Does the Impact of Smoking on Coronary Heart Disease Differ by Low-Density Lipoprotein Cholesterol Level?

— The Atherosclerosis Risk in Communities (ARIC) Study —

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Background The association of smoking with coronary heart disease (CHD) occurrence has been reported to be weaker for populations with lower plasma cholesterol levels. Recent studies suggest that low-density lipoprotein cholesterol (LDL-C) and smoking contribute to different stages of atherosclerosis, so the present study was designed to test the hypothesis that smoking is a stronger risk factor for CHD when LDL-C is high.

Methods and Results The study group of 13,410 middle-aged adults who were initially free of stroke and CHD were followed and over 13.3 years there were 932 incident CHD events. Tests for multiplicative interaction were performed using proportional hazards models. Both smoking and increased LDL-C were risk factors for CHD incidence. The relative hazard (RH) of CHD in relation to smoking tended to be larger among higher LDL-C categories compared with lower LDL-C categories. For example, when the participants were dichotomized into 4 categories, using smoking ≥ 15 cigarettes per day and LDL-C ≥ 130 mg/dl as cutoffs, those with high LDL-C and heavier cigarette smoking showed a very high RH of CHD (RH=2.81) compared with that expected from the product of the RHs of high LDL-C (RH=1.15) only $\times$ heavy smoking only (RH=1.71) (p for interaction=0.04).

Conclusions These results suggest positive multiplicative interactions between smoking and LDL-C for CHD incidence. (Circ J 2006; 70: 1105–1110)

Key Words: Coronary heart disease; Interactions; LDL-cholesterol; Prospective studies; Smoking

Cigarette smoking is a strong risk factor for coronary heart disease (CHD) incidence,¹ although some epidemiological studies suggest that the strength of the association of smoking with CHD incidence may vary among populations. Smoking is a weaker risk factor in Asian countries compared with Western countries,^{2,3} and the Seven Countries Study showed that the relationship of smoking with CHD incidence was weaker in southern Europe than in Northern Europe and Yugoslavia.⁴ This geographical difference in the effect of smoking with CHD might be explained by ethnic, cultural or environmental factors; for example, the level of total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C). People who live in Asia and in southern Europe at the time of the early follow-up of the Seven Countries Study had low average total and LDL-C levels.^{2–4}

Recent studies comparing the contribution of cigarette smoking or LDL-C suggest that LDL-C is more important for early atheroma formation, whereas smoking affects the

later stages of atherosclerosis.^{5,6} These findings suggest that smoking may depend on elevated LDL-C levels to maximize its effect on CHD risk.

Thus, both international comparison and biological considerations suggest that smoking is a weaker CHD risk factor when LDL-C is low, and a stronger risk factor when LDL-C is high. However, epidemiological studies to date have failed to find clear differences in the relative risk of smoking for CHD across TC or LDL-C levels.^{7–9}

We compared the relative hazards (RH) of CHD in relation to cigarette smoking status and cigarette-years of smoking in participants with lower vs higher LDL-C levels using the Atherosclerosis Risk in Communities (ARIC) Study cohort.

Methods

Study Design and Subjects

The ARIC Study is a prospective study of atherosclerotic disease in 4 US communities: (1) Forsyth County, North Carolina, (2) Jackson, Mississippi, (3) Washington County, Maryland and (4) the northwest suburbs of Minneapolis, Minnesota.¹⁰ The cohort comprised, at baseline in 1987–89, 15,792 men and women aged 45–64 years who were selected by list or area probability sampling. Only African-Americans were recruited in the Jackson study center. The baseline home interview assessed participants' sociodemographic characteristics, smoking and alcohol-drinking habits, medication use, reproductive history, and personal history of diseases. A clinic examination included measurement of various risk factors and cardiovascular conditions, B-mode ultrasound examinations of the carotid and

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Table 1 Prevalences or Mean Values of Baseline Participant Characteristics According to Approximate Quartiles of Plasma LDL-C and Smoking Status: Atherosclerosis Risk in Communities (ARIC) Study, 1987–1989

	Serum LDL-C (mg/dl)						Smoking status			
	<99	100–129	130–159	160–189	≥190	p-value	Current	Former	Never	p-value
<i>N</i>	2,175	3,887	3,393	2,231	1,184		3,392	4,257	5,761	
Age (years) (Mean)	52.7	53.5	54.3	54.9	55.2	<0.01	53.4	54.6	53.9	<0.01
Men (%)	36.0	41.4	46.4	48.3	39.5	<0.01	44.8	59.5	29.7	<0.01
African-American (%)	29.1	24.2	22.8	23.7	32.5	<0.01	28.7	18.8	27.9	<0.01
Diabetes (Yes) (%)	8.1	8.0	9.9	10.0	12.9	<0.01	8.4	9.1	10.1	0.03
Smoking										
Current (%)	25.8	24.6	24.2	26.7	27.6	0.18	100.0	0.0	0.0	<0.01
Former (%)	30.9	31.5	32.5	31.7	31.5		0.0	100.0	0.0	
Never (%)	43.3	43.9	43.3	41.6	40.9		0.0	0.0	100.0	
Education										
Less than high-school (%)	20.8	20.3	21.7	23.6	26.4	<0.01	28.8	20.2	19.1	<0.01
High-school (%)	28.8	32.7	34.1	33.8	35.6		34.1	30.1	34.3	
More than high-school (%)	50.3	46.9	44.0	42.5	38.0		37.1	49.7	46.4	
Use of antihypertensive medication (%)	26.6	25.1	27.1	27.8	33.4	<0.01	25.1	26.6	28.7	<0.01
Systolic blood pressure (mmHg) (Mean)	118.9	119.8	121.4	121.4	123.2	<0.01	119.1	121.0	121.5	<0.01
LDL-C (mg/dl) (Mean)	82.5	116.0	144.3	172.8	214.1	<0.01	138.1	136.9	136.4	0.11
HDL-C (mg/dl) (Mean)	60.1	53.7	50.5	48.4	48.5	<0.01	50.1	51.3	54.8	<0.01
Triglyceride (mg/dl) (Mean)	107.0	113.4	125.7	137.5	147.5	<0.01	127.2	127.2	117.4	<0.01
Ethanol intake (g/week) (Mean)	49.1	42.3	40.1	39.9	38.1	<0.01	66.1	52.8	19.8	<0.01
Waist-to-hip ratio (Mean)	0.90	0.92	0.93	0.94	0.94	<0.01	0.92	0.94	0.91	<0.01
Body mass index (kg/m ²) (Mean)	26.6	27.5	27.8	27.9	28.2	<0.01	26.3	27.8	28.1	<0.01
Sports index (Mean)	2.4	2.4	2.5	2.5	2.4	<0.01	2.3	2.6	2.4	<0.01

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
p-value was assessed by ²-test or analysis of variance as appropriate.

popliteal arteries, and a 12-lead electrocardiogram (ECG).

Baseline Examination

Methods for blood collection and processing in ARIC have been described in detail.¹¹ Fasting plasma TC and triglycerides (TG) were measured by enzymatic methods.^{12,13} High-density lipoprotein cholesterol (HDL-C) level was measured by the method of Warnick et al,¹⁴ and LDL-C concentration was calculated by the Friedewald formula.¹⁵ The classification of LDL-C subgroups was that defined by the Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III): that is, <100 mg/dl: Optimal; 100–129 mg/dl: Near optimal/above optimal; 130–159 mg/dl: Borderline high; 160–189 mg/dl: High; and ≥190 mg/dl: Very high.¹⁶ An intra-individual variability study demonstrated excellent short-term repeatability in ARIC, with a reliability coefficients ≥0.85 for LDL-C, HDL-C, and TG.¹⁷

Usual ethanol intake and smoking status (current, former, or never smokers) were assessed by interview.¹⁸ Smokers (current or former) were asked the average numbers of daily cigarettes smoked during the time they smoked. Cigarette-years of smoking were calculated as the average number of cigarettes per day multiplied by the number of years of smoking. Sitting blood pressures (BP) were measured 3 times using a random-zero sphygmomanometer after a 5-min rest.¹⁹ The mean of the last 2 measurements was used for analysis. Use of antihypertensive medications within the past 2 weeks of the baseline interview was self-reported.¹⁸ Serum glucose was measured by a hexokinase/glucose-6-phosphate dehydrogenase method. Diabetes mellitus was defined as a fasting glucose ≥126 mg/dl, or a reported history of physician-diagnosed diabetes, or current use of diabetes medication. Body weight was measured to the nearest pound and height was measured to the nearest

centimeter. Body mass index (BMI) was computed as weight (kg) divided by square of height (m²). Waist-to-hip ratio (WHR), an indicator of fat distribution, was computed as the circumference of the waist (umbilical level, cm) divided by the maximum circumference of the hips (cm). The sports index, derived from the survey of Baekke et al,²⁰ ranged from 1 (low) to 5 (high) for physical activity during leisure time.

Pre-existing CHD at baseline was defined by self-reported prior physician diagnosis of myocardial infarction (MI) or coronary revascularization, or by prevalent MI on the ARIC ECG.²¹ Pre-existing stroke was defined by any self-reported prior physician diagnosis of stroke.

Ascertainment of Incident CHD Events

Interviewers contacted participants annually. All identified hospital records were reviewed and those suggesting CHD were abstracted for validation.^{10,22} MI was validated using presenting signs and symptoms, peak cardiac enzyme levels, and Minnesota Coding²³ from up to 3 ECGs. Death certificates were also surveyed to identify CHD deaths. For validation of out-of-hospital deaths, the death certificate was used in combination with interviews of next of kin and questionnaires completed by the patients' physicians. Autopsy and coroner reports were also used. For this analysis, CHD was defined as a validated definite or probable MI or definite CHD death through to December 31, 2002. All possible clinical CHD events were reviewed by members of the ARIC Morbidity and Mortality Classification Committee, using published criteria.²²

Statistical Analysis

Of the 15,792 ARIC participants at baseline, we excluded 329 who had a history of stroke, 1,028 who had a history of CHD or who could not be classified by a history of CHD, and 399 without LDL-C data (192 of these because TG >400 mg/dl). We also excluded, due to small numbers, non-

Table 2 RH (95% Confidence Interval) of CHD Incidence With Cigarette Smoking Status According to LDL-C Level

		LDL-C level (mg/dl)				
		<100	100–129	130–159	160–189	≥190
<i>Cigarettes per day</i>						
Former smoker	RH	1.02 (0.59–1.76)	1.13 (0.79–1.61)	1.19 (0.87–1.65)	1.10 (0.77–1.58)	1.12 (0.72–1.76)
Never smoked	RH	1	1	1	1	1
Current 1–14	RH	1.84 (0.91–3.74)	1.76 (1.07–2.91)	1.76 (1.05–2.93)	1.34 (0.72–2.48)	2.07 (1.02–4.18)
Current 15–29	RH	1.33 (0.66–2.67)	2.09 (1.39–3.13)	2.91 (2.01–4.21)	2.08 (1.37–3.17)	2.25 (1.33–3.82)
Current 30+	RH	2.13 (0.98–4.61)	2.46 (1.43–4.24)	3.80 (2.37–6.07)	2.23 (1.29–3.85)	3.80 (1.98–7.29)
Slope*	RH	1.23 (0.97–1.57)	1.39 (1.19–1.62)	1.61 (1.40–1.85)	1.36 (1.16–1.59)	1.53 (1.26–1.86)
<i>Cigarette-years of smoking</i>						
Never smoked	RH	1	1	1	1	1
Ever 1–399	RH	1.39 (0.83–2.35)	1.09 (0.75–1.60)	1.19 (0.83–1.69)	0.88 (0.58–1.33)	1.11 (0.69–1.79)
Ever 400+	RH	1.32 (0.78–2.24)	1.79 (1.29–2.49)	2.12 (1.57–2.85)	1.86 (1.33–2.59)	2.06 (1.35–3.13)
Slope†	RH	1.15 (0.89–1.48)	1.35 (1.14–1.60)	1.47 (1.26–1.71)	1.39 (1.17–1.65)	1.46 (1.18–1.80)

RH, relative hazard; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol.

*Slope per 1 category increase not including former smokers; †slope per 1 category increase.

RH of CHD incidence for smoking status compared with never smoking adjusted for age, sex, race (African-American, white), education (less than high-school graduate, high-school graduate, greater than high-school graduate), systolic blood pressure (continuous variable), antihypertensive medication (yes, no), triglycerides, high-density lipoprotein cholesterol, ethanol intake, body mass index, waist-to-hip ratio, sports index and diabetes (yes, no).

Fig 1. Relative hazard (RH) (95% confidence interval) of coronary heart disease incidence by levels of smoking (cutoff points for cigarette smoking were 15 per day (a) or 400 cigarette-years (b) and for low-density lipoprotein cholesterol (LDL-C) the cutoff level was 130 mg/dl). The area with vertical lines shows the excess RH compared with the RH estimated from the product of RHs of high LDL-C and heavy smoking. The RH were adjusted for age, sex, race (African-American, white), education (less than high-school graduate, high-school graduate, greater than high-school graduate), systolic blood pressure (continuous variable), antihypertensive medication (yes, no), triglycerides, high-density lipoprotein cholesterol, ethanol intake, body mass index, waist-to-hip ratio, sports index and diabetes (yes, no). Fig 1(a) does not include former smokers.

white and non-African-American subjects (N=42). Subjects who did not have complete information on cigarette smoking (N=9), did not fast (N=451) or who were missing other confounding factors (N=124) were also excluded. In all, 13,410 participants were included in the analysis.

The associations of baseline LDL-C and smoking with other risk factors were assessed using analysis of variance or the chi²-test, as appropriate. Risk factor associations with CHD incidence were estimated from Cox proportional hazard models. RH of CHD for the smoking and LDL-C categories of risk factors were computed using 'never smokers' as the references. In all analyses, we adjusted for age, race (African-American, white), sex, education (less than high-school graduate, high-school graduate, greater than high-school graduate), systolic BP (continuous variable), antihypertensive medication (yes, no), TG, HDL-C, ethanol intake, BMI, WHR, sports index and diabetes (yes, no). Slopes were calculated as the RH of CHD per 1 category increase in smoking. When we calculated the slope for current smoking status, we did not include former smokers in the calculation.

The p-values for multiplicative interactions between LDL-C and smoking status for CHD were usually calcu-

lated using LDL-C dichotomized at 130 mg/dl and dichotomizing smoking status at 15 cigarettes per day or 400 cigarette-years, and by including cross-product terms in the regression models because slopes were higher in heavier smokers and those with higher LDL-C. In tests for interaction involving current smoking status, we ignored the former smokers.

Two-tailed p-values <0.05 were considered statistically significant. All statistical analyses were performed using SAS software, version 8.2 (SAS Institute, Cary, NC, USA).

Results

LDL-C, Smoking and Other Cardiovascular Risk Factors

The mean value ± SD of LDL-C was 137 ± 39 mg/dl (maximum 504 mg/dl). Table 1 shows the association of LDL-C categories with other risk factors for CHD. Mean values of age, systolic BP, TG, WHR and BMI were higher in higher LDL-C categories. Conversely, mean values of HDL-C and ethanol intake were lower in the higher LDL-C categories. The proportion of subjects who were men, diabetic, antihypertensive medication users, and less educated increased across the LDL-C categories.

Table 3 Race- or Sex-Specific RH (95% Confidence Interval) of Coronary Heart Disease in Relation to Smoking Status and LDL-C Level

	Cigarette smoking <15 per day*				Cigarette smoking ≥15 per day*				Cigarette-years of smoking <400				Cigarette-years of smoking ≥400			
	LDL-C <130 mg/dl		LDL-C ≥130 mg/dl		LDL-C <130 mg/dl		LDL-C ≥130 mg/dl		LDL-C <130 mg/dl		LDL-C ≥130 mg/dl		LDL-C <130 mg/dl		LDL-C ≥130 mg/dl	
	1	Expected RH†	1	Expected RH†	1	Expected RH†	1	Expected RH†	1	Expected RH†	1	Expected RH†	1	Expected RH†	1	Expected RH†
White	1	1.28 (0.98–1.69)	1.96 (1.39–2.76)	3.24 (2.44–4.31)	1	2.51	1	1.19 (0.95–1.50)	1.51 (1.15–1.99)	2.44 (1.94–3.06)	1	1.80	1.51 (1.15–1.99)	2.44 (1.94–3.06)	1	1.80
African-American	1	0.99 (0.70–1.42)	1.41 (0.87–2.29)	2.09 (1.33–3.28)	1	1.40	1	1.13 (0.81–1.56)	1.47 (0.95–2.26)	1.98 (1.35–2.92)	1	1.66	1.47 (0.95–2.26)	1.98 (1.35–2.92)	1	1.66
Men	1	1.25 (0.90–1.73)	1.59 (1.09–2.32)	2.67 (1.93–3.71)	1	1.99	1	1.28 (0.98–1.66)	1.42 (1.06–1.90)	2.23 (1.73–2.87)	1	1.82	1.42 (1.06–1.90)	2.23 (1.73–2.87)	1	1.82
Women	1	1.09 (0.81–1.46)	1.95 (1.27–2.97)	3.04 (2.15–4.29)	1	2.13	1	1.05 (0.80–1.37)	1.76 (1.20–2.57)	2.53 (1.86–3.45)	1	1.85	1.76 (1.20–2.57)	2.53 (1.86–3.45)	1	1.85

Abbreviations see in Table 2.

Adjusted for age, sex, race (African-American, white), education (less than high-school graduate, high-school graduate, greater than high-school graduate), systolic blood pressure (continuous variable), antihypertensive medication (yes, no), triglycerides, high-density lipoprotein cholesterol, ethanol intake, body mass index, waist-to-hip ratio, sports index and diabetes (yes, no).

*Excludes the former smokers; †estimated as the product of the RH for lighter smoking with high LDL-C times the RH for heavier smoking with low LDL-C.

Of the sample, 25% were current smokers, 32% were former smokers and 43% were never smokers. Among current smokers, the mean number of cigarettes smoked per day was 19.1±10.1 and 2,390 (70%) smoked 15 cigarettes or more per day. Compared with never smokers, ever smokers were more often men and were less well educated. Ever smokers had lower BMI, HDL-C and systolic BP, and higher ethanol intake and TG values than never smokers.

Association of Smoking Status With CHD According to LDL-C

Over a mean duration of follow-up of 13.3 years (maximum 16.1 years), 932 incident CHD events occurred. Incidence rates of CHD per 1,000 person-years were 8.38 for current smokers, 5.07 for former smoker and 3.60 for never smokers. Incidence rates also increased across LDL-C groups classified according to NCEP guidelines: 3.28, 4.16, 5.10, 7.04 and 9.38 per 1,000 person-years for optimal (<100 mg/dl), near optimal/above optimal (100–129 mg/dl), borderline high (130–159 mg/dl), high (160–189 mg/dl) and very high (≥190 mg/dl), respectively.

Table 2 shows the multivariable-adjusted RH of CHD incidence for smoking status according to LDL-C category. The slopes of current smoking per 1 smoking category increase were steeper in higher LDL-C groups than in lower LDL-C groups. This was also true when we used cigarette-years of smoking instead of numbers of cigarettes smoked per day. Similarly, the slope of LDL-C according to smoking status was steeper in heavier smokers 15–29 cigarettes per day, (slope per 1 LDL-C category increase: 1.25; 95% confidence interval (CI): 1.10–1.41), ≥30 cigarettes per day, (slope per 1 LDL-C category increase: 1.32; 95% CI: 1.11–1.57), than never (slope per 1 LDL-C category increase: 1.15; 95% CI: 1.04–1.28) or light smokers (<15 cigarettes per day, slope per 1 LDL-C category increase: 1.05; 95% CI: 0.86–1.27). The slope of LDL-C in former smokers was intermediate (slope per 1 LDL-C category increase: 1.22; 95% CI: 1.11–1.35).

When we used 130 mg/dl as the cutoff for LDL-C and never or current smoking as the cutoff for cigarette smoking, although the RH of current smoking with high LDL-C (RH: 2.88 (95% CI: 2.25–3.69)) was higher than the expected RH of 2.46, obtained by multiplying the RH for high LDL with never smoking (RH=1.99) by current smoking with lower LDL-C (RH=1.23), the p-value for interaction was not significant (p=0.34). However, when we used 130 mg/dl as the cutoff for LDL-C and 15 cigarettes per day as the cutoff for cigarette smoking, the RH of high smoking exposure with high LDL-C was very high (RH=2.81) compared with lower smoking and lower LDL-C (RH=1.00, reference) (Fig 1a). This value of 2.81 is higher than the expected RH of 1.97, obtained by multiplying the RH for high LDL with lower smoking (RH=1.15) by heavy smoking with lower LDL-C (RH=1.71), p-value for interaction=0.04. This finding was also observed when we used 400 cigarette-years of smoking as the cutoff point (Fig 1b), and the p-value for interaction was 0.05. These relationships were consistently found in men, women, whites, and African-Americans (Table 3); that is, the RH of high smoking exposure with high LDL-C was consistently higher than the expected RH, obtained by multiplying the RH for high LDL-C with lower smoking by heavy smoking with lower LDL-C.

Discussion

In this prospective cohort study, the CHD risk associated with heavier smoking and elevated LDL-C were greater than expected from the product of the individual RHs. Although the statistical significance of these interactions was modest, our findings offer support for the hypothesis that the effect of smoking on CHD risk is greater in the presence of an elevated LDL-C level, and conversely, the effect of smoking is less in the presence of a low LDL-C level.

It is well known that incidence rates of CHD among populations with lower cholesterol, such as in eastern Asia and southern Europe in the 1960s, are lower than for contemporary Western populations, despite a higher prevalence of smoking in men.²⁻⁴ Such differences have led to the belief that smoking is a less important risk factor for CHD in populations with lower cholesterol than in those with higher cholesterol. Well-known factors that differ between higher and lower cholesterol countries are BMI, TC, diet and physical activity²⁴ and these might modify the smoking and CHD associations. Therefore, lower blood TC levels and saturated fatty acid intake are leading candidates to explain why CHD rates are low in these populations, despite a high smoking prevalence.

Recent studies that assessed the impact of smoking or cholesterol on different stages of atherosclerosis have revealed that smoking is associated more strongly with advanced, rather than early, subclinical atherosclerosis.^{5,6} For example, Sharrett et al showed in the ARIC study that the odds ratio of smoking for several stages of atherosclerosis was larger for severe atherosclerosis (lower extremity artery disease or severe carotid artery intimal medial thickness (IMT)) than for moderate IMT.⁵ Similar findings were reported by the Multiethnic Study of Atherosclerosis.⁶ In contrast, in both those studies LDL-C, relative to smoking, was the more important determinant of the earliest ultrasound-detectable stage of atherosclerosis, in particular, the ultrasound-assessed echolucent lesions indicative of early atheroma with substantial cholesterol-filled cores and minimal fibrous caps.^{5,6} Similarly, a study of young adults reported that the determinants of carotid IMT were only lifetime LDL-C and (inversely) HDL-C, with no substantial associations for smoking pack-years or diabetes,²⁵ supporting a principal role for LDL-C in early atherosclerosis. Furthermore, the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study, which collected information on coronary artery atherosclerosis in persons aged 15–34 years, showed that smokers had a greater prevalence of severe atherosclerosis than non-smokers,²⁶ from which those researchers concluded that smoking accelerates the transition from atheroma, with their cholesterol-filled cores, to fibroatheroma, as classified by American Heart Association criteria.²⁷ Our findings of a multiplicative interaction between smoking and LDL-C may be consistent with the view that smoking accelerates the further progression of cholesterol-filled lesions. It is also possible that the interaction might be explained by other factors that are strongly related to smoking status, such as C-reactive protein, platelet count, leukocyte count,²⁸ or impaired endothelial dysfunction due to cigarette smoking-induced oxidative stress.²⁹ Further studies are warranted to clarify the mechanism.

Only Cullen et al⁸ in a smaller study, has previously reported the association of smoking with CHD according to LDL-C levels. Among men aged 40–65 and followed for 8 years 132 major coronary events occurred in 1,444 current

smokers and 126 major coronary events in 3,195 never or ex-smokers. Unadjusted RRs of CHD for smokers vs non-smokers were 2.8, 1.7 and 2.5 within low, middle and high LDL-C tertiles, respectively. Thus, the prior literature does not suggest a multiplicative interaction of smoking with LDL-C or with TC.⁷⁻⁹ Our study also did not show a statistically significant interaction when we used 'never smoking' as a cutoff point. However, we found modest but significant interaction when we compared the heavy smokers with light smokers. Our finding suggests that sufficient smoking exposure might be needed to show a significant synergistic effect of LDL-C and smoking on CHD incidence.

The strengths of our study are that it included a large, bi-racial population-based cohort, careful assessment of CHD incidence over an extended follow-up period, and an ability to adjust our findings for many CHD risk factors. However, even using such a large cohort, the interaction was significant at only modest levels. Studies with even larger numbers of subjects with lower LDL-C may be needed to confirm our hypothesis.

Our data show a much higher risk CHD with heavy cigarette smoking in the presence of higher LDL-C than lower LDL-C, which reinforces the importance of smoking cessation in those with elevated cholesterol. Together with cholesterol reduction, this may synergize in preventing CHD. Furthermore, if we hypothesize that our findings would be applicable to countries with lower cholesterol, such as eastern Asia, where the lifestyle is becoming more westernized^{30,31} and where the prevalence of smoking is still high among men, clinicians should be mindful of a potential rise in CHD incidence. Unless smoking is reduced or LDL-C is appropriately controlled in smokers with higher LDL-C levels, the incidence of CHD in Asian countries may increase dramatically in the future.

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