Cigarette Smoking and Progression of Atherosclerosis

The Atherosclerosis Risk in Communities (ARIC) Study

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Context.—Cigarette smoking is a powerful risk factor for incident heart disease and stroke, but the relationship of active and passive smoking with the progression of atherosclerosis has not been described.

Objective.—To examine the impact of active smoking and exposure to environmental tobacco smoke (ETS) on the progression of atherosclerosis.

Design.—A longitudinal assessment of the relationship between smoking exposure evaluated at the initial visit and the 3-year change in atherosclerosis.

Setting.—A population-based cohort of middle-aged adults from 4 communities in the United States.

Participants.—A total of 10 914 participants from the Atherosclerosis Risk in Communities (ARIC) study enrolled between 1987 and 1989.

Main Outcome Measure.—Change in atherosclerosis from baseline to the 3-year follow-up as indexed by intimal-medial thickness of the carotid artery assessed by ultrasound and adjusted for demographic characteristics, cardiovascular risk factors, and lifestyle variables.

Results.—Exposure to cigarette smoke was associated with progression of atherosclerosis. Relative to never smokers and after adjustment for demographic characteristics, cardiovascular risk factors, and lifestyle variables, current cigarette smoking was associated with a 50% increase in the progression of atherosclerosis (mean progression rate over 3 years, 43.0 µm for current and 28.7 µm for never smokers, regardless of ETS exposure), and past smoking was associated with a 25% increase (mean progression rate over 3 years, 35.8 µm for past smokers and 28.7 µm for never smokers). Relative to those not exposed to ETS, exposure to ETS was associated with a 20% increase (35.2 µm for those exposed to ETS vs 29.3 µm for those not exposed). The impact of smoking on atherosclerosis progression was greater for subjects with diabetes and hypertension. Although more pack-years of exposure was independently associated with faster progression ($P<.001$), after controlling for the number of pack-years, the progression rates of current and past smokers did not differ ($P=.11$).

Conclusions.—Both active smoking and ETS exposure are associated with the progression of an index of atherosclerosis. Smoking is of particular concern for patients with diabetes and hypertension. The fact that pack-years of smoking but not current vs past smoking was associated with progression of atherosclerosis suggests that some adverse effects of smoking may be cumulative and irreversible.

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CIGARETTE SMOKING is widely accepted as a major risk factor for the development of clinical cardiovascular disease resulting from direct effects on atherosclerosis and hemostasis.[1] Cross-sectional studies have shown a relationship between active smoking and carotid artery atherosclerosis in population-based cohorts.[2,3] In addition, atherosclerosis has been associated with both current[3] and past[4] exposure to environmental tobacco smoke (ETS). Previous longitudinal studies in small populations have examined the association of smoking with the progression of atherosclerosis with mixed results. While an association was observed between duration of smoking and progression of carotid atherosclerosis among 100 Finnish men,[5] no difference in the rate of atherosclerosis progression was shown between current smokers and those not currently

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smoking cigarettes in 3 other studies.[6-8] To our knowledge, no report has examined the impact of smoking, including ETS, in a large longitudinal cohort.

Systematic differences in other atherosclerosis risk factors and behaviors between smokers and never smokers may confound the relationship between smoking and atherosclerosis. While passive smoking has been associated with clinical cardiovascular diseases,[9-11] the association between ETS exposure and atherosclerosis has only been shown in cross-sectional analyses.[3,4] This article assesses the relationship of active smoking and exposure to ETS with a 3-year change in carotid artery intimal-medial thickness (IMT).

METHODS

Patient Population

The Atherosclerosis Risk in Communities (ARIC) study is a population-based investigation of approximately 16 000 persons aged 45 to 64 years at the baseline visit conducted between 1987 and 1989. Approximately 4000 participants were examined at each of the centers in Minneapolis, Minn; Washington County, Maryland; Jackson, Miss; and Forsyth County, North Carolina. Participants were reexamined after 3 years, and this report will focus on the atherosclerosis progression during that time. Further details on the ARIC study design have been published elsewhere.[12]

Study Variables

The primary outcome variable in this article is "progression of atherosclerosis" between 2 visits approximately 3 years apart. There has been growing acceptance of B-mode real-time ultrasound to serve as a surrogate measure of atherosclerosis, offering a noninvasive index of atherosclerosis that has proven reliable and valid.[13-20] In this study, ultrasound was used to assess the common carotid IMT in a 1-cm segment proximal to the dilation of the carotid bulb. Assessments were made at the baseline visit and at a follow-up visit approximately 3 years later. A total of 6 sites were examined by ultrasound imaging, and 3 measurements were taken in each carotid artery at different angles of interrogation. Additional measurements of carotid IMT were made over the 1-cm segment proximal to the flow divider (the "bifurcation") and the 1-cm distal to the flow divider in the internal carotid artery. Measurements at these sites were more frequently missing and had more variability; hence, we restricted our analysis to the common carotid artery. The ultrasound images were recorded on videotape and forwarded to a central reading center for interpretation. The ultrasound readers were masked from patient characteristics, including smoking status. For each of the 6 images from the common carotid artery, attempts were made to measure the IMT over a 1-cm distance at 1-mm increments (a total of up to 11 measurements); the mean wall thickness for each segment was calculated. A mean common carotid IMT adjusted for reader differences and reading date was then calculated. This protocol produces a single index of atherosclerosis with improved precision provided by the averaging of multiple IMT assessments. This approach is similar to the approaches used in a wide range of epidemiologic studies[13-17] and clinical trials.[18-20] Specific details of the ultrasound scanning[14] and reading[15] protocols are provided elsewhere.

Smoking history was assessed by participant self-report. For these analyses, participants were first classified as current smokers, past smokers (more than 100 cigarettes in the past), and never smokers. Exposure to ETS was assessed using the following question: "During the past year, about how many hours per week, on average, were you in close contact with people when they were smoking? For example, in your home, in a car, at work, or other close quarters." Never smokers and past smokers were classified as exposed to ETS if they reported being in close contact with smokers for more than 1 hour per week. This categorization yields 5 strata: current smokers, past smokers exposed to ETS, past smokers not exposed to ETS, never smokers exposed to ETS, and never smokers not exposed to ETS. Current smokers were not stratified by exposure to ETS because we felt that exposure to active smoking would overwhelm any potential effect of ETS in this group. Pack-years of exposure (number of packs per day multiplied by years of smoking) was calculated among the current and past smoker groups. The number of hours of ETS exposure was calculated for secondary analysis among past and never smokers.

Methods for assessment of cardiovascular risk factors used as covariates in these analyses have been described elsewhere,[12] but we briefly describe them here. Hypertension was defined as either systolic blood pressure greater than 140 mm Hg, diastolic blood pressure greater than 90 mm Hg, or self-reported use of antihypertensive medications. Low-density lipoprotein cholesterol concentration was estimated using the Friedewald formula.[21] Participants were defined as having diabetes if they reported having diabetes, if they were taking blood glucose–lowering medications, or if they had an 8-hour fasting glucose level of at least 11.1 mmol/L (200 mg/dL). Fat intake was assessed by Keys score as calculated from a modified Willett food frequency questionnaire.[22] Reported leisure-time physical activity was assessed by an interviewer-administered questionnaire.[23] Participants were categorized as current, past, or never alcohol users based on self-report. Body mass index was calculated as a measure of weight in kilograms divided by the square of the height in meters.

Statistical Methods

Analyses in this report were restricted to participants who were black or white (48 subjects who were neither black nor white were excluded); participants who had good-quality B-mode ultrasound evaluations of the common carotid artery both at the baseline and at the 3-year follow-up (the first 1255 subjects at the beginning of visit 1 were excluded because of less than adequate ultrasound examinations, 775 with ultrasound data missing from visit 1, 1256 who failed to return for visit 2, and 395 who were missing ultrasound data from visit 2); participants who were not current users of other tobacco products (304 current pipe, cigar, and cigarello smokers were excluded); and participants who responded to the smoking history questionnaire at the baseline visit (845 were excluded). After exclusions, 10 914 participants remained for these analyses.

Statistical analyses were performed using linear regression analysis. The primary independent variable was the smoking category, while the outcome variable was the progression of atherosclerosis as reflected by the difference in IMT as measured at the baseline and follow-up (3 years later) visits. The relationship between smoking category and progression of atherosclerosis was explored using 3 models that were specified a priori. In the first model, the effects of smoking category on progression of atherosclerosis were estimated after adjustment for age, race, sex, and baseline IMT (demographic model). The second model adjusted for these factors and also for hypertension, low-density lipoprotein cholesterol, prevalent coronary heart disease (CHD), and diabetes (cardiovascular risk factor model). The final model adjusted for all preceding factors and also for Keys score, education, leisure-time physical activity, body mass index, and alcohol intake (lifestyle model). Secondary analyses were also performed to assess the relationship between pack-years of smoking and atherosclerosis progression in current and past smokers and the relationship between the number of hours of ETS exposure and progression of atherosclerosis in past and never smokers. These models included all the variables described in the

Table 1.—Description of Study Population by Smoking Status: ARIC Baseline Survey, 1987-1989*

Variables	Total Sample (N=10 914)	Smoking Status				
		Current (n=2956)	Past+ETS (n=1849)	Past−ETS (n=1344)	Never+ETS (n=2449)	Never−ETS (n=2316)
Age, mean (SD), y	54 (6)	53 (6)	54 (6)	55 (6)	54 (6)	54 (6)
% White	80	74	92	91	74	79
% Female	57	53	37	42	70	72
% With hypertension	32	29	32	31	34	33
% With diabetes	8	7	7	7	9	8
% With previous coronary heart disease	5	5	8	6	2	3
LDL-C, mean (SD), mmol/L (mg/dL)	3.5 (1.0)(136 [39])	3.6 (1.1)(138 [41])	3.5 (1.0)(136 [37])	3.5 (1.0)(136 [38])	3.5 (1.0)(137 [39])	3.5 (1.0)(134 [37])
Pack-years, mean (SD), No.	15 (21)	33 (21)	25 (23)	20 (19)	0 (0)	0 (0)
Weekly ETS, mean (SD), h	10 (18)	. . .	20 (22)	0 (0)	18 (20)	0 (0)
Alcohol use, %						
Current	59	65	69	68	48	47
Past	17	21	22	22	14	11
Never	24	14	9	10	38	42
Educational level, %						
Not high school graduate	20	28	18	13	19	16
High school graduate	43	43	45	37	47	41
College graduate	37	29	36	50	34	43
Weekly leisure activity, mean (SD), h	2.39 (0.56)	2.27 (0.56)	2.43 (0.54)	2.49 (0.55)	2.40 (0.55)	2.47 (0.56)
Keys score, mean (SD), No.	42.1 (9.4)	43.3 (9.7)	42.2 (9.5)	40.7 (8.9)	42.3 (9.2)	41.2 (9.1)
Body mass index, mean (SD), kg/m²†	27.2 (5.0)	26.1 (4.6)	27.6 (4.7)	27.4 (4.5)	28.0 (5.3)	27.4 (5.1)
Baseline IMT (µm)	644 (136)	656 (145)	657 (139)	657 (143)	627 (122)	626 (125)
Average IMT progression, µm/3 y	35.0 (105)	37 (109)	37 (109)	31 (109)	37 (101)	32 (97)

*ARIC indicates Atherosclerosis Risk in Communities study; Current, current smoker; Past+ETS, past smoker exposed to environmental tobacco smoke; Past−ETS, past smoker not exposed to ETS; Never+ETS, never smoker exposed to ETS; Never−ETS, never smoker not exposed to ETS; LDL-C, low-density lipoprotein cholesterol; IMT, intimal-medial thickness of carotid artery; and ellipses, not available.
†Body mass index is a measure of weight in kilograms divided by the square of height in meters.

Table 2.—Three-Year Atherosclerosis Progression Rates by Smoking Groups: Adjusted Mean Change in IMT Over a 3-Year Period*

Covariates	Mean Progression Rates, Mean (SD)					Differences Between Groups, Mean (SD) [*P* Value]		
	Current	Past+ETS	Past−ETS	Never+ETS	Never−ETS	ETS Effect	Past vs Never	Current vs Past
Demographic model								
Age, race, sex, and baseline IMT	41.0 (1.8)	39.6 (2.3)	32.5 (2.6)	33.2 (2.0)	27.0 (2.0)	6.7 (2.2)[.003]	5.9 (2.3)[.01]	4.9 (2.5)[.05]
Risk factor model								
Demographic model and hypertension, LDL-C, previous coronary heart disease, and diabetes	41.2 (1.8)	39.8 (2.3)	33.4 (2.7)	32.7 (2.0)	26.9 (2.0)	6.1 (2.2)[.007]	6.7 (2.3)[.004]	4.6 (2.5)[.07]
Life-style model								
Risk factor model and Keys score, education, leisure-time activity, BMI, and alcohol use	43.0 (1.9)	38.8 (2.3)	32.8 (2.7)	31.6 (2.0)	25.9 (2.1)	5.9 (2.3)[.010]	7.0 (2.4)[.004]	7.3 (2.6)[.006]

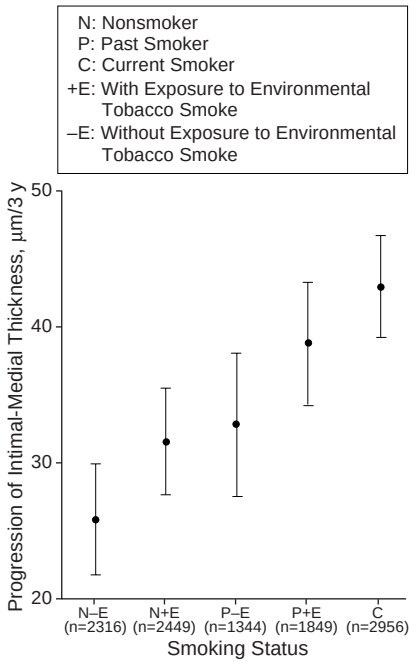
*IMT indicates intimal-medial thickness of carotid artery; Current, current smoker; Past+ETS, past smoker exposed to environmental tobacco smoke; Past−ETS, past smoker not exposed to ETS; Never+ETS, never smoker exposed to ETS; Never−ETS, never smoker not exposed to ETS; LDL-C, low-density lipoprotein cholesterol; and BMI, body mass index, which is a measure of weight in kilograms divided by the square of height in meters.

lifestyle model. Two-way interactions between smoking strata and other risk factors were also assessed.

RESULTS

Of the 10 914 participants, 2956 (27%) were current smokers, 1849 (17%) were past smokers exposed to ETS, 1344 (12%) were past smokers not exposed to ETS, 2449 (22%) were never smokers exposed to ETS, and 2316 (21%) were never smokers not exposed to ETS (Table 1). No differences were observed in the mean age across the smoking groups. Past smokers were much more likely to be white and male, while women were more likely to be never smokers. The need for covariate adjustment is supported by the dramatic differences in the prevalence of cardiovascular risk factors and lifestyle variables. Because of these differences in risk factors across smoking categories, the comparison of unadjusted atherosclerosis progression rates across the smoking strata (which shows increased progression rates with increased cigarette smoke exposure) should be made cautiously. The actual mean time between the 2 ARIC visits was 1062 days, with an SD of 74 days, so the 3-year visit interval was well performed for most participants (and deviations are unlikely to influence results).

Table 2 shows mean IMT progression (and SEs) after adjustment for demographic characteristics (model 1), cardiovascular risk factors (model 2), and lifestyle variables (model 3). After adjustment for demographic factors, a consistent relationship between smoking exposure and progression of atherosclerosis is apparent. In the demographic model, the progression rate was lowest (27.0 µm per 3 years) for never smokers not exposed to ETS and increased in never smokers exposed to ETS (33.2 µm per 3 years), in past smokers not exposed to ETS (32.5 µm per 3 years), and in past smokers exposed to ETS (39.6 µm per 3 years). The highest progression rate was observed in current smokers (41.0 µm per 3 years). Exposure to ETS was estimated to increase the progression rate by 6.7 µm per 3 years (the average difference between those exposed and not exposed to ETS among never and past smokers), a difference that proved significant (P=.003). Past smokers were estimated to progress an average of 5.9 µm per 3 years more rapidly than never smokers, and current smokers were estimated to progress an average of 4.9 µm per 3 years more rapidly than past smok-



Mean and 95% confidence intervals of 3-year progression in the intimal-medial thickness of the carotid artery assessed by ultrasound, shown by smoking status category, after adjustment for demographic characteristics, cardiovascular risk factors, and lifestyle variables (see lifestyle model in Table 2).

Table 3.—Atherosclerosis 3-Year Progression Rate of Smoking Groups Shown for Risk Factors With Statistical Evidence of an Interaction ($P<.05$)*

	Smoking Status, Mean (SE), µm/3 Years					
Risk Factors	Current	Past+ETS	Past−ETS	Never+ETS	Never−ETS	*P* Value
Diabetes						
Without diabetes	40.1 (1.9)	37.4 (2.4)	31.5 (2.8)	30.7 (2.1)	25.9 (2.2)	.004
With diabetes	80.1 (6.8)	55.8 (8.8)	48.4 (10.5)	43.9 (6.9)	26.6 (7.4)	
Hypertension						
Without hypertension	36.8 (22)	36.9 (2.8)	30.8 (3.2)	30.0 (2.5)	22.0 (2.5)	.04
With hypertension	58.0 (3.5)	42.8 (4.2)	36.9 (4.9)	35.9 (3.5)	34.7 (3.7)	
Prevalent coronary heart disease (CHD)						
No previous CHD	42.9 (1.9)	37.8 (2.4)	31.8 (2.8)	32.3 (2.0)	26.0 (2.1)	.04
Previous CHD	46.2 (8.6)	51.4 (8.1)	49.5 (10.9)	0.2 (13.5)	22.1 (12.8)	

*Current indicates current smoker; Past+ETS, past smoker exposed to environmental tobacco smoke; Past−ETS, past smoker not exposed to ETS; Never+ETS, never smoker exposed to ETS; and Never−ETS, never smoker not exposed to ETS

ers ($P=.01$ and $P=.05$, respectively). Further adjustment for cardiovascular risk factors and lifestyle variables proved (1) to make the ordered response between smoking and progression of IMT more consistent, (2) to marginally decrease the estimated ETS effect on progression of IMT from 6.7 µm per 3 years to 5.9 µm per 3 years, (3) to increase marginally the estimated difference in progression of IMT between past and never smokers from 5.9 µm per 3 years to 7.0 µm per 3 years, and (4) to increase the estimated difference in progression between current and past smokers from 4.9 µm per 3 years to 7.3 µm per 3 years. This further adjustment for cardiovascular risk factors and lifestyle variables made the relationship between increased progression of atherosclerosis and smoking exposure clear and consistent, and the significance of the effects between groups (ie, the ETS effect, etc) persisted after adjustment (Figure). The progression rate for current smokers was estimated to be 43.0 µm, and the average progression rate of the 2 groups of never smokers was 28.7 µm ([31.6 µm+25.9 µm]/2), implying that a 50% increase in the progression of atherosclerosis is attributable to current smoking ([43.0 µm−28.7 µm]/28.7 µm).

Interactions between smoking exposure and all covariates were also evaluated (after adjustment for all other factors included in the final model including lifestyle variables). A clear interaction was observed between smoking category and diabetes ($P=.004$), hypertension ($P=.04$), and prevalent CHD ($P=.04$); otherwise, differences between smoking strata were consistent across strata defined by other risk factors ($P>.05$). The observed interaction with diabetes reflects larger differences at each step of smoking exposure in participants with diabetes as compared with their counterparts without diabetes (Table 3). For participants with hypertension, a marginally significant interaction was largely a product of a substantially faster rate of progression for current smokers with hypertension (58.0 µm per 3 years) than participants in other smoking categories (34.7 µm per 3 years to 42.8 µm per 3 years). A similar increase was not observed for current smokers without hypertension, where progression rates were similar to those observed for past smokers (36.8 µm per 3 years compared with 36.9 µm per 3 years for past smokers exposed to ETS and 30.8 µm for past smokers not exposed to ETS). This suggests that the impact of smoking exposure is larger among participants with diabetes than for participants without diabetes, and the impact of current smoking may be particularly large for participants with hypertension. While the interaction for prevalent CHD was marginally significant ($P=.04$), the relatively small proportion of participants with prevalent CHD who never smoked (<3% of the population that never smoked) resulted in unstable estimates for participants with prevalent disease, making the significant interaction more likely a chance happening.

In a secondary analysis, the impact of pack-years of smoking on progression rates was estimated for current and past smokers (with and without exposure to ETS). All analyses were performed in the lifestyle model, which contained adjustments for demographic characteristics, cardiovascular risk factors, and lifestyle variables. There was no interaction between pack-years of exposure and smoking status ($P=.33$), suggesting increases in pack-years of exposure had a similar impact on the progression rates for current smokers, past smokers exposed to ETS, and past smokers not exposed to ETS. However, in models with both pack-years and smoking status category included, pack-years of exposure was highly significant ($P<.001$), while smoking status category was not ($P=.11$). This would suggest that the primary explanation of differences between these smoking groups was the increasing exposure to smoking as measured by pack-years. Note that in Table 1, the mean pack-years for past smokers not exposed to ETS was 19, as compared with 24 for past smokers exposed to ETS and 31 for current smokers.

In addition to assessing the impact of the presence or absence of exposure to ETS, the ARIC investigators also asked those exposed to ETS to estimate the number of hours per week that they were in the immediate presence of smokers. These data were analyzed in the 2 ETS groups (never smokers exposed to ETS and past smokers exposed to ETS) to assess if those participants exposed to more hours of ETS per week had a faster progression rate than those exposed to fewer hours of ETS. In an analysis conducted using the lifestyle model, there was no evidence of a dose-response relationship between increasing weekly hours of ETS exposure and increased progression rates ($P=.38$) among those exposed to ETS.

COMMENT

These longitudinal ARIC data show a consistent relationship between increasing exposure to cigarette smoke and greater progression of carotid atherosclerosis

rosis. Large differences were observed in the progression rates between past smokers and never smokers (7.0 µm per 3 years or 24% [7.0/([31.6+25.9]/2)] greater) and in the progression rates of current and past smokers (7.3 µm per 3 years or 20% [7.3/([38.8+32.8]/2)] greater). The increase in atherosclerosis progression attributable to this modifiable risk factor is among the most substantial of any of the cardiovascular risk factors assessed by the ARIC study.[24] After adjustment for demographic characteristics, cardiovascular risk factors, and lifestyle variables, exposure to ETS was also estimated to increase progression by 5.9 µm over a 3-year period. The difference in progression rates between those participants least exposed to cigarette smoke (never smokers not exposed to ETS) and those most exposed (current smokers) was 17.1 µm per 3 years. Since exposure to ETS was estimated to increase progression of atherosclerosis by 5.9 µm per 3 years, the impact of exposure to ETS was 34% (5.9/17.1) as great as the impact of active smoking on the progression of atherosclerosis.

Some groups argue that the exposure to passive smoke measured in "cigarette equivalents" rarely exceeds a single cigarette a day.[25] However, as reported by Glantz and Parmley,[9] the content of ETS is potentially more toxic than "mainstream" smoke, and the cardiovascular system of an individual exposed to passive smoke may be more sensitive than that of an active smoker because of the lack of a fully developed protective response. Thus, the increased progression of atherosclerosis associated with ETS exposure should be considered in light of the estimated 30 000 to 60 000 annual deaths in the United States attributable to ETS.[9-11]

Differences in the profile of cardiovascular risk factor burden could potentially confound differences in atherosclerosis progression between active and passive smokers and between those exposed and those not exposed to ETS.[26] However, adjustment for a wide range of other cardiovascular risk factors and lifestyle variables had only modest impact on the estimated effect of exposure to ETS, reducing it by only 12%, from an estimated 3-year progression rate of 6.7 µm to 5.9 µm. Thus, it is unlikely that further control for other risk factors would explain the ETS effect.

Progression of atherosclerosis among past smokers was higher than among never smokers—despite past smokers' nonsmoking status over the period during which progression was measured. In support of this striking observation, our secondary analysis found no difference between past and current smokers after controlling for the number of pack-years of exposure. Atherosclerosis progression appears to be largely related to the pack-years of cigarette exposure and not to present smoking status. These 2 observations suggest that the effect of smoking on atherosclerosis progression may be cumulative, proportional to lifetime pack-years of exposure, and perhaps irreversible. If this is true, the primary benefit from quitting smoking on the progression of atherosclerosis would be to prevent further accumulation of exposure. This hypothesis is not consistent with data from previous cross-sectional reports of clinical populations that have suggested the rate of progression slows in people who quit relative to those who continue to smoke.[27] Given that cigarette smoking may increase the risk of cardiovascular heart disease by promoting atherosclerosis progression and other triggering factors (eg, by changes in hemostasis), our observations are not inconsistent with clinical data suggesting that the risk of coronary events in many smokers returns to that of never smokers 3 to 5 years after quitting.[28] Alternatively, it is possible that past smokers have stopped their habit because of smoking-related respiratory and cardiovascular symptoms. If this is the case, then past smokers would have a higher average atherosclerosis burden and may be more likely to continue to progress at a higher rate, one that is indistinguishable from current smokers. However, this explanation seems unlikely since covariate adjustment for cardiovascular risk factors, including prevalent cardiovascular disease, actually increased the difference in the progression rates between past and current smoking groups.

A greater impact of smoking on IMT progression was observed in participants with diabetes compared with those without diabetes. That smoking may accelerate the atherosclerotic process in participants with diabetes is plausible, given that participants with diabetes are more likely to have widespread vascular damage as a consequence of their disease.[29] In a 10-year follow-up report of the National Health and Nutrition Examination Survey I cohort, the relative risk (RR) for CHD mortality among 492 patients with diabetes was 2.5 for current smokers compared with never smokers; the RR for smoking was 1.7 among nearly 12 000 subjects without diabetes.[30] Among men screened for the Multiple Risk Factor Intervention Trial, the 12-year cardiovascular disease death rate increased more steeply across increasing levels of cigarettes per day for men with diabetes than for men without diabetes.[31] Both Gay et al[32] and Suarez and Barrett-Connor[33] have reported an important interaction between smoking and diabetes status in relation to multiple measures of morbidity and mortality. These authors suggest that the vascular damage resulting from both diabetes and smoking may be a possible mechanism compounding this effect. The finding of a greater impact of smoking on progression of IMT in participants with diabetes as compared with participants without diabetes is consistent with these reports of morbidity and mortality. Participants with hypertension are also likely to have similarly widespread disease, and current smoking may similarly provide an impetus for more rapid progression. It is not clear why an increasing progression rate was not observed for participants with hypertension who smoked in the past.

Several potential limitations should be considered in assessing this report. First, in secondary analyses we found no relationship between the number of hours of ETS exposure and the progression of atherosclerosis. We believe that while it is relatively easy for a participant to determine whether they are exposed to ETS or not, quantifying the number of hours per week is a difficult task.[34] In addition, we asked the participant to report the average weekly exposure and did not collect data on specific sources (eg, home, work, etc). It is possible that the ability to quantify the amount of exposure differs between the sources, again introducing differential measurement error on the amount (but not presence) of exposure to ETS. For both these reasons, our failure to demonstrate a dose-response relationship between ETS exposure and progression of atherosclerosis may be the result of a measurement error in the quantification of ETS. Second, after control for pack-years of exposure, there was no significant difference between past smokers exposed to ETS and past smokers not exposed to ETS. We cannot be sure whether the difference in progression of atherosclerosis between these 2 past-smoking groups should be attributed to increased pack-years or to exposure to ETS. However, the similarity of the ETS effect in past and never smokers supports the existence of the ETS effect. Finally, it is possible that measurement error, particularly in the assessment of IMT, could introduce bias or noise in the estimates of progression rates. However, this index of atherosclerosis has proven to be a powerful predictor of incident coronary events in this same population, with the prevalence among women increasing from 0.6 per 1000 person-years for participants with IMT of less than 600 µm as compared with 11.7 per 1000 person-years for participants with IMT of greater than 1000 µm.

Prevalence increased in men from 3.0 per 1000 to 12.9 per 1000 for the same contrast of IMT.[35]

In conclusion, these data represent the first report, to our knowledge, from a large population-based study of the impact of active smoking and exposure to ETS on the progression of atherosclerosis. Active smoking was found to play a major role in the progression of atherosclerosis, as did the duration of smoking measured by pack-years of exposure. The impact of exposure to ETS on atherosclerosis progression was not only detected but was also surprisingly large, increasing the progression rate by 11% above those not so exposed. Smoking especially increased atherosclerosis progression rates among participants with diabetes and hypertension. Finally, these data suggest that the effects of smoking on the progression rate of atherosclerosis may be both cumulative and irreversible.

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