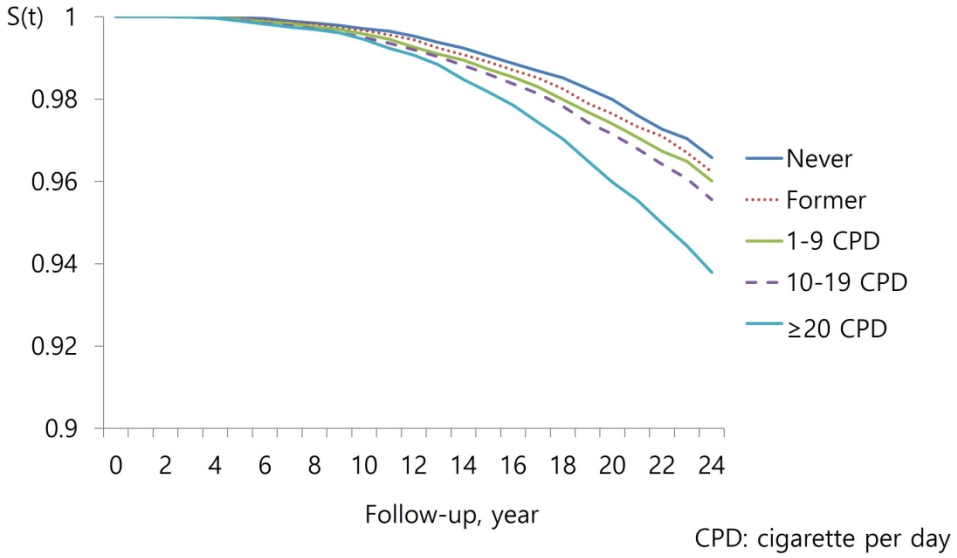

Figure 2

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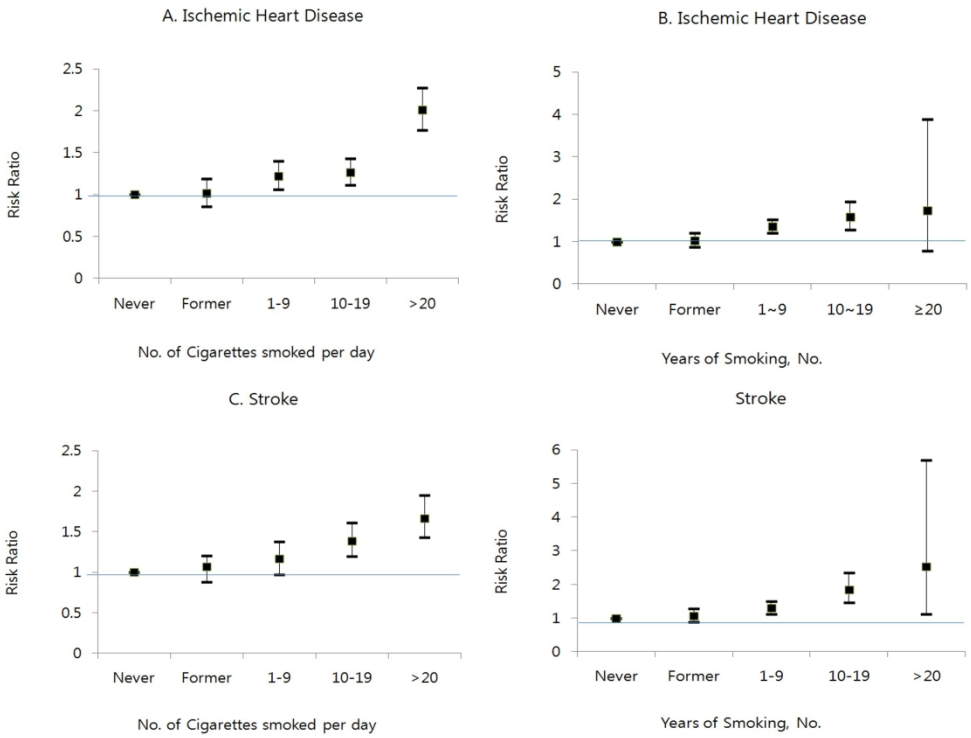

Figure 3

254x190mm (300 x 300 DPI)

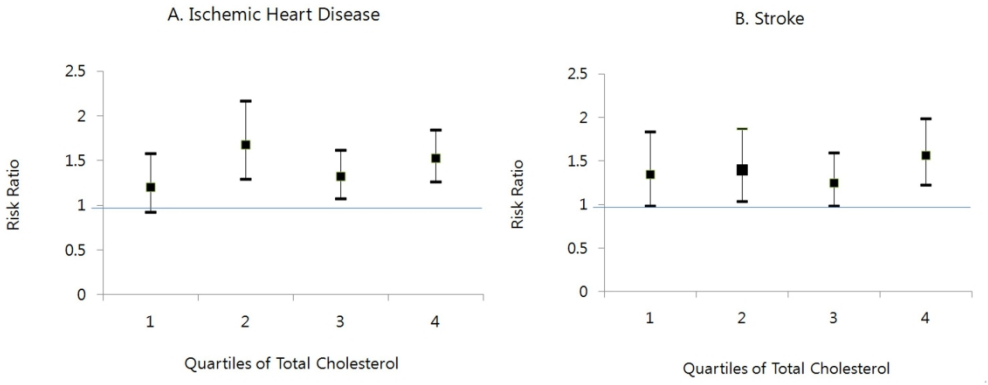

Figure 4

254x190mm (300 x 300 DPI)

Title: smoking is the first leading cause of cardiovascular disease in young men.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract page 3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found page 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported page 5
Objectives	3	State specific objectives, including any prespecified hypotheses page 6, para 1.
Methods		
Study design	4	Present key elements of study design early in the paper page 6, para 2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection page 6-7.
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up page 6, page 8
		(b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable page 7, para 3, page 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group page 6, page 7
Bias	9	Describe any efforts to address potential sources of bias page 14.
Study size	10	Explain how the study size was arrived at page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why page 8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding page 8
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) If applicable, explain how loss to follow-up was addressed page 8
		(e) Describe any sensitivity analyses page 9-10
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed page 10
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram page 7. (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders page 10
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount) page 10 (23 years of follow-up)
Outcome data	15*	Report numbers of outcome events or summary measures over time page 10.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included page 10, para 1 (Table 2)
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses page 11 (Figure 4)
Discussion		
Key results	18	Summarise key results with reference to study objectives page 12 para 2
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias page 14, para 2.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence page 14
Generalisability	21	Discuss the generalisability (external validity) of the study results page 14
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based page 15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Smoking and Atherosclerotic Cardiovascular Disease Risk in Young Men: The Korean Life Course Health Study

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Smoking and Atherosclerotic Cardiovascular Disease Risk in Young Men: The Korean Life Course Health Study

Yongho Jee, MPH[1,2], Keum Ji Jung, PhD[2,4], Sunmi Lee, PhD[3], Joung Hwan Back, PhD[3], Sun Ha Jee, PhD[2,4*], Sung-il Cho, MD, PhD[1*]

[1] Department of Public Health, Seoul National University, Seoul, Republic of Korea

[2] Institute for Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Republic of Korea

[3] Health Insurance Policy Research Institute, Wonju, Republic of Korea

[4] Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Republic of Korea

Running title: Smoking is the first leading cause of Cardiovascular Disease

*These last authors contributed equally to this work

*Corresponding authors. Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Republic of Korea.

E-mail address: jsunha@yuhs.ac (S.H. Jee).

Department of Public Health, Seoul National University, Seoul, Republic of Korea

E-mail address: scho@snu.ac.kr (S.I. Cho).

These two authors equally contributed as corresponding author.

Word count: 3828

Table 3, Figure 4

Abstract

Objective: To examine the effect of smoking on risk of atherosclerotic cardiovascular disease (ASCVD) in Korean young men and to examine whether serum total cholesterol levels could modify the effect of smoking on ASCVD.

Design: A prospective cohort study within a national insurance system.

Setting: Health screenings provided by national insurance in 1992 and 1994.

Participants: 118,531 young men between 20 and 29 years of age and were followed up for 23 years.

Outcome measure: To assess the independent effects of smoking on the risk of Ischemic Heart Disease (IHD), stroke, and ASCVD, Cox proportional hazards regression models were used, controlling for age, hypertension, diabetes, hypercholesterolemia, and alcohol drinking.

Results: The total number of current smokers was 78,455 (66.2%), and 94,113 (79.7%) of the sample recorded a total cholesterol level < 200 mg/dl measured at baseline. Between 1993 and 2015, 2,786 cases of IHD (53/100,000 person year), 2,368 cases of stroke (45.4/100,000 person year), and 6,368 ASCVD (122.7/100,000 person year) occurred. The risk of IHD, stroke, and total ASCVD events was found to increase for current smokers, with a hazard ratios (HR) with 95% Confidence Interval (CI) of 1.5 (95% CI: 1.3,1.6), 1.4 (95% CI: 1.2,1.6), and 1.4 (95% CI: 1.3,1.5), respectively. Further, the risks above were also found throughout the range of serum levels of cholesterol.

Conclusions: Smoking among Korean young adult men was independently associated with increased risk of IHD, stroke and ASCVD. The concentration of cholesterol in Korean men did not modify the effect of smoking on ASCVD.

Keywords: Smoking, Cardiovascular Disease, Young adults

Strengths and limitations of this study

- Novel result from Korean young adults is that smoking is the first leading cause of Cardiovascular Disease (CVD) while smoking is the second leading cause of CVD in middle aged adults.
- The large sample size of cohort with 118,531 young men between 20 and 29 years of age and were followed up for 23 years.
- The limitations of this study include possible measurement errors and the non-random sample used.

INTRODUCTION

Atherosclerotic cardiovascular diseases (ASCVD) are the leading cause of death globally, with more people dying from ASCVD than any other causes of death annually. A total of 17.7 million people died as a result of ASCVDs in 2015 globally, comprising 31% of all deaths. Of these deaths, 7.4 million are estimated to have been the result of coronary heart disease, whilst 6.7 million were due to stroke[1]. According to previous studies published in the western countries, tobacco use has been reported to be a major risk factor for ASCVD following hypertension.[1]

A growing concern is that for young adults, cigarette smoking may be the first leading cause of ASCVD, owing to the high prevalence of cigarette smoking in comparison to lower levels of alternate risk factors, including hypertension, diabetes, and high cholesterol levels. However, despite these observations, there remain only a small number of studies considering the relationship between smoking and ASCVD in Korea and other countries in East Asia. [2-5]

Further, comparisons with Western populations may be less informative owing to the relatively lower levels of cholesterol commonly present in Asian countries. Biological studies have explored the interaction between smoking and serum cholesterol levels.[6-9] Nevertheless, very few studies have analyzed the interaction effects of smoking and serum cholesterol on ASCVD in young adults

'World No Tobacco Day 2018' is a campaign, with the primary objective of raising awareness of the link between tobacco use and negative health outcomes, predominantly heart and other cardiovascular diseases (CVD) including stroke. It will

also seek to expand the range of potential strategies key public actors such as governmental and public bodies can take to reduce the health risks of tobacco use. If there is an established link between tobacco smoking in young adults and CVD, the campaign will further increase awareness on smoking in young adults. The government and the public can then subsequently take actions to reduce risks of smoking at earlier stage. Unfortunately, however, the association between smoking and CVD in young adults has not received much attention because at least a long term (over 20 years) follow-up study is needed. This serves as motivation for this study, in which we aimed to examine the effect of smoking on risk of ASCVD in Korean young adults with relatively low serum cholesterol levels. We also investigated whether the effect of smoking can be modified by serum levels of cholesterol.

METHOD

Study participants

In Korea, the Korean Medical Insurance Corporation (KMIC) provided health insurance for private school staff and civil servants prior to the current insurance system, under which it was integrated as National Health Insurance.[2] A total of 4,862,438 (10.7%) of the Korean population were covered by KMIC insurance, of which 1,297,833 were employees, and 3,364,605 were dependents. All insured participants are required to participate in a biennial health checkup.[2] Approximately 94% of the insured participants in 1992 and 1994 were examined biennially. We established a prospective cohort for participants (aged 20-29) who routinely responded to the questionnaire on disease risk

factors and chronic diseases, naming this study the Korean Life Course Health Study (KLCHS). The KLCHS cohort included 307,041 Koreans (142,461 males, 164,580 females) who were screened by KMIC in 1992 and 1994. Of these participants, 205,840 (67.0%) were registered in 1992 and 101,201 (33.0%) were registered in 1994.

Of these 307,041 participants, 71,760 (23.4%) who had incomplete data height, blood pressure, fasting glucose, total cholesterol, or body mass index were excluded. We also excluded 6,170 people from our analysis who reported a past history of cancer and ASCVD, as well as 2,091 people who had missing information on smoking, exercise, or alcohol drinking, and 65 people who died before start of follow-up. Female participants were excluded, because of the low prevalence of smoking for females in Korea, resulting in a total of 118,531 eligible participants for the analysis. The study proposal obtained an approval by the Institutional Review Board of Human Research, Yonsei University (4-2001-0029). This study was a retrospective cohort using past routine laboratory data and did not receive consent.

Data collection

The biennial KMIC screening was provided at local hospitals by medical practitioners according to standard protocols. During the two-year interval examination from 1992 to 2008, we examined the variables related to the lifestyle of participants, such as daily smoking amount, duration of smoking, and variables related to drinking. From data collected at baseline, participants were defined as ‘current smokers’ if they were smoking currently, ‘never smokers’ if they had no prior history of smoking, and ‘ex-

smokers' if they had previously smoked but at the time of measurement did not smoke. Current smokers were further categorized by amount of cigarettes consumed on average per day (1–9, 10–19, and 20 or greater) as well as duration of smoking (1–9, 10–19, and 20 or more years) following the example of previous studies.[2,10,11]

The definition of hypertension was a systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg.[12] Body mass index (BMI) was measured as weight (kg) / height $(m)^2$. Serum total cholesterol was grouped as desirable (<200 mg/dl), borderline-high (200-239 mg/dl), and high (≥240 mg/dl).[13] Definition of diabetes was fasting blood glucose ≥ 126 mg / dl.[14]

Follow-up and outcomes

The main outcome variables used in the analysis were morbidity and mortality categorized by IHD, stroke, and ASCVD. For IHD, alone (ICD 10 codes, I20–I25), acute myocardial infarction (AMI) alone (I21), and angina pectoris (AP) alone (ICD 10 codes, I20) are used. For stroke, stroke alone (I60-I69) was used. Finally, with regard to ASCVD, we used total ASCVD, including disease of hypertensive (I10–I15), ischemic heart disease (I20–I25), all stroke (I60–I69), other heart disease (I44–I51), sudden death (R96), and other vascular disease (I70–I74).

The study outcomes were identified through diagnosis information recorded in hospital admission, and from causes of death using death certificates. The study follow-up was nearly 100% complete, as we were able to search ASCVD event data electronically by

KMIC registrants regarding the morbidity information of ASCVD. The period of follow-up was 23 years from January 1st, 1993 to December 31st, 2015. Data on causes of death were available during years 1993–2015, and incidence could be tracked during years 1995–2015. The time frames over which these outcomes could be assessed varied with data availability (Figure 1).

A validation study was conducted by 20 internists from the Korean Society of Cardiology in 2009.[15] For the participants who provided written permission for the use of their personal information, 673 CHD events between 1994 and 2007 were confirmed with individual hospital medical records, showing that 73% of designated myocardial infarctions were valid. The validation study was updated in 2013 with a value of 93%.[16] The validation study on mortality data has not been conducted.

Statistical analysis

First, we examined relationships between smoking status and established ASCVD risk factors at baseline. In considering continuous ASCVD risk factors, we used ordinary least squares regression and coded smoking quantity as an ordinal variable. In this study, the Mantel Haenszel method was applied for dichotomous variables.[17]

To assess the independent effects of smoking on the risk of IHD, stroke, and ASCVD, Cox proportional hazards models were used, controlling for age and the confounding variables such as hypertension, diabetes, high cholesterol, and alcohol drinking. The proportional assumption was also tested utilizing Schoenfeld residuals, and the survival curve according to smoking status was plotted using the life-table method. We used

Levins formula for calculating population attributable risk (PAR).[18] In additional analyses, we excluded all events that had occurred in the first 4 years of follow-up. These analyses ensured sensitivity in our results. In all analyses, a two-sided significance level of 0.05 was used.

Patient and Public Involvement

Patients and or public were not involved.

RESULTS

The average age of the study participants was 26.7 ± 2.0 (SD) years. Among the 118,531 men, 78,455 (66.2%) were current smokers, 15,126 (12.8%) were ex-smokers, and 92,403 (78%) had hypertension. For total cholesterol, 94,413 (79.7%) had a total serum cholesterol level < 200 mg/dL, 19,764 (16.6%) had a borderline level of 200-240 mg/dL, and 4,444 (3.8%) had a level of 240 mg/dL or higher. In terms of amount of smoking, 28.9% smoked more than 20 cigarettes per day while 45.5% and 25.6% of current smokers smoked 1 to 9 and 10 to 19 cigarettes per day, respectively. Among current smokers, 92.0% smoked for less than 10 years while 7.6% and 0.4% of current smokers smoked for 10 to 19 years and more than 20 years, respectively.

Population characteristics by smoking status are presented in Table 1. After adjusting for age, current smokers had a significantly higher body mass index (P for trend = 0.0056), higher consumption of alcohol drinking (P for trend <.0001), and higher

prevalence of diabetes (P for trend = 0.0060) than nonsmokers.

During 23 years of follow up (5,191,823 person-years), 2,786 (90 fatal) IHD cases (53/100,000 person year), stroke cases 2,368 (126 fatal) (45.4/100,000 person year), and 6,368 ASCVD cases (306 fatal) (122.7/100,000 person year) occurred

The independent effects of smoking on IHD, stroke, and ASCVD were analyzed controlling for confounding factors through Cox proportional hazards models, as shown in Table 2. The hazard ratios (HR) relating to IHD for current smokers were 1.5 (P <.0001), and those of ex-smokers were 1.0 (P=0.8567). The HR of stroke was 1.4 (P <.0001) for current smokers and 1.1 (P = 0.5008) on ex-smokers.

Compared to nonsmokers, the HR for any ASCVD event was 1.4 (P < 0.0001) in current smokers and 1.1 in ex-smokers (P = 0.1406). Figure 2 shows the survival probability by smoking history (never, former, 1-9, 10-19, ≥20 cigarette per day among current smokers) and the corresponding unadjusted association with ASCVD. The overall results demonstrated that smoking among young men increased the risk for ASCVD relative to nonsmokers. After adjusting for age and traditional ASCVD risk factors, the HRs for IHD and stroke were estimated for groups classified by amount of smoking (A and B in Figure 3) and duration of smoking (C and D in Figure 3). For IHD and stroke, the risk of events increased linearly with higher amount of cigarette per day (P for trend, <.0001 and <.0001, respectively) and longer duration of smoking (P for trend, <.0001 and <.0001, respectively).

To examine whether serum total cholesterol levels could modify the effect of smoking on ASCVD, we divided the cohort participants into quartile of total cholesterol. The

risks above were also found throughout the range of serum levels of cholesterol demonstrating that serum total cholesterol levels did not modify the effect of smoking on ASCVD (Figure 4).

Estimated risk factor prevalence in current studies of smoking and other additional risk factors were used to estimate the PARs for IHD alone, stroke alone and total ASVCD (Table 3). For IHD, current smoking accounts for about 24.9% of events, and hypertension accounts for 8.1% of events. In the case of stroke, smoking was estimated to account for 20.9%, whilst hypertension was estimated to be responsible for 13.3% of stroke cases.

DISCUSSION

Our study investigated the association between smoking and risk of ASCVD among Korean young men within a cohort study with a 23 year of follow-up. To our knowledge, this is the first study focusing on Korean young adults. In our study, smoking was the most crucial risk factor attributing to 20% of ASCVD mortality in middle age.

Diabetes, hypertension, and hyperlipidemia are well known risk factors for ASCVD[10]. However, for young adults with relatively low incidence of diabetes, hypertension and hyperlipidemia, smoking is the most important and an independent risk factor for predicting ASCVD in the present study. Furthermore, the high smoking rate among young people is important with respect to the development of middle-aged hypertension and transition to ASCVD.[19-20] Thus, middle-aged ASCVD morbidity is likely

predominantly predicted by smoking in young adulthood.

The body of research centered upon the health effects of smoking is steadily increasing, with findings reported from many countries around the world. However, few studies have examined the effect of smoking on ASCVD in young adults.[21] Here, we present evidence that current smoking is an independent risk factor affecting the incidence of IHD, stroke and ASCVD.

These risk associations have been estimated across total serum cholesterol groups. A cohort study in Hasayama Japan found that smoking showed positive association with coronary heart disease in people with high levels of serum cholesterol above 180 mg / dl, but not with people with low level of cholesterol less than 180 mg / dl.[22-23] Afterward, six epidemiological studies were conducted. Among them, one study from Puerto Rico Heart Health Program[24] showed similar results, but not all.[7-11] Of course, all studies were conducted among adult populations. To the best of our knowledge, no study has been done on young adults with much lower levels of serum cholesterol. In addition, the high smoking rate among young adults is likely to be, even directly, linked to high blood pressure among the adult population who developed ASCVD as a major health problem.

In our analysis, there was no observed increase in risk of IHD or stroke among ex-smokers. That is, the risk of ASCVD in ex-smokers was similar with that of never smokers. These findings suggest that the risk of IHD lasts for an unknown period, while the high risk for ASCVD decreases after smoking cessation. In this study, the risk of ASCVD in ex-smokers was not significant. These findings can be interpreted in two

ways. First, it can be an effect on quitting smoking. Second, even if young people aged 20-29 quit smoking, they did not have a long period of life-time cigarette smoking, which obviously did not have to do with the increased risk of heart disease. It is the part that needs to be studied further. Previous studies shown that reducing adult smoking pays more immediate dividends, both in terms of health improvements and cost savings.[25] In particular, most of the excess risk of vascular mortality due to smoking in women may be eliminated rapidly upon cessation and within 20 years for lung diseases.[26] Although it is too late smoking cessation, cancer diagnosis itself may cause smoking cessation.[27]

There are several studies regarding cardiovascular risk among young people. According to a study conducted by Bernaards et al.,[28] blood pressure and waist circumference were decreased by lowering weekly tobacco consumption in younger participants. However, they did not report the risk of developing cardiovascular disease events due to changes in smoking. This seems to be another significant topic relating to the health of young adults. Another study conducted by Morotti et al.[21] on young women with polycystic ovary syndrome (PCOS) reported an association between smoking habitude in lean PCOS patients, and the increase of soft markers of cardiovascular risk. For young adult African Americans, the association between cigarette smoking and carotid intima assuming the genetic variation of smokers was reported and the -930$^{A/G}$ polymorphism modified the association among young healthy adults.[29] The study on association between second hand smoking among childhood and cardiovascular event in adulthood was conducted and found that the carotid plaque risk in adulthood is increased in children whose parents had smoked.[30-31]

This LCHS study has several strengths, such as high follow-up rates and a large, national sample. The large sample size of cohort allowed us to investigate the association of smoking with various levels of serum cholesterol. The civil servants and private school teachers who participated in this study accounted for about 11% of the total population in 1992. We did not compare the characteristics of the 89% population not included in the study. Therefore, this study will not represent the whole population. Moreover, selection bias may be a potential issue, since the final sample contains a subset of over 118,531 young male adults (38.6%) out of 307,041 subjects initially selected for our study. We therefore urge conservative interpretations of our study results with regard to the general population.

In conclusion, smoking is a leading cause of ASCVD among young adults in Korea, a country with a low total cholesterol level and a high smoking rate. Moreover, the association was not modified by total cholesterol level. Smoking among Korean young adult men was independently associated with increased risk of IHD, stroke and ASCVD. The concentration of cholesterol in Korean men did not modify the effect of smoking on ASCVD. Therefore, smoking cessation on young adult smokers is essential to prevent CVD later in adult life. Moreover, clinical practice guidelines and policies should emphasize to treat nicotine addiction in young smokers.

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Contributors: Data analysis was undertaken by YJ and KJJ. The article was drafted by YJ. SL, JHB, SHJ, and SC substantially contributed to the conception or design of the work, revising the work, approved the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interests: None to declare.

Ethics approval: The study proposal obtained an approval by the Institutional Review Board of Human Research, Yonsei University (4-2001-0029).

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data are available.

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Figure legends

Figure 1. Timeline for data collection in the Korean Life Course Health Study

Figure 2. Survival of atherosclerotic cardiovascular disease event by smoking history in Korean young adult men, 1992-2015

Figure 3. Hazard ratios with 95% confidence intervals for from ischemic heart disease, and stroke by cigarette per day and duration of smoking

Figure 4. Hazard ratios with 95% confidence intervals for ischemic heart disease and stroke by total cholesterol groups of smokers compared with nonsmokers: Each group of total cholesterol levels are as follows: first, 149 mg/dl; second, 150-169 mg/dL; third, 170-194 mg/dL; fourth, ≥195 mg/dL. The reference group is non-smokers in each quartile of total cholesterol.

Table 1. Baseline Characteristics of the Korean Life Course Health Study, 1992-1994, According to Smoking Status*

Characteristic	Nonsmokers (n=24,950)	Ex-smokers (n=15,126)	No. of cigarettes per day among current smokers			
			1-9 (n=22,642)	10-19 (n=35,690)	≥20 (n=20,123)	*P* for Trend¶
Age, year	26.6 (2.1)	26.9 (1.9)	26.6 (2.0)	26.8 (1.9)	26.8 (1.9)	0.1622
Systolic Blood Pressure, mmHg	120.4 (11.6)	120.0 (11.8)	119.8 (11.6)	120.1 (11.6)	120.3 (11.6)	0.2558
Diastolic Blood Pressure mmHg	78.0 (9.0)	77.7 (9.1)	77.5 (9.0)	77.8 (9.0)	78.0 (9.0)	0.1122
Total cholesterol, mg/dL	173.4 (32.9)	173.4 (32.6)	172.9 (33.1)	174.5 (33.4)	177.2 (34.4)	0.9543
Body mass index, kg/m^2	22.3 (2.4)	22.4 (2.4)	22.3 (2.4)	22.5 (2.5)	22.9 (2.6)	0.0056
Fasting serum glucose, mg/dL	86.7 (13.3)	86.6 (13.5)	86.2 (14.1)	86.4 (14.1)	86.6 (15.3)	0.4821
Alcohol consumption, g per day	7.3 (17.7)	9.7 (19.7)	12.2 (22.6)	14.5 (25.1)	20.4 (36.1)	<.0001
Conditions, %						
Hypertension†	15.7	15.1	14.5	15.6	15.7	0.7987
Hypercholesterolemia‡	3.4	3.3	3.3	3.9	4.7	0.0743
Diabetes§	0.7	0.8	0.9	0.9	1.0	0.0060
Alcohol use‖	61.2	81.3	88.2	88.3	86.9	0.1035
Physical activity	24.9	26.8	22.9	17.5	13.0	<.0001

*Data are expressed as means (SD) unless otherwise indicated; †Systolic blood pressure of at least 140 mmHg and/or diastolic blood pressure of at least

90 mmHg; ‡Total cholesterol level of at least 6.21 mmol/L (240 mg/dL); § Fasting serum glucose value of at least 6.99 mmol/L (126 mg/L); ‖Consumption of Soju which is a colorless distilled beverage of Korean origin; ¶Testing for trend across nonsmokers and current smokers; ex-smokers were excluded.

Table 2. Risk of Morbidity from Ischemic Heart Disease, Cerebrovascular Disease, and Atherosclerotic Cardiovascular Disease in Korean Men in the Korean Life Course Health Study, 1992-2015*

	Ischemic Heart Disease		Cerebrovascular Disease		Atherosclerotic Cardiovascular Disease	
Variables and Categories	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (5-year age group)	1.4 (1.2 – 1.6)	<.0001	1.4 (1.3 – 1.6)	<.0001	1.3 (1.2 – 1.4)	<.0001
Cigarette smoking						
Ex-smoker	1.0 (0.9 – 1.2)	0.8567	1.1 (0.9 – 1.3)	0.5008	1.1 (1.0 – 1.2)	0.1406
Current smoker	1.5 (1.3 – 1.6)	<.0001	1.4 (1.2 – 1.6)	<.0001	1.4 (1.3 – 1.5)	<.0001
Blood Pressure†						
High normal	1.2 (1.1 – 1.4)	<.0001	1.2 (1.0 – 1.3)	0.0152	1.2 (1.1 – 1.3)	<.0001
Stage 1 hypertension	1.6 (1.4 – 1.8)	<.0001	1.7 (1.5 – 2.0)	<.0001	1.7 (1.5 – 1.8)	<.0001
Stage 2 hypertension	2.0 (1.6 – 2.5)	<.0001	3.2 (2.5 – 4.0)	<.0001	2.9 (2.5 – 3.3)	<.0001
Total cholesterol‡						
Borderline-high cholesterol	1.4 (1.3 – 1.6)	<.0001	1.4 (1.3 – 1.6)	<.0001	1.4 (1.3 – 1.5)	<.0001
High cholesterol	2.5 (2.1 – 2.8)	<.0001	1.7 (1.4 – 2.1)	<.0001	2.1 (1.8 – 2.3)	<.0001
Fasting blood sugar§						
Diabetes	1.3 (0.9 – 1.9)	0.1375	1.6 (1.1 – 2.3)	0.0222	1.5 (1.2 – 1.9)	0.0008
Physical activity						
No exercise	1.1 (1.0 – 1.3)	0.0122	1.1 (1.0 – 1.3)	0.2156	1.1 (1.0 – 1.3)	0.0075

*Hazard ratio (HRs) and 95% confidence intervals (CIs) from multivariable Cox proportional hazards models. †The reference category is normal (systolic

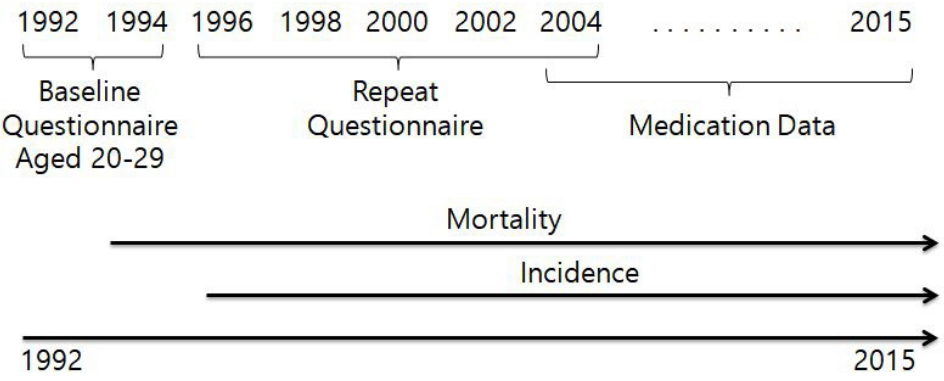
blood pressure<140 mmHg and diastolic blood pressure<90mm Hg). ‡ The reference category is desirable (serum cholesterol level, < 5.17 mmol/L [200 mg/dL]). §The reference category is a fasting serum glucose level of less than 6.99 mmol/L (126 mg/dL).

Table 3. Population Attributable Risks (PARs) and 95% Confidence Intervals (CIs) From Smoking and Other Risk Factors of Ischemic Heart Disease, Cerebrovascular Disease, and Atherosclerotic Cardiovascular Disease in Korean Men: The Korean Life Course Health Study

Variables and Categories	Prevalence	Ischemic Heart Disease	Cerebrovascular Disease	Atherosclerotic Cardiovascular Disease
	%	PAR (95% CI)	PAR (95% CI)	PAR (95% CI)
Smoking				
Current smoker	66.2	24.9 (16.6 – 28.4)	20.9 (11.7 -28.4)	20.9 (16.5 – 24.9)
Blood Pressure*				
Hypertension	22.0	8.1 (6.2 – 9.9)	13.3 (9.9 – 14.9)	9.9 (9.9 – 11.7)
Total cholesterol†				
Borderline	16.6	6.2 (4.7 – 9.1)	6.2 (4.7 – 7.7)	6.2 (4.7 – 7.6)
High	3.8	5.4 (4.0 – 6.4)	4.0 (2.9 – 4.7)	4.0 (2.9 – 4.7)
Fasting blood sugar‡				
Diabetes	0.9	0.3 (-0.9 – 0.8)	0.5 (0.08 – 1.1)	0.4 (0.2 – 0.8)
Physical activity				
No exercise	0.8	7.4 (0 – 19.3)	7.4 (0 – 19.3)	7.4 (0 – 19.3)

*The reference category is normal (systolic blood pressure < 140 mmHg and diastolic blood pressure < 90mm Hg). †The reference category is desirable (serum cholesterol level < 5.17 mmol/L [200 mg/dL]). ‡ The reference category is a fasting serum glucose level of less than 6.99 mmol/L (126 mg/dL).

Figure 1



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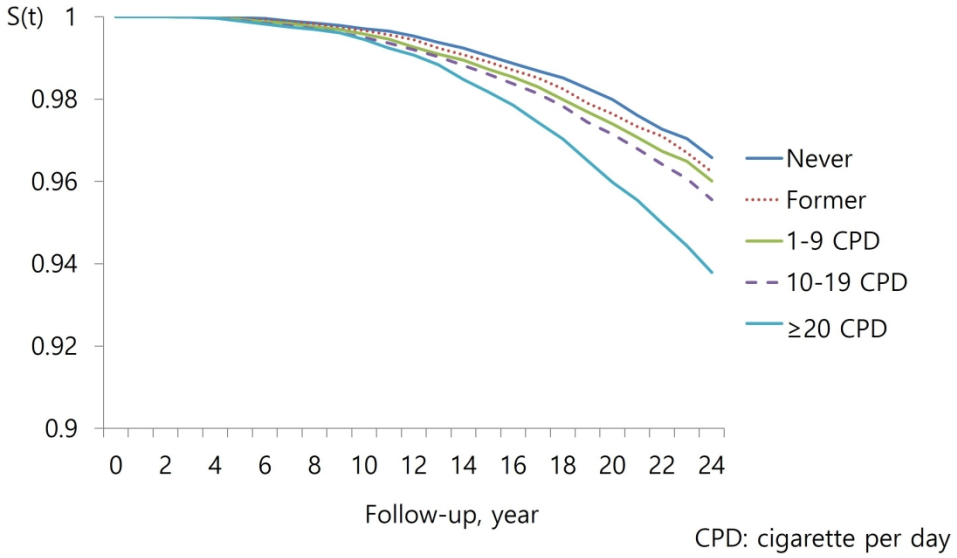

Figure 2

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Figure 3.

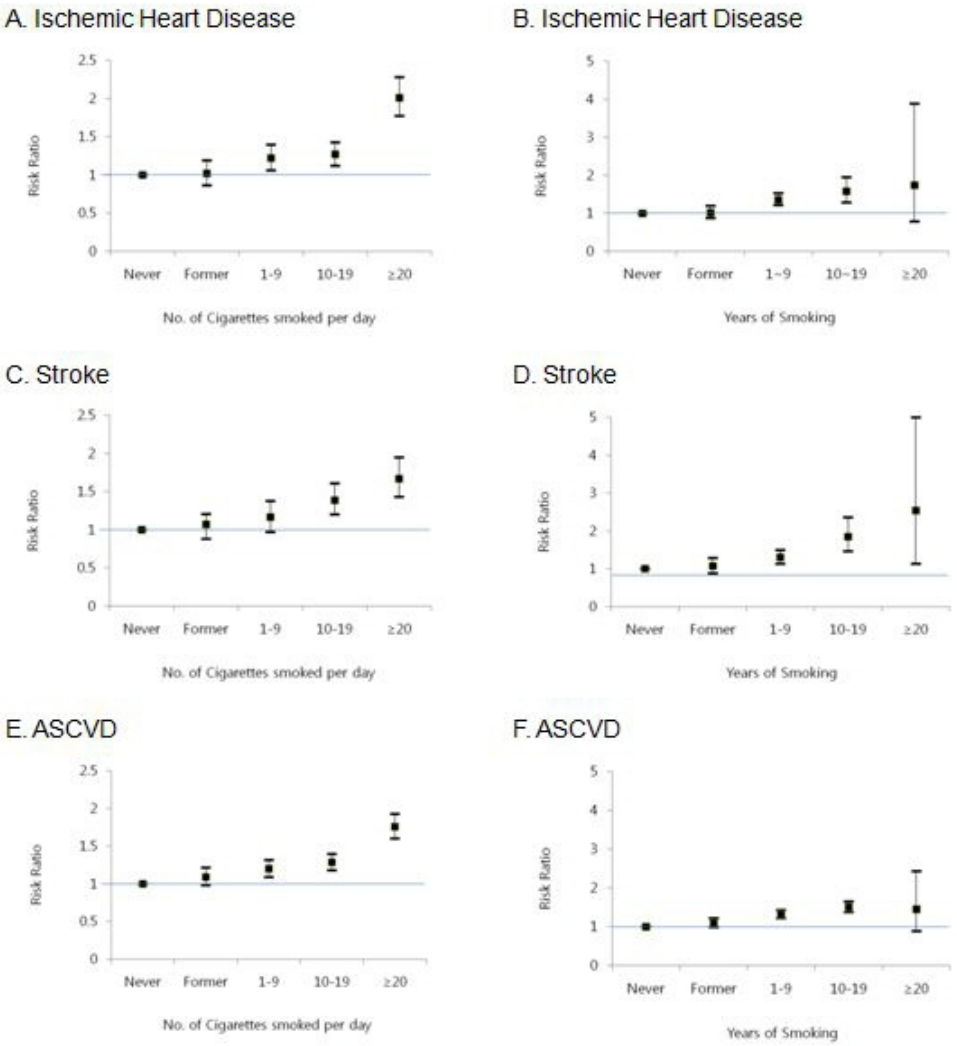

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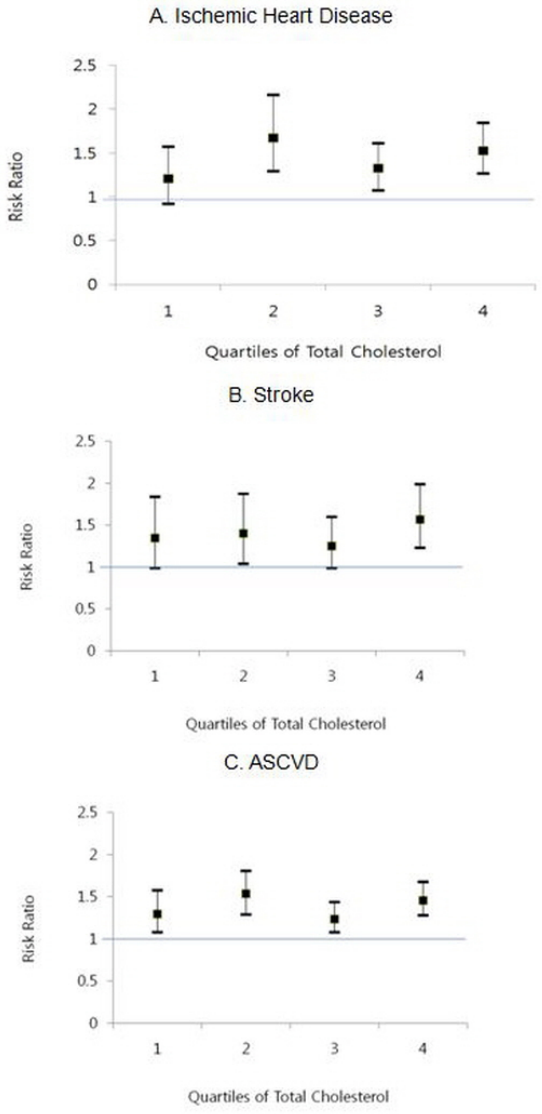
Figure 4.



46x94mm (300 x 300 DPI)

Title: smoking is the first leading cause of cardiovascular disease in young men.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract page 3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found page 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported page 5
Objectives	3	State specific objectives, including any prespecified hypotheses page 6, para 1.
Methods		
Study design	4	Present key elements of study design early in the paper page 6, para 2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection page 6-7.
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up page 6, page 8
		(b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable page 7, para 3, page 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group page 6, page 7
Bias	9	Describe any efforts to address potential sources of bias page 14.
Study size	10	Explain how the study size was arrived at page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why page 8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding page 8
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) If applicable, explain how loss to follow-up was addressed page 8
		(e) Describe any sensitivity analyses page 9-10
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed page 10
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram page 7. (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders page 10
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount) page 10 (23 years of follow-up)
Outcome data	15*	Report numbers of outcome events or summary measures over time page 10.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included page 10, para 1 (Table 2)
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses page 11 (Figure 4)
Discussion		
Key results	18	Summarise key results with reference to study objectives page 12 para 2
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias page 14, para 2.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence page 14
Generalisability	21	Discuss the generalisability (external validity) of the study results page 14
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based page 15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Smoking and Atherosclerotic Cardiovascular Disease Risk in Young Men: The Korean Life Course Health Study

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Smoking and Atherosclerotic Cardiovascular Disease Risk in Young Men: The Korean Life Course Health Study

Yongho Jee, MPH[1,2], Keum Ji Jung, PhD[2,4], Sunmi Lee, PhD[3], Joung Hwan Back, PhD[3], Sun Ha Jee, PhD[2,4*], Sung-il Cho, MD, PhD[1*]

[1] Department of Public Health, Seoul National University, Seoul, Republic of Korea

[2] Institute for Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Republic of Korea

[3] Health Insurance Policy Research Institute, Wonju, Republic of Korea

[4] Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Republic of Korea

Running title: Smoking is the first leading cause of Cardiovascular Disease

*These last authors contributed equally to this work

*Corresponding authors. Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Republic of Korea.

E-mail address: jsunha@yuhs.ac (S.H. Jee).

Department of Public Health, Seoul National University, Seoul, Republic of Korea

E-mail address: scho@snu.ac.kr (S.I. Cho).

These two authors equally contributed as corresponding author.

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Table 3, Figure 4

Abstract

Objective: To examine the effect of smoking on risk of atherosclerotic cardiovascular disease (ASCVD) in Korean young men and to examine whether serum total cholesterol levels could modify the effect of smoking on ASCVD.

Design: A prospective cohort study within a national insurance system.

Setting: Health screenings provided by national insurance in 1992 and 1994.

Participants: 118,531 young men between 20 and 29 years of age and were followed up for 23 years.

Outcome measure: To assess the independent effects of smoking on the risk of Ischemic Heart Disease (IHD), stroke, and ASCVD, Cox proportional hazards regression models were used, controlling for age, hypertension, diabetes, hypercholesterolemia, and alcohol drinking.

Results: The total number of current smokers was 78,455 (66.2%), and 94,113 (79.7%) of the sample recorded a total cholesterol level < 200 mg/dl measured at baseline. Between 1993 and 2015, 2,786 cases of IHD (53/100,000 person year), 2,368 cases of stroke (45.4/100,000 person year), and 6,368 ASCVD (122.7/100,000 person year) occurred. The risk of IHD, stroke, and total ASCVD events was found to increase for current smokers, with a hazard ratios (HR) with 95% Confidence Interval (CI) of 1.5 (95% CI: 1.3,1.6), 1.4 (95% CI: 1.2,1.6), and 1.4 (95% CI: 1.3,1.5), respectively. Further, the risks above were also found throughout the range of serum levels of cholesterol.

Conclusions: Smoking among Korean young adult men was independently associated with increased risk of IHD, stroke and ASCVD. The concentration of cholesterol in Korean men did not modify the effect of smoking on ASCVD.

Keywords: Smoking, Cardiovascular Disease, Young adults

Strengths and limitations of this study

- Novel result from Korean young adults is that smoking is the first leading cause of Cardiovascular Disease (CVD) while smoking is the second leading cause of CVD in middle aged adults.
- The large sample size of cohort with 118,531 young men between 20 and 29 years of age and were followed up for 23 years.
- The limitations of this study include possible measurement errors and the non-random sample used.

INTRODUCTION

Atherosclerotic cardiovascular diseases (ASCVD) are the leading cause of death globally, with more people dying from ASCVD than any other causes of death annually. A total of 17.7 million people died as a result of ASCVDs in 2015 globally, comprising 31% of all deaths. Of these deaths, 7.4 million are estimated to have been the result of coronary heart disease, whilst 6.7 million were due to stroke[1]. According to previous studies published in the western countries, tobacco use has been reported to be a major risk factor for ASCVD following hypertension.[1]

A growing concern is that for young adults, cigarette smoking may be the first leading cause of ASCVD, owing to the high prevalence of cigarette smoking in comparison to lower levels of alternate risk factors, including hypertension, diabetes, and high cholesterol levels. However, despite these observations, there remain only a small number of studies considering the relationship between smoking and ASCVD in Korea and other countries in East Asia. [2-5]

Further, comparisons with Western populations may be less informative owing to the relatively lower levels of cholesterol commonly present in Asian countries. Biological studies have explored the interaction between smoking and serum cholesterol levels.[6-9] Nevertheless, very few studies have analyzed the interaction effects of smoking and serum cholesterol on ASCVD in young adults

'World No Tobacco Day 2018' is a campaign, with the primary objective of raising awareness of the link between tobacco use and negative health outcomes, predominantly heart and other cardiovascular diseases (CVD) including stroke. It will

also seek to expand the range of potential strategies key public actors such as governmental and public bodies can take to reduce the health risks of tobacco use. If there is an established link between tobacco smoking in young adults and CVD, the campaign will further increase awareness on smoking in young adults. The government and the public can then subsequently take actions to reduce risks of smoking at earlier stage. Unfortunately, however, the association between smoking and CVD in young adults has not received much attention because at least a long term (over 20 years) follow-up study is needed. This serves as motivation for this study, in which we aimed to examine the effect of smoking on risk of ASCVD in Korean young adults with relatively low serum cholesterol levels. We also investigated whether the effect of smoking can be modified by serum levels of cholesterol.

METHOD

Study participants

In Korea, the Korean Medical Insurance Corporation (KMIC) provided health insurance for private school staff and civil servants prior to the current insurance system, under which it was integrated as National Health Insurance.[2] A total of 4,862,438 (10.7%) of the Korean population were covered by KMIC insurance, of which 1,297,833 were employees, and 3,364,605 were dependents. All insured participants are required to participate in a biennial health checkup.[2] Approximately 94% of the insured participants in 1992 and 1994 were examined biennially. We established a prospective cohort for participants (aged 20-29) who routinely responded to the questionnaire on disease risk

factors and chronic diseases, naming this study the Korean Life Course Health Study (KLCHS). The KLCHS cohort included 307,041 Koreans (142,461 males, 164,580 females) who were screened by KMIC in 1992 and 1994. Of these participants, 205,840 (67.0%) were registered in 1992 and 101,201 (33.0%) were registered in 1994.

Of these 307,041 participants, 71,760 (23.4%) who had incomplete data height, blood pressure, fasting glucose, total cholesterol, or body mass index were excluded. We also excluded 6,170 people from our analysis who reported a past history of cancer and ASCVD, as well as 2,091 people who had missing information on smoking, exercise, or alcohol drinking, and 65 people who died before start of follow-up. Female participants were excluded, because of the low prevalence of smoking for females in Korea, resulting in a total of 118,531 eligible participants for the analysis. The study proposal obtained an approval by the Institutional Review Board of Human Research, Yonsei University (4-2001-0029). This study was a retrospective cohort using past routine laboratory data and did not receive consent.

Data collection

The biennial KMIC screening was provided at local hospitals by medical practitioners according to standard protocols. During the two-year interval examination from 1992 to 2008, we examined the variables related to the lifestyle of participants, such as daily smoking amount, duration of smoking, and variables related to drinking. From data collected at baseline, participants were defined as ‘current smokers’ if they were smoking currently, ‘never smokers’ if they had no prior history of smoking, and ‘ex-

smokers' if they had previously smoked but at the time of measurement did not smoke. Current smokers were further categorized by amount of cigarettes consumed on average per day (1–9, 10–19, and 20 or greater) as well as duration of smoking (1–9, 10–19, and 20 or more years) following the example of previous studies.[2,10,11]

The definition of hypertension was a systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg.[12] Body mass index (BMI) was measured as weight (kg) / height $(m)^2$. Serum total cholesterol was grouped as desirable (<200 mg/dl), borderline-high (200-239 mg/dl), and high (≥ 240 mg/dl).[13] Definition of diabetes was fasting blood glucose ≥ 126 mg / dl.[14]

Follow-up and outcomes

The main outcome variables used in the analysis were morbidity and mortality categorized by IHD, stroke, and ASCVD. For IHD, alone (ICD 10 codes, I20–I25), acute myocardial infarction (AMI) alone (I21), and angina pectoris (AP) alone (ICD 10 codes, I20) are used. For stroke, stroke alone (I60-I69) was used. Finally, with regard to ASCVD, we used total ASCVD, including disease of hypertensive (I10–I15), ischemic heart disease (I20–I25), all stroke (I60–I69), other heart disease (I44–I51), sudden death (R96), and other vascular disease (I70–I74).

The study outcomes were identified through diagnosis information recorded in hospital admission, and from causes of death using death certificates. The study follow-up was nearly 100% complete, as we were able to search ASCVD event data electronically by

KMIC registrants regarding the morbidity information of ASCVD. The period of follow-up was 23 years from January 1st, 1993 to December 31st, 2015. Data on causes of death were available during years 1993–2015, and incidence could be tracked during years 1995–2015. The time frames over which these outcomes could be assessed varied with data availability (Figure 1).

A validation study was conducted by 20 internists from the Korean Society of Cardiology in 2009.[15] For the participants who provided written permission for the use of their personal information, 673 CHD events between 1994 and 2007 were confirmed with individual hospital medical records, showing that 73% of designated myocardial infarctions were valid. The validation study was updated in 2013 with a value of 93%.[16] The validation study on mortality data has not been conducted.

Statistical analysis

First, we examined relationships between smoking status and established ASCVD risk factors at baseline. In considering continuous ASCVD risk factors, we used ordinary least squares regression and coded smoking quantity as an ordinal variable. In this study, the Mantel Haenszel method was applied for dichotomous variables.[17]

To assess the independent effects of smoking on the risk of IHD, stroke, and ASCVD, Cox proportional hazards models were used, controlling for age and the confounding variables such as hypertension, diabetes, high cholesterol, and alcohol drinking. The proportional assumption was also tested utilizing Schoenfeld residuals, and the survival curve according to smoking status was plotted using the life-table method. We used

Levins formula for calculating population attributable risk (PAR).[18] In additional analyses, we excluded all events that had occurred in the first 4 years of follow-up. These analyses ensured sensitivity in our results. In all analyses, a two-sided significance level of 0.05 was used.

Patient and Public Involvement

Patients and or public were not involved.

RESULTS

The average age of the study participants was 26.7 ± 2.0 (SD) years. Among the 118,531 men, 78,455 (66.2%) were current smokers, 15,126 (12.8%) were ex-smokers, and 92,403 (15.4%) had hypertension. For total cholesterol, 94,413 (79.7%) had a total serum cholesterol level < 200 mg/dL, 19,764 (16.6%) had a borderline level of 200-240 mg/dL, and 4,444 (3.8%) had a level of 240 mg/dL or higher. In terms of amount of smoking, 28.9% smoked more than 20 cigarettes per day while 45.5% and 25.6% of current smokers smoked 1 to 9 and 10 to 19 cigarettes per day, respectively. Among current smokers, 92.0% smoked for less than 10 years while 7.6% and 0.4% of current smokers smoked for 10 to 19 years and more than 20 years, respectively.

Population characteristics by smoking status are presented in Table 1. After adjusting for age, current smokers had a significantly higher body mass index (P for trend = 0.0056), higher consumption of alcohol drinking (P for trend <.0001), and higher prevalence of diabetes (P for trend = 0.0060) than nonsmokers.

During 23 years of follow up (5,191,823 person-years), 2,786 (90 fatal) IHD cases (53/100,000 person year), stroke cases 2,368 (126 fatal) (45.4/100,000 person year), and 6,368 ASCVD cases (306 fatal) (122.7/100,000 person year) occurred

The independent effects of smoking on IHD, stroke, and ASCVD were analyzed controlling for confounding factors through Cox proportional hazards models, as shown in Table 2. The hazard ratios (HR) relating to IHD for current smokers were 1.5 (P <.0001), and those of ex-smokers were 1.0 (P=0.8567). The HR of stroke was 1.4 (P <.0001) for current smokers and 1.1 (P = 0.5008) on ex-smokers.

Compared to nonsmokers, the HR for any ASCVD event was 1.4 (P < 0.0001) in current smokers and 1.1 in ex-smokers (P = 0.1406). Figure 2 shows the survival probability by smoking history (never, former, 1-9, 10-19, ≥ 20 cigarette per day among current smokers) and the corresponding unadjusted association with ASCVD. The overall results demonstrated that smoking among young men increased the risk for ASCVD relative to nonsmokers. After adjusting for age and traditional ASCVD risk factors, the HRs for IHD and stroke were estimated for groups classified by amount of smoking (A and B in Figure 3) and duration of smoking (C and D in Figure 3). For IHD and stroke, the risk of events increased linearly with higher amount of cigarette per day (P for trend, <.0001 and <.0001, respectively) and longer duration of smoking (P for trend, <.0001 and <.0001, respectively).

To examine whether serum total cholesterol levels could modify the effect of smoking on ASCVD, we divided the cohort participants into quartile of total cholesterol. The risks above were also found throughout the range of serum levels of cholesterol

demonstrating that serum total cholesterol levels did not modify the effect of smoking on ASCVD (Figure 4).

Estimated risk factor prevalence in current studies of smoking and other additional risk factors were used to estimate the PARs for IHD alone, stroke alone and total ASVCD (Table 3). For IHD, current smoking accounts for about 24.9% of events, and hypertension accounts for 8.1% of events. In the case of stroke, smoking was estimated to account for 20.9%, whilst hypertension was estimated to be responsible for 13.3% of stroke cases.

DISCUSSION

Our study investigated the association between smoking and risk of ASCVD among Korean young men within a cohort study with a 23 year of follow-up. To our knowledge, this is the first study focusing on Korean young adults. In our study, smoking was the most crucial risk factor attributing to 20% of ASCVD mortality in middle age.

Diabetes, hypertension, and hyperlipidemia are well known risk factors for ASCVD[10]. However, for young adults with relatively low incidence of diabetes, hypertension and hyperlipidemia, smoking is the most important and an independent risk factor for predicting ASCVD in the present study. Furthermore, the high smoking rate among young people is important with respect to the development of middle-aged hypertension and transition to ASCVD.[19-20] Thus, middle-aged ASCVD morbidity is likely predominantly predicted by smoking in young adulthood.

The body of research centered upon the health effects of smoking is steadily increasing, with findings reported from many countries around the world. However, few studies have examined the effect of smoking on ASCVD in young adults.[21] Here, we present evidence that current smoking is an independent risk factor affecting the incidence of IHD, stroke and ASCVD.

These risk associations have been estimated across total serum cholesterol groups. A cohort study in Hasayama Japan found that smoking showed positive association with coronary heart disease in people with high levels of serum cholesterol above 180 mg / dl, but not with people with low level of cholesterol less than 180 mg / dl.[22-23] Afterward, six epidemiological studies were conducted. Among them, one study from Puerto Rico Heart Health Program[24] showed similar results, but not all.[7-11] Of course, all studies were conducted among adult populations. To the best of our knowledge, no study has been done on young adults with much lower levels of serum cholesterol. In addition, the high smoking rate among young adults is likely to be, even directly, linked to high blood pressure among the adult population who developed ASCVD as a major health problem.

In this study, the non-significant risk of ASCVD among ex-smokers can be interpreted in two ways. First, this result may simply reflect the effect of smoking cessation. Most previous studies have shown that the effects of smoking cessation are immediate in CVD (most of the excess risk of vascular mortality due to smoking may be eliminated rapidly upon cessation), while lung cancer occurs within 20 years[25, 26]. In particular, most of the excess risk of vascular mortality due to smoking in women may be eliminated rapidly upon cessation and within 20 years for lung diseases.[26] Second, even if a number of young adult ex-smokers, aged 20-29 years, may have smoked continuously from adolescence, it is still a short term of smoking, compared to adults. Previous study shown that reducing adult smoking pays more immediate dividends, both in terms of health improvements and cost savings.[27] While present study lacks

information on smoking duration of ex-smokers, current smokers who continued to smoke seem to have increased risk of CVD by 40%. Therefore, while the smoking duration of ex-smokers is unknown, it may be reasonable to consider the results were mainly affected by the smoking cessation. Further research on the effects of smoking cessation among young adults is necessary.

There are several studies regarding cardiovascular risk among young people. According to a study conducted by Bernaards et al.,[28] blood pressure and waist circumference were decreased by lowering weekly tobacco consumption in younger participants. However, they did not report the risk of developing cardiovascular disease events due to changes in smoking. This seems to be another significant topic relating to the health of young adults. Another study conducted by Morotti et al.[21] on young women with polycystic ovary syndrome (PCOS) reported an association between smoking habitude in lean PCOS patients, and the increase of soft markers of cardiovascular risk. For young adult African Americans, the association between cigarette smoking and carotid intima assuming the genetic variation of smokers was reported and the -930$^{A/G}$ polymorphism modified the association among young healthy adults.[29] The study on association between second hand smoking among childhood and cardiovascular event in adulthood was conducted and found that the carotid plaque risk in adulthood is increased in children whose parents had smoked.[30-31]

This LCHS study has several strengths, such as high follow-up rates and a large, national sample. The large sample size of cohort allowed us to investigate the association of smoking with various levels of serum cholesterol. The civil servants and private school teachers who participated in this study accounted for about 11% of the total population in 1992. We did not compare the characteristics of the 89% population not included in the study. Therefore, this study will not represent the whole population.

Moreover, selection bias may be a potential issue, since the final sample contains a subset of over 118,531 young male adults (38.6%) out of 307,041 subjects initially selected for our study. We therefore urge conservative interpretations of our study results with regard to the general population.

In conclusion, smoking is a leading cause of ASCVD among young adults in Korea, a country with a low total cholesterol level and a high smoking rate. Moreover, the association was not modified by total cholesterol level. Smoking among Korean young adult men was independently associated with increased risk of IHD, stroke and ASCVD. The concentration of cholesterol in Korean men did not modify the effect of smoking on ASCVD. Therefore, smoking cessation on young adult smokers is essential to prevent CVD later in adult life. Moreover, clinical practice guidelines and policies should emphasize to treat nicotine addiction in young smokers.

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or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interests: None declared

Ethics approval: The study proposal obtained an approval by the Institutional Review Board of Human Research, Yonsei University (4-2001-0029).

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Data sharing statement: No additional data are available.

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Figure legends

Figure 1. Timeline for data collection in the Korean Life Course Health Study

Figure 2. Survival of atherosclerotic cardiovascular disease event by smoking history in Korean young adult men, 1992-2015

Figure 3. Hazard ratios with 95% confidence intervals for from ischemic heart disease,

and stroke by cigarette per day and duration of smoking

Figure 4. Hazard ratios with 95% confidence intervals for ischemic heart disease and stroke by total cholesterol groups of smokers compared with nonsmokers: Each group of total cholesterol levels are as follows: first, 149 mg/dl; second, 150-169 mg/dL; third, 170-194 mg/dL; fourth, ≥195 mg/dL. The reference group is non-smokers in each quartile of total cholesterol.

Table 1. Baseline Characteristics of the Korean Life Course Health Study, 1992-1994, According to Smoking Status*

Characteristic	Nonsmokers (n=24,950)	Ex-smokers (n=15,126)	No. of cigarettes per day among current smokers			
			1-9 (n=22,642)	10-19 (n=35,690)	≥20 (n=20,123)	*P* for Trend¶
Age, year	26.6 (2.1)	26.9 (1.9)	26.6 (2.0)	26.8 (1.9)	26.8 (1.9)	0.1622
Systolic Blood Pressure, mmHg	120.4 (11.6)	120.0 (11.8)	119.8 (11.6)	120.1 (11.6)	120.3 (11.6)	0.2558
Diastolic Blood Pressure mmHg	78.0 (9.0)	77.7 (9.1)	77.5 (9.0)	77.8 (9.0)	78.0 (9.0)	0.1122
Total cholesterol, mg/dL	173.4 (32.9)	173.4 (32.6)	172.9 (33.1)	174.5 (33.4)	177.2 (34.4)	0.9543
Body mass index, kg/m^2	22.3 (2.4)	22.4 (2.4)	22.3 (2.4)	22.5 (2.5)	22.9 (2.6)	0.0056
Fasting serum glucose, mg/dL	86.7 (13.3)	86.6 (13.5)	86.2 (14.1)	86.4 (14.1)	86.6 (15.3)	0.4821
Alcohol consumption, g per day	7.3 (17.7)	9.7 (19.7)	12.2 (22.6)	14.5 (25.1)	20.4 (36.1)	<.0001
Conditions, %						
Hypertension†	15.7	15.1	14.5	15.6	15.7	0.7987
Hypercholesterolemia‡	3.4	3.3	3.3	3.9	4.7	0.0743
Diabetes§	0.7	0.8	0.9	0.9	1.0	0.0060
Alcohol use‖	61.2	81.3	88.2	88.3	86.9	0.1035
Physical activity	24.9	26.8	22.9	17.5	13.0	<.0001

*Data are expressed as means (SD) unless otherwise indicated; †Systolic blood pressure of at least 140 mmHg and/or diastolic blood pressure of at least

90 mmHg; ‡Total cholesterol level of at least 6.21 mmol/L (240 mg/dL); § Fasting serum glucose value of at least 6.99 mmol/L (126 mg/L); ‖Consumption of Soju which is a colorless distilled beverage of Korean origin; ¶Testing for trend across nonsmokers and current smokers; ex-smokers were excluded.

Table 2. Risk of Morbidity from Ischemic Heart Disease, Cerebrovascular Disease, and Atherosclerotic Cardiovascular Disease in Korean Men in the Korean Life Course Health Study, 1992-2015*

	Ischemic Heart Disease		Cerebrovascular Disease		Atherosclerotic Cardiovascular Disease	
Variables and Categories	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (5-year age group)	1.4 (1.2 – 1.6)	<.0001	1.4 (1.3 – 1.6)	<.0001	1.3 (1.2 – 1.4)	<.0001
Cigarette smoking						
Ex-smoker	1.0 (0.9 – 1.2)	0.8567	1.1 (0.9 – 1.3)	0.5008	1.1 (1.0 – 1.2)	0.1406
Current smoker	1.5 (1.3 – 1.6)	<.0001	1.4 (1.2 – 1.6)	<.0001	1.4 (1.3 – 1.5)	<.0001
Blood Pressure†						
High normal	1.2 (1.1 – 1.4)	<.0001	1.2 (1.0 – 1.3)	0.0152	1.2 (1.1 – 1.3)	<.0001
Stage 1 hypertension	1.6 (1.4 – 1.8)	<.0001	1.7 (1.5 – 2.0)	<.0001	1.7 (1.5 – 1.8)	<.0001
Stage 2 hypertension	2.0 (1.6 – 2.5)	<.0001	3.2 (2.5 – 4.0)	<.0001	2.9 (2.5 – 3.3)	<.0001
Total cholesterol‡						
Borderline-high cholesterol	1.4 (1.3 – 1.6)	<.0001	1.4 (1.3 – 1.6)	<.0001	1.4 (1.3 – 1.5)	<.0001
High cholesterol	2.5 (2.1 – 2.8)	<.0001	1.7 (1.4 – 2.1)	<.0001	2.1 (1.8 – 2.3)	<.0001
Fasting blood sugar§						
Diabetes	1.3 (0.9 – 1.9)	0.1375	1.6 (1.1 – 2.3)	0.0222	1.5 (1.2 – 1.9)	0.0008
Physical activity						
No exercise	1.1 (1.0 – 1.3)	0.0122	1.1 (1.0 – 1.3)	0.2156	1.1 (1.0 – 1.3)	0.0075

*Hazard ratio (HRs) and 95% confidence intervals (CIs) from multivariable Cox proportional hazards models. †The reference category is normal (systolic

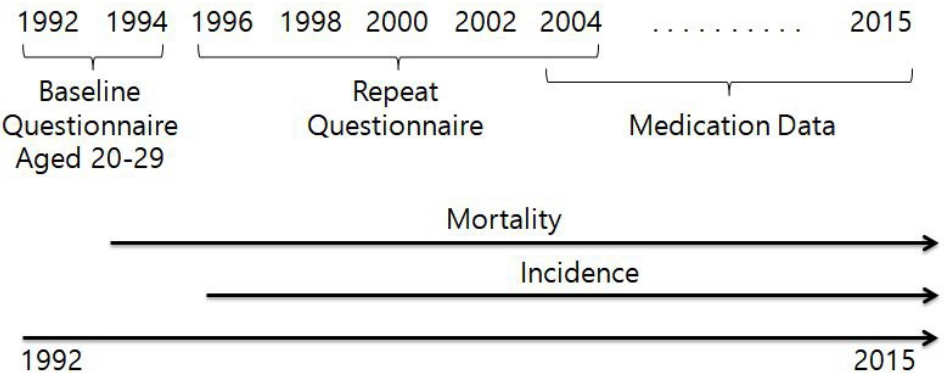
blood pressure<140 mmHg and diastolic blood pressure<90mm Hg). ‡ The reference category is desirable (serum cholesterol level, < 5.17 mmol/L [200 mg/dL]). §The reference category is a fasting serum glucose level of less than 6.99 mmol/L (126 mg/dL).

Table 3. Population Attributable Risks (PARs) and 95% Confidence Intervals (CIs) From Smoking and Other Risk Factors of Ischemic Heart Disease, Cerebrovascular Disease, and Atherosclerotic Cardiovascular Disease in Korean Men: The Korean Life Course Health Study

Variables and Categories	Prevalence	Ischemic Heart Disease	Cerebrovascular Disease	Atherosclerotic Cardiovascular Disease
	%	PAR (95% CI)	PAR (95% CI)	PAR (95% CI)
Smoking				
Current smoker	66.2	24.9 (16.6 – 28.4)	20.9 (11.7 -28.4)	20.9 (16.5 – 24.9)
Blood Pressure*				
Hypertension	22.0	8.1 (6.2 – 9.9)	13.3 (9.9 – 14.9)	9.9 (9.9 – 11.7)
Total cholesterol†				
Borderline	16.6	6.2 (4.7 – 9.1)	6.2 (4.7 – 7.7)	6.2 (4.7 – 7.6)
High	3.8	5.4 (4.0 – 6.4)	4.0 (2.9 – 4.7)	4.0 (2.9 – 4.7)
Fasting blood sugar‡				
Diabetes	0.9	0.3 (-0.9 – 0.8)	0.5 (0.08 – 1.1)	0.4 (0.2 – 0.8)
Physical activity				
No exercise	0.8	7.4 (0 – 19.3)	7.4 (0 – 19.3)	7.4 (0 – 19.3)

*The reference category is normal (systolic blood pressure < 140 mmHg and diastolic blood pressure < 90mm Hg). †The reference category is desirable (serum cholesterol level < 5.17 mmol/L [200 mg/dL]). ‡ The reference category is a fasting serum glucose level of less than 6.99 mmol/L (126 mg/dL).

Figure 1



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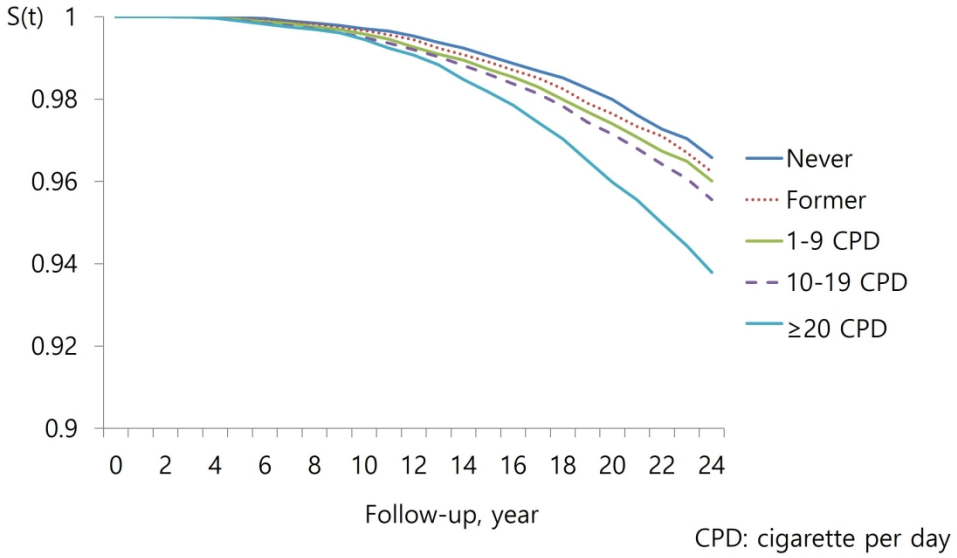

Figure 2

254x190mm (300 x 300 DPI)

Figure 3.

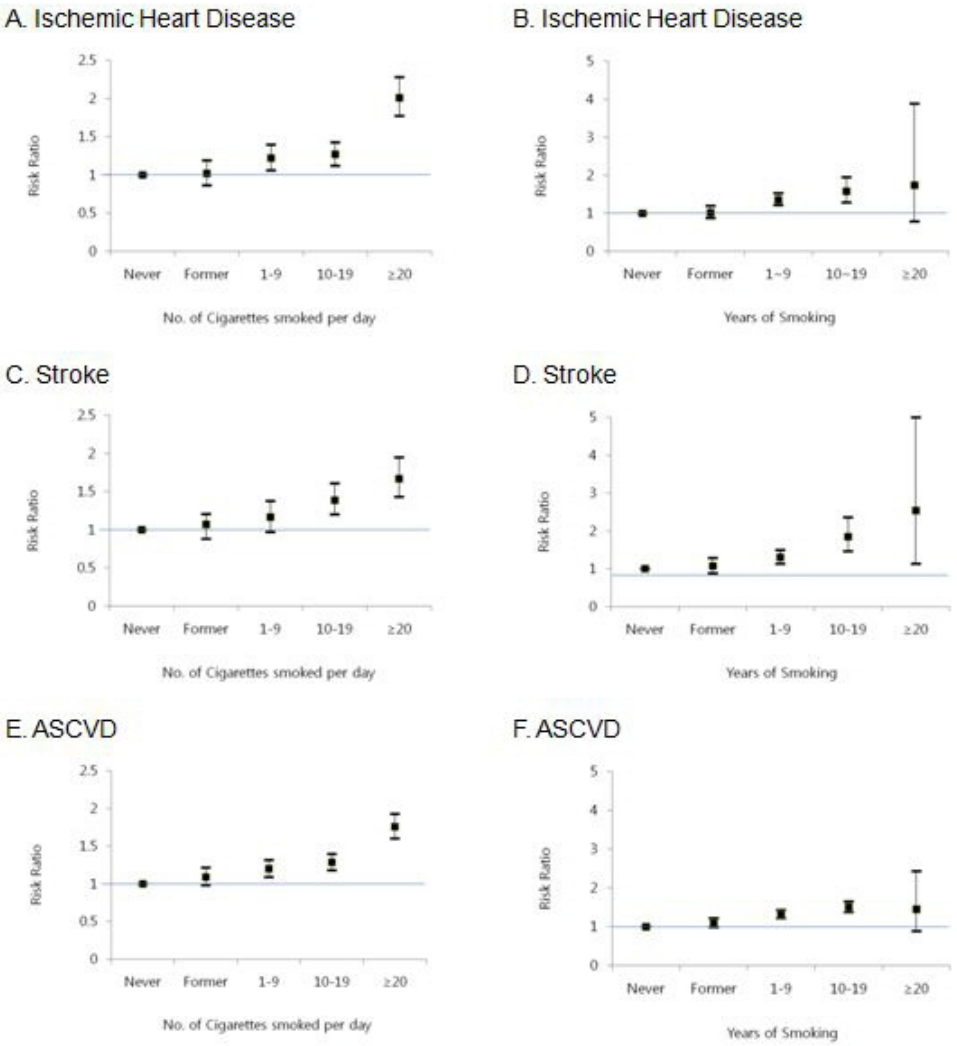

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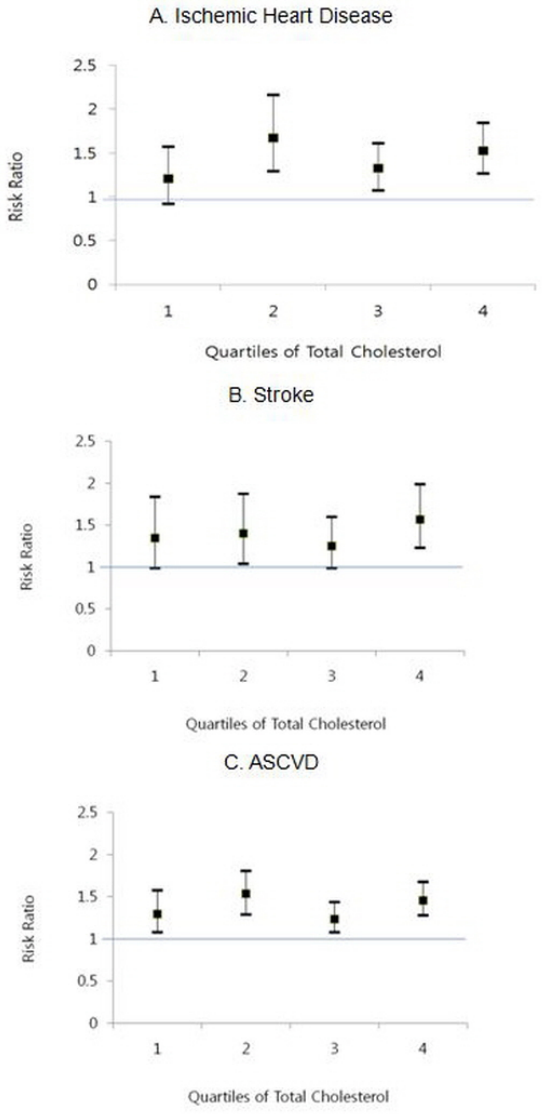
Figure 4.



46x94mm (300 x 300 DPI)

Title: smoking is the first leading cause of cardiovascular disease in young men.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract page 3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found page 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported page 5
Objectives	3	State specific objectives, including any prespecified hypotheses page 6, para 1.
Methods		
Study design	4	Present key elements of study design early in the paper page 6, para 2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection page 6-7.
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up page 6, page 8
		(b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable page 7, para 3, page 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group page 6, page 7
Bias	9	Describe any efforts to address potential sources of bias page 14.
Study size	10	Explain how the study size was arrived at page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why page 8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding page 8
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) If applicable, explain how loss to follow-up was addressed page 8
		(e) Describe any sensitivity analyses page 9-10
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed page 10
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram page 7. (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders page 10
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount) page 10 (23 years of follow-up)
Outcome data	15*	Report numbers of outcome events or summary measures over time page 10.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included page 10, para 1 (Table 2)
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses page 11 (Figure 4)
Discussion		
Key results	18	Summarise key results with reference to study objectives page 12 para 2
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias page 14, para 2.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence page 14
Generalisability	21	Discuss the generalisability (external validity) of the study results page 14
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based page 15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Complete List of Authors:	Jee, Yongho; Seoul National University, Department of Public Health Jung, Keum Ji; Yonsei University Graduate School Institute for Health Promotion, Dept. of Public Health Lee, Sunmi; National Health Insurance Service, Health Insurance Policy Research Institute Back, Joung Hwan; Health Insurance Policy Research Institute Jee, Sun Ha; Graduate School of Public Health, Yonsei University, Epidemiology Cho, Sung-il ; Seoul National University, Department of Public Health
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Smoking and Atherosclerotic Cardiovascular Disease Risk in Young Men: The Korean Life Course Health Study

Yongho Jee, MPH[1,2], Keum Ji Jung, PhD[2,4], Sunmi Lee, PhD[3], Joung Hwan Back, PhD[3], Sun Ha Jee, PhD[2,4*], Sung-il Cho, MD, PhD[1*]

[1] Department of Public Health Science, Graduate School of Public Health, Seoul National University, Seoul, Republic of Korea

[2] Institute for Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Republic of Korea

[3] Health Insurance Policy Research Institute, Wonju, Republic of Korea

[4] Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Republic of Korea

Running title: Smoking and Atherosclerotic Cardiovascular Disease

*These last authors contributed equally to this work

*Corresponding authors.
Department of Public Health Science, Graduate School of Public Health, Seoul National University, Seoul, Republic of Korea

E-mail address: scho@snu.ac.kr (S.I. Cho).

Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Republic of Korea.

E-mail address: jsunha@yuhs.ac (S.H. Jee).

These two authors equally contributed as corresponding author.

Word count: 3,048

Table 3, Figure 4

Abstract

Objective: To examine the effect of smoking on risk of atherosclerotic cardiovascular disease (ASCVD) in Korean young men and to examine whether serum total cholesterol levels could modify the effect of smoking on ASCVD.

Design: A prospective cohort study within a national insurance system.

Setting: Health screenings provided by national insurance in 1992 and 1994.

Participants: 118,531 young men between 20 and 29 years of age and were followed up for an average of 23 years.

Outcome measure: To assess the independent effects of smoking on the risk of Ischemic Heart Disease (IHD), stroke, and ASCVD, Cox proportional hazards regression models were used, controlling for age, hypertension, diabetes, hypercholesterolemia, and alcohol drinking.

Results: The total number of current smokers was 78,455 (66.2%), and 94,113 (79.7%) of the sample recorded a total cholesterol level < 200 mg/dl measured at baseline. Between 1993 and 2015, 2,786 cases of IHD (53/100,000 person year), 2,368 cases of stroke (45.4/100,000 person year), and 6,368 ASCVD (122.7/100,000 person year) occurred. The risk of IHD, stroke, and total ASCVD events was found to increase for current smokers, with a hazard ratios (HR) with 95% Confidence Interval (CI) of 1.5 (95% CI: 1.3,1.6), 1.4 (95% CI: 1.2,1.6), and 1.4 (95% CI: 1.3,1.5), respectively. Further, the risks above were also found throughout the range of serum levels of cholesterol.

Conclusions: Smoking among Korean young adult men was independently associated with increased risk of IHD, stroke and ASCVD. The concentration of cholesterol in Korean men did not modify the effect of smoking on ASCVD.

Keywords: Smoking, Cardiovascular Disease, Young adults

Strengths and limitations of this study

- Novel result from Korean young adults is that smoking is the first leading cause of Cardiovascular Disease (CVD) while smoking is the second leading cause of CVD in middle aged adults.
- The large sample size of cohort with 118,531 young men between 20 and 29 years of age and were followed up for an average of 23 years.
- The limitations of this study include possible measurement errors and the non-random sample used.

INTRODUCTION

Atherosclerotic cardiovascular diseases (ASCVD) are the leading cause of death globally, with more people dying from ASCVD than any other causes of death annually. A total of 17.7 million people died as a result of ASCVDs in 2015 globally, comprising 31% of all deaths. Of these deaths, 7.4 million are estimated to have been the result of coronary heart disease, whilst 6.7 million were due to stroke[1]. According to previous studies published in the western countries, tobacco use has been reported to be a major risk factor for ASCVD following hypertension.[1]

A growing concern is that for young adults, cigarette smoking may be the first leading cause of ASCVD, owing to the high prevalence of cigarette smoking in comparison to lower levels of alternate risk factors, including hypertension, diabetes, and high cholesterol levels. However, despite these observations, there remain only a small number of studies considering the relationship between smoking and ASCVD in Korea and other countries in East Asia. [2-5]

Further, comparisons with Western populations may be less informative owing to the relatively lower levels of cholesterol commonly present in Asian countries. Biological studies have explored the interaction between smoking and serum cholesterol levels.[6-9] Nevertheless, very few studies have analyzed the interaction effects of smoking and serum cholesterol on ASCVD in young adults

'World No Tobacco Day 2018' is a campaign, with the primary objective of raising awareness of the link between tobacco use and negative health outcomes, predominantly heart and other cardiovascular diseases (CVD) including stroke. It will

also seek to expand the range of potential strategies key public actors such as governmental and public bodies can take to reduce the health risks of tobacco use. If there is an established link between tobacco smoking in young adults and CVD, the campaign will further increase awareness on smoking in young adults. The government and the public can then subsequently take actions to reduce risks of smoking at earlier stage. Unfortunately, however, the association between smoking and CVD in young adults has not received much attention because at least a long term (over 20 years) follow-up study is needed. This serves as motivation for this study, in which we aimed to examine the effect of smoking on risk of ASCVD in Korean young adults with relatively low serum cholesterol levels. We also investigated whether the effect of smoking can be modified by serum levels of cholesterol.

METHOD

Study participants

In Korea, the Korean Medical Insurance Corporation (KMIC) provided health insurance for private school staff and civil servants prior to the current insurance system, under which it was integrated as National Health Insurance.[2] A total of 4,862,438 (10.7%) of the Korean population were covered by KMIC insurance, of which 1,297,833 were employees, and 3,364,605 were dependents. All insured participants are required to participate in a biennial health checkup.[2] Approximately 94% of the insured participants in 1992 and 1994 were examined biennially. We established a prospective cohort for participants (aged 20-29) who routinely responded to the questionnaire on disease risk

factors and chronic diseases, naming this study the Korean Life Course Health Study (KLCHS). The KLCHS cohort included 307,041 Koreans (142,461 males, 164,580 females) who were screened by KMIC in 1992 and 1994. Of these participants, 205,840 (67.0%) were registered in 1992 and 101,201 (33.0%) were registered in 1994.

Of these 307,041 participants, 71,760 (23.4%) who had incomplete data height, blood pressure, fasting glucose, total cholesterol, or body mass index were excluded. We also excluded 6,170 people from our analysis who reported a past history of cancer and ASCVD, as well as 2,091 people who had missing information on smoking, exercise, or alcohol drinking, and 65 people who died before start of follow-up. Female participants were excluded, because of the low prevalence of smoking for females in Korea, resulting in a total of 118,531 eligible participants for the analysis. The study proposal obtained an approval by the Institutional Review Board of Human Research, Yonsei University (4-2001-0029) and the Seoul National University (E1812/001-010). This study was a retrospective cohort using past routine laboratory data and did not receive consent.

Data collection

The biennial KMIC screening was provided at local hospitals by medical practitioners according to standard protocols. During the two-year interval examination from 1992 to 2008, we examined the variables related to the lifestyle of participants, such as daily smoking amount, duration of smoking, and variables related to drinking. From data collected at baseline, participants were defined as ‘current smokers’ if they were

smoking currently, 'never smokers' if they had no prior history of smoking, and 'ex-smokers' if they had previously smoked but at the time of measurement did not smoke. Current smokers were further categorized by amount of cigarettes consumed on average per day (1–9, 10–19, and 20 or greater) as well as duration of smoking (1–9, 10–19, and 20 or more years) following the example of previous studies.[2,10,11]

The definition of hypertension was a systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg.[12] Body mass index (BMI) was measured as weight (kg) / height $(m)^2$. Serum total cholesterol was grouped as desirable (<200 mg/dl), borderline-high (200-239 mg/dl), and high (≥ 240 mg/dl).[13] Definition of diabetes was fasting blood glucose ≥ 126 mg / dl.[14]

Follow-up and outcomes

The main outcome variables used in the analysis were morbidity and mortality categorized by IHD, stroke, and ASCVD. For IHD, alone (ICD 10 codes, I20–I25), acute myocardial infarction (AMI) alone (I21), and angina pectoris (AP) alone (ICD 10 codes, I20) are used. For stroke, stroke alone (I60-I69) was used. Finally, with regard to ASCVD, we used total ASCVD, including disease of hypertensive (I10–I15), ischemic heart disease (I20–I25), all stroke (I60–I69), other heart disease (I44–I51), sudden death (R96), and other vascular disease (I70–I74).

The study outcomes were identified through diagnosis information recorded in hospital admission, and from causes of death using death certificates. The study follow-up was

nearly 100% complete, as we were able to search ASCVD event data electronically by KMIC registrants regarding the morbidity information of ASCVD. The period of follow-up was 23 years from January 1st, 1993 to December 31st, 2015. Data on causes of death were available during years 1993–2015, and incidence could be tracked during years 1995–2015. The time frames over which these outcomes could be assessed varied with data availability (Figure 1).

A validation study was conducted by 20 internists from the Korean Society of Cardiology in 2009.[15] For the participants who provided written permission for the use of their personal information, 673 CHD events between 1994 and 2007 were confirmed with individual hospital medical records, showing that 73% of designated myocardial infarctions were valid. The validation study was updated in 2013 with a value of 93%.[16] The validation study on mortality data has not been conducted.

Statistical analysis

First, we examined relationships between smoking status and established ASCVD risk factors at baseline. In considering continuous ASCVD risk factors, we used ordinary least squares regression and coded smoking quantity as an ordinal variable. In this study, the Mantel Haenszel method was applied for dichotomous variables.[17]

To assess the independent effects of smoking on the risk of IHD, stroke, and ASCVD, Cox proportional hazards models were used, controlling for age and the confounding variables such as hypertension, diabetes, high cholesterol, and alcohol drinking. The proportional assumption was also tested utilizing Schoenfeld residuals, and the survival

curve according to smoking status was plotted using the life-table method. We used Levins formula for calculating population attributable risk (PAR).[18] In additional analyses, we excluded all events that had occurred in the first 4 years of follow-up. These analyses ensured sensitivity in our results. In all analyses, a two-sided significance level of 0.05 was used.

Patient and Public Involvement

Patients and or public were not involved.

RESULTS

The average age of the study participants was 26.7 ± 2.0 (SD) years. Among the 118,531 men, 78,455 (66.2%) were current smokers, 15,126 (12.8%) were ex-smokers, and 92,403 (15.4) had hypertension. For total cholesterol, 94,413 (79.7%) had a total serum cholesterol level < 200 mg/dL, 19,764 (16.6%) had a borderline level of 200-240 mg/dL, and 4,444 (3.8%) had a level of 240 mg/dL or higher. In terms of amount of smoking, 28.9% smoked more than 20 cigarettes per day while 45.5% and 25.6% of current smokers smoked 1 to 9 and 10 to 19 cigarettes per day, respectively. Among current smokers, 92.0% smoked for less than 10 years while 7.6% and 0.4% of current smokers smoked for 10 to 19 years and more than 20 years, respectively.

Population characteristics by smoking status are presented in Table 1. After adjusting for age, current smokers had a significantly higher body mass index (P for trend =

0.0056), higher consumption of alcohol drinking (P for trend <.0001), and higher prevalence of diabetes (P for trend = 0.0060) than nonsmokers.

The mean length of follow-up was 23 years, for a total of 5,191,823 person-years. During this period, 2,786 (90 fatal) IHD cases (53/100,000 person year), stroke cases 2,368 (126 fatal) (45.4/100,000 person year), and 6,368 ASCVD cases (306 fatal) (122.7/100,000 person year) occurred

The independent effects of smoking on IHD, stroke, and ASCVD were analyzed controlling for confounding factors through Cox proportional hazards models, as shown in Table 2. The hazard ratios (HR) relating to IHD for current smokers were 1.5 (P <.0001), and those of ex-smokers were 1.0 (P=0.8567). The HR of stroke was 1.4 (P <.0001) for current smokers and 1.1 (P = 0.5008) on ex-smokers.

Compared to nonsmokers, the HR for any ASCVD event was 1.4 (P < 0.0001) in current smokers and 1.1 in ex-smokers (P = 0.1406). Figure 2 shows the survival probability by smoking history (never, former, 1-9, 10-19, ≥ 20 cigarette per day among current smokers) and the corresponding unadjusted association with ASCVD. The overall results demonstrated that smoking among young men increased the risk for ASCVD relative to nonsmokers. After adjusting for age and traditional ASCVD risk factors, the HRs for IHD and stroke were estimated for groups classified by amount of smoking (A and B in Figure 3) and duration of smoking (C and D in Figure 3). For IHD and stroke, the risk of events increased linearly with higher amount of cigarette per day (P for trend, <.0001 and <.0001, respectively) and longer duration of smoking (P for trend, <.0001 and <.0001, respectively).

To examine whether serum total cholesterol levels could modify the effect of smoking on ASCVD, we divided the cohort participants into quartile of total cholesterol. The risks above were also found throughout the range of serum levels of cholesterol demonstrating that serum total cholesterol levels did not modify the effect of smoking on ASCVD (Figure 4).

Estimated risk factor prevalence in current studies of smoking and other additional risk factors were used to estimate the PARs for IHD alone, stroke alone and total ASVCD (Table 3). For IHD, current smoking accounts for about 24.9% of events, and hypertension accounts for 8.1% of events. In the case of stroke, smoking was estimated to account for 20.9%, whilst hypertension was estimated to be responsible for 13.3% of stroke cases.

DISCUSSION

Our study investigated the association between smoking and risk of ASCVD among Korean young men within a cohort study with a 23 year of follow-up. To our knowledge, this is the first study focusing on Korean young adults. In our study, smoking was the most crucial risk factor attributing to 20% of ASCVD mortality in middle age.

Diabetes, hypertension, and hyperlipidemia are well known risk factors for ASCVD[10]. However, for young adults with relatively low incidence of diabetes, hypertension and hyperlipidemia, smoking is the most important and an independent risk factor for predicting ASCVD in the present study. Furthermore, the high smoking rate among

young people is important with respect to the development of middle-aged hypertension and transition to ASCVD.[19-20] Thus, middle-aged ASCVD morbidity is likely predominantly predicted by smoking in young adulthood.

The body of research centered upon the health effects of smoking is steadily increasing, with findings reported from many countries around the world. However, few studies have examined the effect of smoking on ASCVD in young adults.[21] Here, we present evidence that current smoking is an independent risk factor affecting the incidence of IHD, stroke and ASCVD.

These risk associations have been estimated across total serum cholesterol groups. A cohort study in Hasayama Japan found that smoking showed positive association with coronary heart disease in people with high levels of serum cholesterol above 180 mg / dl, but not with people with low level of cholesterol less than 180 mg / dl.[22-23] Afterward, six epidemiological studies were conducted. Among them, one study from Puerto Rico Heart Health Program[24] showed similar results, but not all.[7-11] Of course, all studies were conducted among adult populations. To the best of our knowledge, no study has been done on young adults with much lower levels of serum cholesterol. In addition, the high smoking rate among young adults is likely to be, even directly, linked to high blood pressure among the adult population who developed ASCVD as a major health problem.

In this study, the non-significant risk of ASCVD among ex-smokers can be interpreted in two ways. First, this result may simply reflect the effect of smoking cessation. Most previous studies have shown that the effects of smoking cessation are immediate in CVD (most of the excess risk of vascular mortality due to smoking may be eliminated rapidly upon cessation), while lung cancer occurs within 20 years[25, 26]. In particular, most of the excess risk of vascular mortality due to smoking in women may be

eliminated rapidly upon cessation and within 20 years for lung diseases.[26] Second, even if a number of young adult ex-smokers, aged 20-29 years, may have smoked continuously from adolescence, it is still a short term of smoking, compared to adults. Previous study shown that reducing adult smoking pays more immediate dividends, both in terms of health improvements and cost savings.[27] While present study lacks information on smoking duration of ex-smokers, current smokers who continued to smoke seem to have increased risk of CVD by 40%. Therefore, while the smoking duration of ex-smokers is unknown, it may be reasonable to consider the results were mainly affected by the smoking cessation. Further research on the effects of smoking cessation among young adults is necessary.

There are several studies regarding cardiovascular risk among young people. According to a study conducted by Bernaards et al.,[28] blood pressure and waist circumference were decreased by lowering weekly tobacco consumption in younger participants. However, they did not report the risk of developing cardiovascular disease events due to changes in smoking. This seems to be another significant topic relating to the health of young adults. Another study conducted by Morotti et al.[21] on young women with polycystic ovary syndrome (PCOS) reported an association between smoking habitude in lean PCOS patients, and the increase of soft markers of cardiovascular risk. For young adult African Americans, the association between cigarette smoking and carotid intima assuming the genetic variation of smokers was reported and the -930$^{A/G}$ polymorphism modified the association among young healthy adults.[29] The study on association between second hand smoking among childhood and cardiovascular event in adulthood was conducted and found that the carotid plaque risk in adulthood is increased in children whose parents had smoked.[30-31]

This LCHS study has several strengths, such as high follow-up rates and a large, national sample. The large sample size of cohort allowed us to investigate the association of smoking with various levels of serum cholesterol. The civil servants and

private school teachers who participated in this study accounted for about 11% of the total population in 1992. We did not compare the characteristics of the 89% population not included in the study. Therefore, this study will not represent the whole population. Moreover, selection bias may be a potential issue, since the final sample contains a subset of over 118,531 young male adults (38.6%) out of 307,041 subjects initially selected for our study. We therefore urge conservative interpretations of our study results with regard to the general population.

In conclusion, smoking is a leading cause of ASCVD among young adults in Korea, a country with a low total cholesterol level and a high smoking rate. Moreover, the association was not modified by total cholesterol level. Smoking among Korean young adult men was independently associated with increased risk of IHD, stroke and ASCVD. The concentration of cholesterol in Korean men did not modify the effect of smoking on ASCVD. Therefore, smoking cessation on young adult smokers is essential to prevent CVD later in adult life. Moreover, clinical practice guidelines and policies should emphasize to treat nicotine addiction in young smokers.

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accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interests: None declared

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Figure legends

Figure 1. Timeline for data collection in the Korean Life Course Health Study

Figure 2. Survival of atherosclerotic cardiovascular disease event by smoking history in Korean young adult men, 1992-2015

Figure 3. Hazard ratios with 95% confidence intervals for from ischemic heart disease, and stroke by cigarette per day and duration of smoking

Figure 4. Hazard ratios with 95% confidence intervals for ischemic heart disease and stroke by total cholesterol groups of smokers compared with nonsmokers: Each group of total cholesterol levels are as follows: first, 149 mg/dl; second, 150-169 mg/dL; third, 170-194 mg/dL; fourth, ≥195 mg/dL. The reference group is non-smokers in each quartile of total cholesterol.

Table 1. Baseline Characteristics of the Korean Life Course Health Study, 1992-1994, According to Smoking Status*

Characteristic	Nonsmokers (n=24,950)	Ex-smokers (n=15,126)	No. of cigarettes per day among current smokers			
			1-9 (n=22,642)	10-19 (n=35,690)	≥20 (n=20,123)	*P* for Trend¶
Age, year	26.6 (2.1)	26.9 (1.9)	26.6 (2.0)	26.8 (1.9)	26.8 (1.9)	0.1622
Systolic Blood Pressure, mmHg	120.4 (11.6)	120.0 (11.8)	119.8 (11.6)	120.1 (11.6)	120.3 (11.6)	0.2558
Diastolic Blood Pressure mmHg	78.0 (9.0)	77.7 (9.1)	77.5 (9.0)	77.8 (9.0)	78.0 (9.0)	0.1122
Total cholesterol, mg/dL	173.4 (32.9)	173.4 (32.6)	172.9 (33.1)	174.5 (33.4)	177.2 (34.4)	0.9543
Body mass index, kg/m^2	22.3 (2.4)	22.4 (2.4)	22.3 (2.4)	22.5 (2.5)	22.9 (2.6)	0.0056
Fasting serum glucose, mg/dL	86.7 (13.3)	86.6 (13.5)	86.2 (14.1)	86.4 (14.1)	86.6 (15.3)	0.4821
Alcohol consumption, g per day	7.3 (17.7)	9.7 (19.7)	12.2 (22.6)	14.5 (25.1)	20.4 (36.1)	<.0001
Conditions, %						
Hypertension†	15.7	15.1	14.5	15.6	15.7	0.7987
Hypercholesterolemia‡	3.4	3.3	3.3	3.9	4.7	0.0743
Diabetes§	0.7	0.8	0.9	0.9	1.0	0.0060
Alcohol use‖	61.2	81.3	88.2	88.3	86.9	0.1035
Physical activity	24.9	26.8	22.9	17.5	13.0	<.0001

*Data are expressed as means (SD) unless otherwise indicated; †Systolic blood pressure of at least 140 mmHg and/or diastolic blood pressure of at least

90 mmHg; ‡Total cholesterol level of at least 6.21 mmol/L (240 mg/dL); § Fasting serum glucose value of at least 6.99 mmol/L (126 mg/L); ‖Consumption of Soju which is a colorless distilled beverage of Korean origin; ¶Testing for trend across nonsmokers and current smokers; ex-smokers were excluded.

Table 2. Risk of Morbidity from Ischemic Heart Disease, Cerebrovascular Disease, and Atherosclerotic Cardiovascular Disease in Korean Men in the Korean Life Course Health Study, 1992-2015*

	Ischemic Heart Disease		Cerebrovascular Disease		Atherosclerotic Cardiovascular Disease	
Variables and Categories	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (5-year age group)	1.4 (1.2 – 1.6)	<.0001	1.4 (1.3 – 1.6)	<.0001	1.3 (1.2 – 1.4)	<.0001
Cigarette smoking						
Ex-smoker	1.0 (0.9 – 1.2)	0.8567	1.1 (0.9 – 1.3)	0.5008	1.1 (1.0 – 1.2)	0.1406
Current smoker	1.5 (1.3 – 1.6)	<.0001	1.4 (1.2 – 1.6)	<.0001	1.4 (1.3 – 1.5)	<.0001
Blood Pressure†						
High normal	1.2 (1.1 – 1.4)	<.0001	1.2 (1.0 – 1.3)	0.0152	1.2 (1.1 – 1.3)	<.0001
Stage 1 hypertension	1.6 (1.4 – 1.8)	<.0001	1.7 (1.5 – 2.0)	<.0001	1.7 (1.5 – 1.8)	<.0001
Stage 2 hypertension	2.0 (1.6 – 2.5)	<.0001	3.2 (2.5 – 4.0)	<.0001	2.9 (2.5 – 3.3)	<.0001
Total cholesterol‡						
Borderline-high cholesterol	1.4 (1.3 – 1.6)	<.0001	1.4 (1.3 – 1.6)	<.0001	1.4 (1.3 – 1.5)	<.0001
High cholesterol	2.5 (2.1 – 2.8)	<.0001	1.7 (1.4 – 2.1)	<.0001	2.1 (1.8 – 2.3)	<.0001
Fasting blood sugar§						
Diabetes	1.3 (0.9 – 1.9)	0.1375	1.6 (1.1 – 2.3)	0.0222	1.5 (1.2 – 1.9)	0.0008
Physical activity						
No exercise	1.1 (1.0 – 1.3)	0.0122	1.1 (1.0 – 1.3)	0.2156	1.1 (1.0 – 1.3)	0.0075

*Hazard ratio (HRs) and 95% confidence intervals (CIs) from multivariable Cox proportional hazards models. †The reference category is normal (systolic

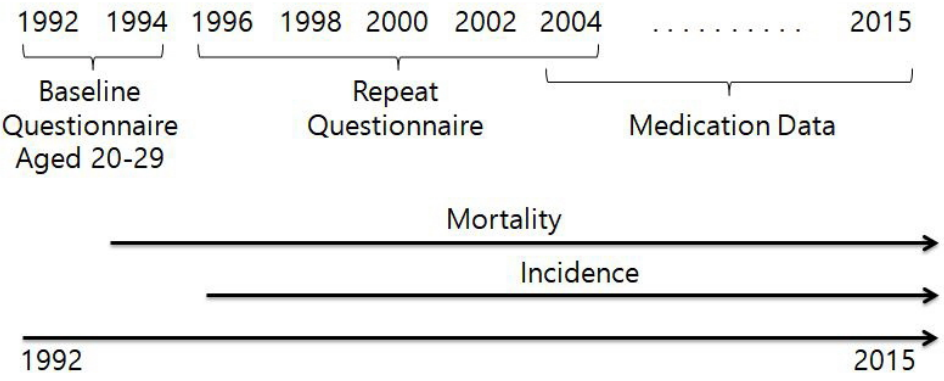
blood pressure<140 mmHg and diastolic blood pressure<90mm Hg). ‡ The reference category is desirable (serum cholesterol level, < 5.17 mmol/L [200 mg/dL]). §The reference category is a fasting serum glucose level of less than 6.99 mmol/L (126 mg/dL).

Table 3. Population Attributable Risks (PARs) and 95% Confidence Intervals (CIs) From Smoking and Other Risk Factors of Ischemic Heart Disease, Cerebrovascular Disease, and Atherosclerotic Cardiovascular Disease in Korean Men: The Korean Life Course Health Study

Variables and Categories	Prevalence	Ischemic Heart Disease	Cerebrovascular Disease	Atherosclerotic Cardiovascular Disease
	%	PAR (95% CI)	PAR (95% CI)	PAR (95% CI)
Smoking				
Current smoker	66.2	24.9 (16.6 – 28.4)	20.9 (11.7 -28.4)	20.9 (16.5 – 24.9)
Blood Pressure*				
Hypertension	22.0	8.1 (6.2 – 9.9)	13.3 (9.9 – 14.9)	9.9 (9.9 – 11.7)
Total cholesterol†				
Borderline	16.6	6.2 (4.7 – 9.1)	6.2 (4.7 – 7.7)	6.2 (4.7 – 7.6)
High	3.8	5.4 (4.0 – 6.4)	4.0 (2.9 – 4.7)	4.0 (2.9 – 4.7)
Fasting blood sugar‡				
Diabetes	0.9	0.3 (-0.9 – 0.8)	0.5 (0.08 – 1.1)	0.4 (0.2 – 0.8)
Physical activity				
No exercise	0.8	7.4 (0 – 19.3)	7.4 (0 – 19.3)	7.4 (0 – 19.3)

*The reference category is normal (systolic blood pressure < 140 mmHg and diastolic blood pressure < 90mm Hg). †The reference category is desirable (serum cholesterol level < 5.17 mmol/L [200 mg/dL]). ‡ The reference category is a fasting serum glucose level of less than 6.99 mmol/L (126 mg/dL).

Figure 1



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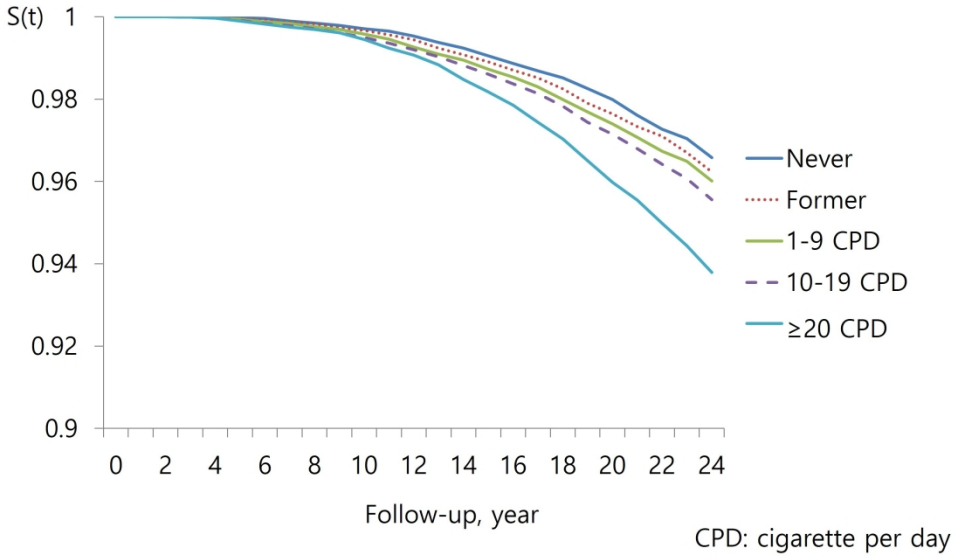

Figure 2

254x190mm (300 x 300 DPI)

Figure 3.

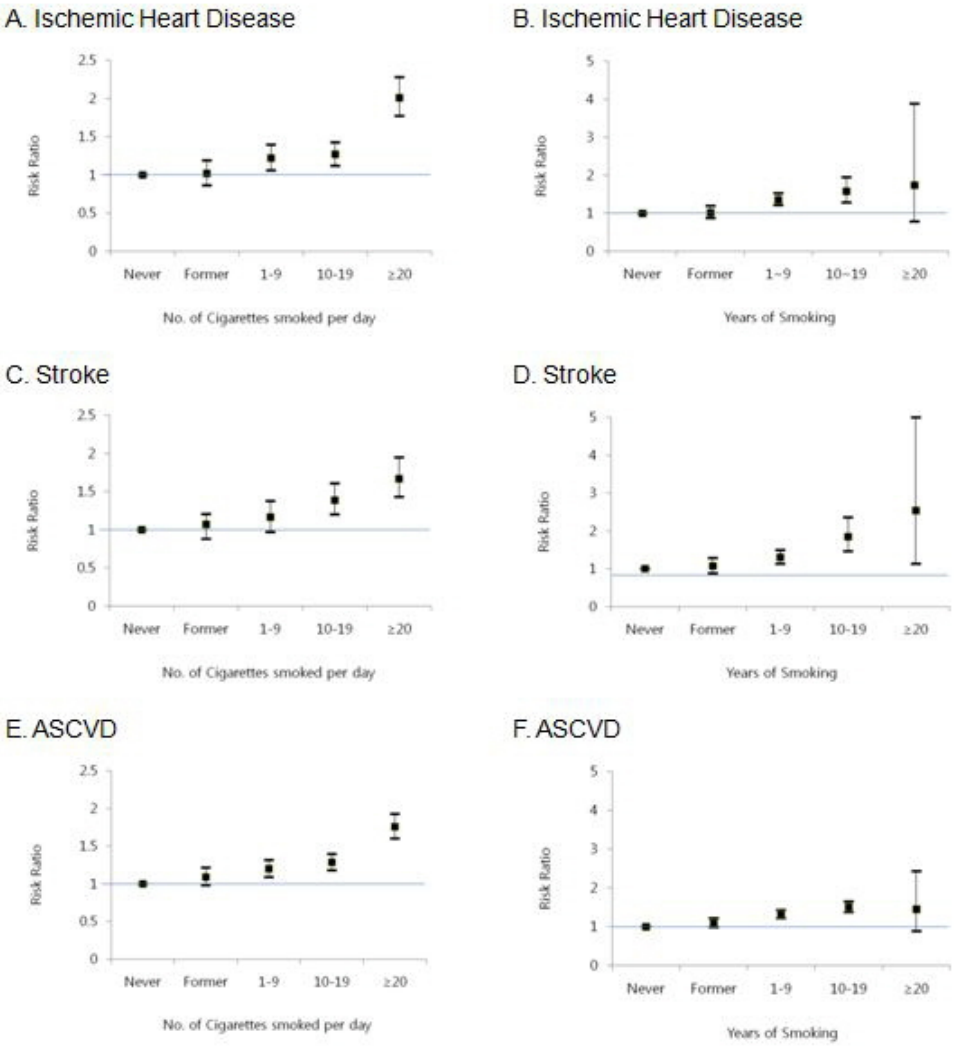

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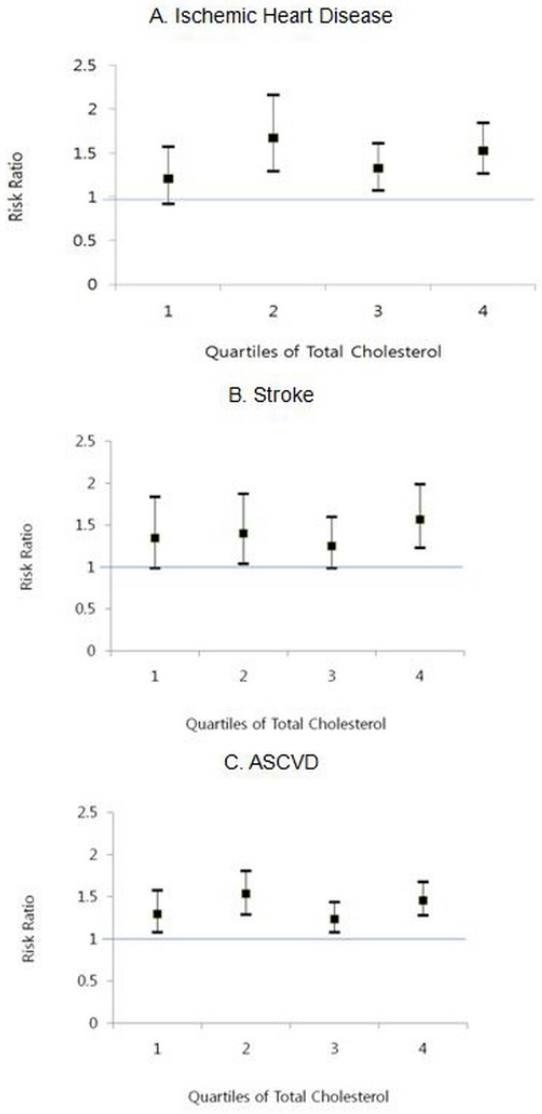
Figure 4.



46x94mm (300 x 300 DPI)

Title: smoking is the first leading cause of cardiovascular disease in young men.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract page 3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found page 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported page 5
Objectives	3	State specific objectives, including any prespecified hypotheses page 6, para 1.
Methods		
Study design	4	Present key elements of study design early in the paper page 6, para 2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection page 6-7.
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up page 6, page 8
		(b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable page 7, para 3, page 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group page 6, page 7
Bias	9	Describe any efforts to address potential sources of bias page 14.
Study size	10	Explain how the study size was arrived at page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why page 8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding page 8
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) If applicable, explain how loss to follow-up was addressed page 8
		(e) Describe any sensitivity analyses page 9-10
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed page 10
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram page 7. (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders page 10
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount) page 10 (23 years of follow-up)
Outcome data	15*	Report numbers of outcome events or summary measures over time page 10.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included page 10, para 1 (Table 2)
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses page 11 (Figure 4)
Discussion		
Key results	18	Summarise key results with reference to study objectives page 12 para 2
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias page 14, para 2.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence page 14
Generalisability	21	Discuss the generalisability (external validity) of the study results page 14
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based page 15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.