Smoking and Atherosclerotic Cardiovascular Disease in Men With Low Levels of Serum Cholesterol
The Korea Medical Insurance Corporation Study

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Context Few studies have examined the interactive effects of smoking and serum cholesterol level on morbidity and mortality from cardiovascular diseases. In East Asia, where the prevalence of smoking is among the highest in the world, morbidity and mortality from ischemic heart disease (IHD) is rapidly escalating.

Objectives To determine whether cigarette smoking is an independent risk factor for atherosclerotic cardiovascular disease (ASCVD) in the Republic of Korea (South Korea), a population that has relatively low levels of serum cholesterol, and to determine whether serum cholesterol levels modify the risk relationship between smoking and ASCVD.

Design Prospective cohort study with a follow-up period of 6 years (1993-1998).

Setting and Subjects A total of 106,745 Korean men aged 35 to 59 years who received health insurance from the Korea Medical Insurance Corporation and who had biennial medical evaluations in 1990 and 1992.

Main Outcome Measures Hospital admissions and deaths from IHD, cerebrovascular disease (CVD), and total ASCVD.

Results At baseline, 61,389 (58%) were current cigarette smokers and 64,482 (60%) had a total cholesterol level of less than 5.17 mmol/L (200 mg/dL). Between 1993 and 1998, 1,006 IHD events (176 per 100,000 person-years), 1,364 CVD events (238 per 100,000 person-years), and 716 other ASCVD events (125 per 100,000 person-years) occurred. In multivariate Cox proportional hazard models controlling for age, hypertension, hypercholesterolemia, and diabetes, current smoking increased the risk of IHD (risk ratio [RR], 2.2; 95% confidence interval [CI], 1.8-2.8), CVD (RR, 1.6; 95% CI, 1.4-1.8), and total ASCVD (RR, 1.6; 95% CI, 1.5-1.8). For each outcome, there were significant dose-response relationships with amount and duration of smoking. Throughout the range of serum cholesterol levels, current smoking significantly increased the risk of IHD and CVD. In the lowest quartile of serum cholesterol levels (<4.42 mmol/L [171 mg/dL]), the RR from current smoking was 3.3 (95% CI, 1.7-6.2) for IHD and 1.6 (95% CI, 1.2-2.3) for CVD. There was no evidence of an interaction between smoking and serum cholesterol (P for interaction = .75, .87, and .92 for IHD, CVD, and total ASCVD, respectively).

Conclusions This study demonstrates that in Korea smoking is a major independent risk factor for IHD, CVD, and ASCVD and that a low cholesterol level confers no protective benefit against smoking-related ASCVD.

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Chinese men,\textsuperscript{11} and 58\% in Japanese men\textsuperscript{14}. Despite the extremely high prevalence of smoking, populations in these countries tend to be leaner and have lower levels of serum cholesterol and perhaps less atherosclerosis than their Western counterparts. Such differences have led to the belief that smoking is a less important risk factor for IHD in East Asian populations. Because smoking mediates its effects, in part, through adverse changes in platelet adhesion and hemostasis, ie, smoking acts as a triggering factor for IHD events in the presence of atherosclerosis,\textsuperscript{13} there is also a biological basis for exploring interactions between smoking and serum cholesterol.

Surprisingly, few studies have examined the interactive effects of smoking and serum cholesterol on IHD morbidity and mortality. Of these studies, virtually all were conducted in Western countries where the effects of serum cholesterol and smoking appear synergistic, at least in populations with high serum cholesterol levels.\textsuperscript{16,17} In contrast, smoking was not an IHD risk factor in several observational studies conducted in populations with low serum cholesterol levels. In the Puerto Rico Heart Health Program, where the mean total cholesterol level was 5.22 mmol/L (202 mg/dL), smoking did not predict the occurrence of IHD.\textsuperscript{18} Likewise, in a widely cited study that compared IHD risk factors in men of Japanese ancestry living in Hawaii with men living in Japan, smoking was significantly associated with IHD in Hawaii but not Japan.\textsuperscript{19} In another prospective study of Japanese adults, smoking was significantly associated with coronary heart disease in persons with total cholesterol levels of 4.65 mmol/L (180 mg/dL) or higher but not in persons with cholesterol levels of less than 4.65 mmol/L (<180 mg/dL).\textsuperscript{10} Even though many of these studies had limited power to detect an association between smoking and ASCVD at low levels of serum cholesterol as well as limited power to detect an interaction between smoking and cholesterol, such results have contributed to the belief that smoking is not an important ASCVD risk factor in populations with low serum cholesterol levels.\textsuperscript{15,19}

In this setting, we examined prospectively the main and interaction effects of smoking and serum cholesterol on ASCVD in Korean men, a population with relatively low levels of serum cholesterol.

METHODS

The Korea Medical Insurance Corporation (KMIC) provides health insurance to civil service workers, teachers, and their dependents in the Republic of Korea (South Korea). Of the entire Korean population (approximately 43 million in 1990), 4 603 361 (11\%) were insured by KMIC, including 1 213 594 workers and their 3 389 767 dependents. All insured workers are required to participate in biennial medical examinations performed by KMIC. In 1990 and 1992, 93\% and 94\% completed biennial examinations.

The KMIC Study is a prospective cohort study designed to assess risk factors for ASCVD in Korean men and women.\textsuperscript{2} Because only 0.6\% of the women smoked, we restricted our analysis to men. The KMIC Study cohort consists of 112 105 men, aged 35 to 59 years, who attended both the 1990 and 1992 examinations; the cohort was a random sample drawn from insured members of the national identification number. Of the 112 105 men, we excluded 5360 smokers (4.8\%) with incomplete data on the amount and/or duration of smoking. Hence, the final sample size was 106 745 (TABLE 1).

Data Collection

The KMIC biennial examinations are conducted in a standardized fashion by medical staff at local hospitals. In 1990, examinations were conducted in 416 hospitals. A questionnaire was administered to each participant 3 to 4 days before the examination. In the 1992 questionnaire, participants were asked to describe their smoking habits, including the number of cigarettes smoked per day and the duration of cigarette smoking in years, along with other health habits, including alcohol consumption. Completed questionnaires were reviewed and edited by trained staff.

The 1990 and 1992 biennial medical examinations included measurements of weight, height, and blood pressure. Blood pressure was measured in the seated position by a registered nurse or blood pressure technician using a standard mercury sphygmomanometer or automatic manometer. In the case of manual manometers, systolic blood pressure and diastolic blood pressure were measured as the first and fifth Korotkoff sounds, respectively. One measurement was taken. A fasting serum specimen was drawn and analyzed for total cholesterol and serum glucose. Each hospital that participated in the examination had internal and external quality control procedures directed by the Korean Association of Laboratory Quality Control.

Using data collected in the 1992 examination, participants were classified as “current” smokers if they smoked currently for at least 1 year, “nonsmokers” if they never smoked, and “ex-smokers” if they smoked but quit. Current smokers were further classified by the average number of cigarettes smoked per day (1-9, 10-19, and \(\geq 20\) cigarettes per day) and duration of smoking (1-19, 20-29, and \(\geq 30\) years). Body mass index was calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as a systolic blood pressure of at least 140 mm Hg or a diastolic blood pressure of at least 90 mm Hg; stages of hypertension were further classified according to the Sixth Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JN C VI) criteria.\textsuperscript{20} Using National Cholesterol Education Program guidelines,\textsuperscript{21} serum total cholesterol was classified as desirable (serum cholesterol level, <5.17 mmol/L [200 mg/dL]), borderline-high (serum cholesterol level, 5.17-6.20 mmol/L [200-239 mg/dL]), and high (serum cholesterol...
level, ≥6.21 mmol/L [240 mg/dL]). Using diagnostic criteria from the National Diabetes Data Group,22 diabetes was defined by a fasting serum glucose level of 6.99 mmol/L (126 mg/dL) or higher. Categories of average alcohol consumption were 0 g/d, 1 to 20 g/d, or higher. Categories of average alcohol level of 6.99 mmol/L (126 mg/dL) was defined by a fasting serum glucose value of at least 6.99 mmol/L (126 mg/dL). Total cholesterol level of at least 6.21 mmol/L (240 mg/dL). Systolic blood pressure of at least 140 mm Hg and/or diastolic blood pressure of at least 90 mm Hg.

The principal outcome variables were morbidity and mortality from (1) IHD alone (International Classification of Diseases, Ninth Revision [ICD-9] codes 410-414), (2) cerebrovascular disease (CVD) alone (ICD-9 codes 430-438), and (3) total ASCVD. The latter category included hypertensive disease (ICD-9 codes 401-405), IHD (ICD-9 codes 410-414), hemorrhagic stroke (ICD-9 codes 430-432), thrombotic stroke (ICD-9 codes 433-434), other stroke (ICD-9 codes 435-438), other heart disease likely related to ASCVD (ICD-9 codes 426-429), sudden death (ICD-9 code 798), and other vascular disease (ICD-9 codes 440-444). For those individuals with more than one event, we used just the first event in our analyses. The follow-up period, which lasted 6 years, was January 1993 to December 1998.

Outcomes were ascertained from diagnoses on hospital discharge summaries and from causes of death on death certificates. In Korea, professionally trained and certified medical chart recorders abstract charts and assign discharge diagnoses in a standardized fashion using World Health Organization codes for common diseases such as stroke and myocardial infarction. Likewise, these recorders complete death certificates using information provided by physicians. Computerized searches of death certificate data from the National Statistical Office in Korea were performed for each of the KMIC enrollees; hence, in terms of mortality, follow-up is likely to be 100% complete. For morbidity, which is defined exclusively by hospital discharge diagnoses, follow-up is likely to be quite high, if not close to 100%, because hospitals cannot receive payments until the bill with discharge diagnoses is submitted to KMIC. For morbidity, the duration of follow-up was 6 years for those persons without an ASCVD event; for those experiencing an ASCVD event, follow-up time was the interval between January 1, 1993, and the date of the event; for those who retired (21.8%) or those who switched medical insurance because of a job change (0.1%), follow-up time was the interval between January 1, 1993, and the date of retirement or job change, respectively. Just 4.4% were unavailable for follow-up.

### Statistical Analysis
In bivariate analyses, we examined the relationship between smoking status and traditional ASCVD risk factors, adjusting for age using the age distribution of the 1990 Korean Census population. In these bivariate analyses, we tested for trends across categories of amount of current smoking, using nonsmokers as the reference. For ASCVD risk factors with a continuous distribution, we used simple linear regression and entered an ordinal variable for the categories of current smoking (“0” for nonsmokers, “1” for 1-9 cigarettes per day, “2” for 10-19 cigarettes per day, “3” for 20 or more cigarettes per day). For categorical variables, we used the chi-square test for trend, excluding ex-smokers.

### Table 1. Baseline Characteristics of 106,745 Men in the Korea Medical Insurance Corporation Study, 1990-1992, According to Smoking Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonsmokers (n = 22,617)</th>
<th>Ex-smokers (n = 22,739)</th>
<th>1-9 (n = 16,599)</th>
<th>10-19 (n = 25,271)</th>
<th>20 or more (n = 19,519)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>45 (6.7)</td>
<td>46 (6.8)</td>
<td>46 (6.8)</td>
<td>44 (6.6)</td>
<td>44 (6.4)</td>
<td>.06</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>127 (14.5)</td>
<td>126 (14.6)</td>
<td>126 (14)</td>
<td>125 (14)</td>
<td>124 (13)</td>
<td>.08</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>83 (9.8)</td>
<td>83 (9.8)</td>
<td>82 (9.6)</td>
<td>82 (9.6)</td>
<td>81 (9.1)</td>
<td>.002</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.99 (0.85)</td>
<td>5.04 (0.85)</td>
<td>4.96 (0.86)</td>
<td>5.02 (0.85)</td>
<td>5.09 (0.88)</td>
<td>.30</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24 (2.4)</td>
<td>24 (2.4)</td>
<td>23 (2.4)</td>
<td>23 (2.4)</td>
<td>24 (2.5)</td>
<td>.34</td>
</tr>
<tr>
<td>Fasting serum glucose, mmol/L</td>
<td>5.16 (1.19)</td>
<td>5.22 (1.18)</td>
<td>5.16 (1.23)</td>
<td>5.16 (1.14)</td>
<td>5.22 (1.27)</td>
<td>.84</td>
</tr>
<tr>
<td>Alcohol consumption, No. of drinks per day</td>
<td>2.2 (3.1)</td>
<td>2.4 (3.0)</td>
<td>2.6 (3.3)</td>
<td>2.7 (3.2)</td>
<td>3.6 (4.2)</td>
<td>.04</td>
</tr>
</tbody>
</table>

**Conditions, %**

- Hypertension†: 31
- Hypertension‡: 7.9
- Diabetes§: 3.0
- Alcohol use: 59

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and “3” for ≥20 cigarettes per day). For dichotomous variables, we used the method of Mantel-Haenszel. In these models, ex-smokers were excluded.

Cox proportional hazards models were used to assess the independent effects of smoking (both current smokers and ex-smokers) on IHD, CVD, and ASCVD events, controlling for age and traditional risk factors (hypertension, hypercholesterolemia, and diabetes). For the CVD analyses, we assessed the impact of smoking with and without adjustment for alcohol consumption. To determine whether smoking was an independent risk factor throughout the range of total cholesterol, we performed separate Cox proportional hazards models within each quartile of serum cholesterol. After excluding ex-smokers, tests of interaction were performed in Cox proportional hazard models adding terms for current smoking (yes/no), cholesterol status (<5.17 mmol/L [200 mg/dL] vs ≥5.17 mmol/L [200 mg/dL]), and a corresponding interaction term. To calculate the population attributable risk from cigarette smoking and other ASCVD risk factors, we used the formula devised by Levin; separate population attributable risk analyses were performed in those with a total cholesterol level of less than 5.17 mmol/L (200 mg/dL). In all analyses, a 2-sided α level of .05 was considered statistically significant.

RESULTS

The mean (SD) age of study participants was 45 (6.7) years. Among the 106745 men, 61389 (58%) were current smokers and 22739 (21%) were ex-smokers; 23022 (22%) had stage 1, 5128 (4.8%) stage 2, and 1721 (1.6%) stage 3 hypertension. With respect to total cholesterol, 64,482 (60%) had a total cholesterol level of less than 5.17 mmol/L (200 mg/dL), 32,973 (31%) had a borderline level of 5.17-6.20 mmol/L (200-239 mg/dL), and 9,286 (8.7%) had a level of 6.21 mmol/L (240 mg/dL) or higher. Among current smokers, 62% smoked for more than 20 years; 27%, 41%, and 32% of current smokers smoked 1 to 9, 10 to 19, and 20 or more cigarettes per day, respectively. Characteristics of nonsmokers, ex-smokers, and current smokers are presented in Table 1. After adjustment for age, current smokers compared with nonsmokers had significantly lower diastolic blood pressure (P for trend = .002), consumed more alcohol (P for trend = .04), and had a lower prevalence of hypertension (P for trend = .008).

During 6 years of follow-up (572,645 person-years), 3086 men (2.9%) were either hospitalized or died of ASCVD. Of these, 1006 IHD events (176/100,000 person-years), 1364 CVD events (238/100,000 person-years), and 716 other ASCVD events (123/100,000 person-years) occurred; these events included 131 deaths (23/100,000 person years) from IHD, 270 deaths (47/100,000 person-years) from CVD, and 168 deaths (29/100,000 person-years) from other ASCVD. These 569 deaths from ASCVD were 18% of all deaths that occurred during follow-up.

The independent effects of smoking on IHD, CVD, and total ASCVD were examined in Cox proportional hazards models that simultaneously controlled for age, hypertension, hypercholesterolemia, and diabetes (Table 2). Compared with nonsmokers, the risk ratio (RR) for IHD was 2.2 in smokers (P < .001) and 2.1 in ex-smokers and had a lower prevalence of hypertension with and without adjustment for alcohol consumption. To determine whether smoking was an independent risk factor throughout the range of total cholesterol, we performed separate Cox proportional hazards models within each quartile of serum cholesterol. After excluding ex-smokers, tests of interaction were performed in Cox proportional hazard models adding terms for current smoking (yes/no), cholesterol status (<5.17 mmol/L [200 mg/dL] vs ≥5.17 mmol/L [200 mg/dL]), and a corresponding interaction term. To calculate the population attributable risk from cigarette smoking and other ASCVD risk factors, we used the formula devised by Levin; separate population attributable risk analyses were performed in those with a total cholesterol level of less than 5.17 mmol/L (200 mg/dL). In all analyses, a 2-sided α level of .05 was considered statistically significant.

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The independent effects of smoking on IHD, CVD, and total ASCVD were examined in Cox proportional hazards models that simultaneously controlled for age, hypertension, hypercholesterolemia, and diabetes (Table 2). Compared with nonsmokers, the risk ratio (RR) for IHD was 2.2 in smokers (P < .001) and 2.1 in ex-smokers.

Table 2. Risk of Morbidity and Mortality From Ischemic Heart Disease, Cerebrovascular Disease, and Total Atherosclerotic Cardiovascular Disease in Korean Men in the Korea Medical Insurance Corporation Study*

<table>
<thead>
<tr>
<th>Variables and Categories</th>
<th>Ischemic Heart Disease</th>
<th>Cerebrovascular Disease</th>
<th>Total Atherosclerotic Cardiovascular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (5-year age group)</td>
<td>RR (95% CI)</td>
<td>P</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Smoker</td>
<td>2.1 (1.6-2.7)</td>
<td>&lt;.001</td>
<td>1.6 (1.4-1.8)</td>
</tr>
<tr>
<td>Blood pressure†</td>
<td>High normal blood pressure</td>
<td>1.4 (1.2-1.7)</td>
<td>.01</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>1.8 (1.5-2.2)</td>
<td>&lt;.001</td>
<td>2.6 (2.3-3.0)</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>2.9 (2.3-3.8)</td>
<td>&lt;.001</td>
<td>4.3 (3.6-5.2)</td>
</tr>
<tr>
<td>Stage 3 hypertension</td>
<td>4.4 (3.2-6.2)</td>
<td>&lt;.001</td>
<td>9.9 (8.1-12)</td>
</tr>
<tr>
<td>Total cholesterol‡</td>
<td>Borderline-high cholesterol</td>
<td>1.4 (1.2-1.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>2.1 (1.7-2.6)</td>
<td>&lt;.001</td>
<td>1.3 (1.1-1.6)</td>
</tr>
<tr>
<td>Fasting blood sugar§</td>
<td>Diabetes</td>
<td>1.6 (1.3-2.1)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* Risk ratios (RRs) and 95% confidence intervals (CIs) from multivariate Cox proportional hazards models. Each model included age (in 5-year groups), smoking, blood pressure, and total and fasting serum glucose levels as defined below.
† The reference category is normal systolic blood pressure (SBP) < 130 mm Hg and diastolic blood pressure (DBP) < 85 mm Hg. Other categories were high normal (SBP 130-139 mm Hg or DBP 85-89 mm Hg), stage 1 hypertension (SBP 140-159 mm Hg or DBP 90-99 mm Hg), stage 2 hypertension (SBP 160-179 mm Hg or DBP 100-109 mm Hg), and stage 3 hypertension (SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg).
‡ The reference category is desirable serum cholesterol level, < 5.17 mmol/L (200 mg/dL); other categories were borderline-high serum cholesterol level, 5.17-6.20 mmol/L (200-239 mg/dL) and high serum cholesterol level, ≥ 6.21 mmol/L (240 mg/dL).
§ The reference category is a fasting serum glucose level of less than 6.99 mmol/L (126 mg/dL); diabetes is defined as a fasting serum glucose level of 6.99 mmol/L (126 mg/dL) or more.

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The means (range) for each quartile of total cholesterol are as follows: first, 3.99 mmol/L [154.5 mg/dL] (<4.42 mmol/L [171 mg/dL]); second, 4.42-4.91 mmol/L [171-190 mg/dL]; third, 5.17-6.20 mmol/L [200-239 mg/dL]; and fourth, 6.14 mmol/L [237.5 mg/dL] (>6.20 mmol/L [240 mg/dL]). The referent group is non-smokers in each quartile of total cholesterol.

Table 3. Population Attributable Risks (PARs) and 95% Confidence Intervals (CIs) from Smoking and Other Risk Factors on Ischemic Heart Disease, Cerebrovascular Disease, and Total Atherosclerotic Cardiovascular Disease in Korean Men: Results from the Korea Medical Insurance Corporation Study

<table>
<thead>
<tr>
<th>Variables and Categories</th>
<th>Prevalence, %</th>
<th>Ischemic Heart Disease, PAR (95% CI)</th>
<th>Cerebrovascular Disease, PAR (95% CI)</th>
<th>Total Atherosclerotic Cardiovascular Disease, PAR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>57</td>
<td>41 (32-51)</td>
<td>26 (19-32)</td>
<td>26 (22-32)</td>
</tr>
<tr>
<td>Blood pressure*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>29</td>
<td>21 (15-26)</td>
<td>35 (32-39)</td>
<td>34 (32-38)</td>
</tr>
<tr>
<td>Total cholesterol†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borderline</td>
<td>31</td>
<td>11 (5.9-12.5)</td>
<td>0.0 (0-0)</td>
<td>5.8 (3.0-8.5)</td>
</tr>
<tr>
<td>High</td>
<td>8.9</td>
<td>8.9 (6.6-14)</td>
<td>2.6 (0.9-5.1)</td>
<td>5.1 (3.4-6.6)</td>
</tr>
<tr>
<td>Fasting blood sugar‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.2</td>
<td>1.9 (1.0-3.4)</td>
<td>2.8 (1.9-4.0)</td>
<td>2.5 (1.6-3.1)</td>
</tr>
</tbody>
</table>

*The reference category is a systolic blood pressure (SBP) of less than 140 mm Hg and a diastolic blood pressure (DBP) of less than 90 mm Hg; hypertension is defined as an SBP of 140 mm Hg or more and/or a DBP of 90 mm Hg or more.

†The reference category is desirable (serum cholesterol level, <5.17 mmol/L [200 mg/dL]); other categories were borderline-high (serum cholesterol level, 5.17-6.20 mmol/L [200-239 mg/dL]) and high (serum cholesterol level, >6.21 mmol/L [240 mg/dL]).

‡The reference category is a fasting serum glucose level of less than 6.99 mmol/L (126 mg/dL); diabetes is defined as a fasting serum glucose level of 6.99 mmol/L (126 mg/dL) or more.

To assess the relationship between smoking and ASCVD events by level of total cholesterol, we divided the cohort into quartiles of total cholesterol (<4.42 mmol/L [171 mg/dL], 4.42-4.91 mmol/L [171-190 mg/dL], 4.92-5.51 mmol/L [191-213 mg/dL], and >5.51 mmol/L [213 mg/dL]). In these quartiles, the number of IHD events was 156, 209, 249, and 392, respectively, while the number of CVD events was 291, 293, 341, and 439, respectively. In each quartile of serum cholesterol, current smoking was significantly associated with both IHD and CVD (Figure 3). The RR from current smoking in the lowest quartile of serum cholesterol was 3.3 (95% confidence interval [CI], 1.7-6.2) for IHD and 1.6 (95% CI, 1.2-2.3) for CVD. In Cox proportional hazards models that tested for interactions between current smoking (yes/no) and total cholesterol level (≥5.17 mmol/L [200 mg/dL] vs <5.17 mmol/L [200 mg/dL]), there was no evidence of an interaction (P for interaction = .75, .87, and .92 for IHD, CVD, and total ASCVD, respectively).

For current smoking and other traditional risk factors, we estimated the population attributable risks for IHD.
alone, CVD alone, and total ASCVD using risk factor prevalence estimates from this study (Table 3). For IHD, current smoking accounted for approximately 41% of events and hypertension for 21% of events. For CVD, corresponding estimates were 26% from smoking and 35% from hypertension. Among men with a total cholesterol level of less than 5.17 mmol/L (200 mg/dL), current smoking accounted for 41% of IHD events and for 29% of CVD events.

**COMMENT**

In this large prospective, observational study of Korean men with relatively low levels of serum cholesterol, we documented that current cigarette smoking was a strong, independent risk factor for IHD, CVD, and total ASCVD events. These risk relationships were present throughout the range of total serum cholesterol, including the lowest quartile (<4.42 mmol/L [171 mg/dL]). Furthermore, in the context of a high prevalence of cigarette smoking, our data indicate that this risk factor accounts for a substantial fraction of ASCVD events in Korean men (ie, >40% of IHD events), even among those individuals with low levels of serum cholesterol.

Previous observation studies conducted in East Asian countries and in other countries with populations that have low levels of serum cholesterol yielded inconsistent results. In 1 recent observational study conducted in China, cigarette smoking was significantly associated with IHD mortality. However, the IHD analyses were only adjusted for age and alcohol intake, not for traditional ASCVD risk factors. In an initial and subsequent report from the Nippon, Honolulu, and San Francisco (NI-HON-SAN) Study, cigarette smoking was a significant, independent risk factor for coronary heart disease in Japanese men living in Hawaii but not in those living in Japan, where serum cholesterol levels were relatively low. In the Hisayama, Japan, cohort study, smoking was significantly associated with coronary heart disease in persons with a total cholesterol level of 4.65 mmol/L (180 mg/dL) or higher but not in persons with a cholesterol level of less than 4.65 mmol/L (180 mg/dL). In an autopsy series from the same study, smoking was not a risk factor for coronary atherosclerosis. Finally, in the Puerto Rico Heart Health Program, where the mean total cholesterol level was 5.22 mmol/L (202 mg/dL), smoking did not predict the occurrence of IHD. In the context of these equivocal results, our study provides unambiguous evidence that current cigarette smoking is a risk factor for IHD and CVD, even among persons with low serum cholesterol levels.

The KMIC Study also demonstrated that cigarette smoking was a significant risk factor for cerebrovascular events and stroke subtypes, both thrombotic and hemorrhagic. In this respect, our data are consistent with observational data from the United States, but not with recent data from China. In the latter study, cigarette smoking did not predict the occurrence of stroke mortality in analyses adjusting for age and alcohol use. This inconsistency may have resulted from differences in study power, ie, 197 events in the Yuan study vs 1364 events in the KMIC Study.

In our analyses, ex-smokers had a similar risk of IHD as current smokers. In contrast, the risk of CVD in ex-smokers was not significantly different from that of nonsmokers. This pattern of findings suggests that the high risk of CVD subsides after cessation of smoking, while the risk of IHD persists for a longer, albeit unknown, period of time. Unfortunately, the KMIC data do not have information on quit dates in ex-smokers.

Among the strengths of the KMIC Study are high follow-up rates, repeated measures of several exposures (blood pressure, total serum cholesterol, fasting serum glucose, weight, and height), and its large, national sample. Other aspects of the study population deserve comment. The participants in the KMIC Study tend to be middle-class, employed individuals, who may be healthier than the general population in Korea. Although incidence rates of disease likely differ by socioeconomic status, there is little reason to suspect that risk factor-disease relationships should markedly differ. Second, because smoking remains uncommon among Korean women (just 0.6%), we restricted our analyses to men. Finally, most KMIC enrollees were middle-aged. Hence, patterns of disease may change as the cohort ages. In particular, proportionate morbidity and mortality from ASCVD should increase with time. Overall, results from this cohort study should be generalizable to other populations in East Asia.

Potential limitations of our study include the relatively brief duration of follow-up, inclusion of individuals with prevalent ASCVD in the cohort, and reliance on diagnoses from discharge summaries and death certificates. Although the duration of follow-up in our analyses is just 6 years, the large size of the cohort (>100 000 participants) provided sufficient statistical power, even in subgroup and dose-response analyses. The inclusion of persons with antecedent ASCVD events could potentially lead to biased estimates. The bias, however, is likely to be conservative, because such individuals tend to adopt desirable habits after clinical ASCVD events; hence, the category of nonsmokers may be differentially enriched with persons who stopped smoking after a myocardial infarction or stroke. The impact of prevalent ASCVD is also diminished because individuals who experienced ASCVD events between January 1990 and December 1992, the years of baseline data collection, were excluded. Reliance on diagnoses from hospitalization and death certificates may introduce random and systematic errors. Random error would tend to diminish the study’s power to detect associations. Systematic error could alter the distribution of events and perhaps risk factor-disease relationships if the errors were related to exposure status.
ings, ie, significant relationships of current smoking within the broad category of ASCVD events as well as the component categories of IHD and CVD events, suggest that major systematic errors related to the coding of ASCVD events was unlikely.

In conclusion, current cigarette smoking is a major, independent risk factor for IHD, CVD, and total ASCVD in Korea, an East Asian country with a population that has a high prevalence of smoking and relatively low levels of serum cholesterol. A low cholesterol level confers no protective benefit against the harmful effects of smoking on ASCVD.

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Only in men's imagination does every truth find an effective and undeniable existence. Imagination, not invention, is the supreme master of art, as of life.
—Joseph Conrad (1857-1924)