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The Relationship of Active and Passive Smoking to Carotid Atherosclerosis 12–14 Years Later[1]

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Background. **Active and passive smoking have been found to be associated with clinical atherosclerotic disease. To explore the effects of smoking on atherogenesis, we investigated the relationship of past and current active and passive smoking to carotid atherosclerosis in middle-aged adults.**

Methods. **The study population consisted of 2,073 middle-aged residents of Washington County, Maryland. Information on active smoking and exposure to environmental tobacco smoke (ETS) was obtained from a 1975 census and from the baseline visit of the Atherosclerosis Risk in Communities (ARIC) Study in 1987–1989. Carotid artery intimal–medial wall thickness, measured by B-mode ultrasound methods in 1987–1989, was used as an indicator of carotid atherosclerosis. Mean intimal–medial wall thickness (IMT) was adjusted for age, gender, cardiovascular risk factors, and education using multiple linear regression.**

Results. **The lowest mean IMT was found among never smokers who had never been exposed to ETS (mean ± standard error: 0.706 ± 0.013 mm). Exposure to ETS in one or both time periods was associated with increased IMT among never smokers (ETS in 1975 only: 0.731 ± 0.022; ETS in 1987–1989 only: 0.738 ± 0.011; ETS in both periods: 0.734 ± 0.012). Active smoking in 1975 was also associated with increased IMT. The greatest mean intimal–medial wall thickness was found among persons who were current smokers in both time periods (0.807 ± 0.009).**

Conclusions. **Both past and current passive and active smoking are associated with increased carotid intimal–medial wall thickness.**

INTRODUCTION

Personal, active smoking is a well-established risk factor for atherosclerotic disease of the aorta, the carotid arteries, and coronary arteries (1–10). Exposure to environmental tobacco smoke, so-called passive smoking, has also been found to be associated with symptomatic atherosclerosis (11, 12). Several pathogenic mechanisms have been postulated as mediators of the relationship between smoking and atherosclerosis. These include processes leading to atherosclerotic lesions such as increased aggregation of blood platelets and damage to endothelial cells (11), as well as those which may cause asymptomatic lesions to become symptomatic, such as reduction in the body's ability to deliver and utilize oxygen (11) and further narrowing of atherosclerotic vessels by increased thrombogenesis (13, 14).

Recently, both active smoking and exposure to environmental tobacco smoke have been shown to be associated cross-sectionally with increased thickness of the intimal–medial portion of the carotid artery wall measured by B-mode ultrasound in the Atherosclerosis Risk in Communities (ARIC) study (15). These cross-sectional data from the ARIC study, however, do not lend themselves to establishing the temporality of the association of smoking with carotid wall thickening.

For one of the populations included in the ARIC study (Washington County, MD), data on active and household smoking were available from a private County census conducted in 1975 and linked to the ARIC study population. Thus, in Washington County, it was possible to assess whether the cross-sectional relationship reported by Howard *et al.* (15) could be confirmed by relating environmental and active smoking in 1975 to carotid intimal–medial wall thickness measured 12–14 years later. Because wall thickness measurements were not available in 1975, the temporal relationship cannot be firmly established. However, if active and passive smoking in 1975 were found to be related to carotid intimal–medial wall thickness in the ARIC baseline visit, the case for a causal relationship would be strengthened.

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MATERIALS AND METHODS

Study Population and Sources of Data

The ARIC study is a prospective investigation of subclinical and clinical atherosclerosis in four U.S. communities (Forsyth County, NC; Jackson City, MS; selected suburbs of Minneapolis, MN; and Washington County, MD) (16). In Washington County, a probability sample of persons between the ages of 45 and 64 years was invited to participate. In addition, persons living in the same households with the invited persons were also asked to participate if they met the criteria for inclusion. Excluded persons were those whose physical disabilities prevented them from coming to a central clinic, those whom the interviewer judged to be mentally incompetent, persons who did not speak English, those who planned to move out of the county in the near future, and those who did not wish to be examined. The final Washington County sample of examined persons consisted of 4,023 persons. The baseline visit of the ARIC study took place in the years 1987–1989 and included a home interview followed by a clinic visit. Information on demographic characteristics, a variety of risk factors for atherosclerosis, and intimal–medial thickness of the carotid artery walls was collected by means of interview, physical examination, and laboratory procedures, including standardized ultrasound examination of the carotid arteries.

The other data source was a private census of Washington County conducted in 1975 by the Johns Hopkins Center for Public Health Research. The response rate in this predominantly white, semirural county is estimated to have been approximately 90%. Information collected in the census included demographic profile, education, housing characteristics, and smoking status for each individual.

The ARIC cohort members were linked to the 1975 census population by means of a computer algorithm which required that name and birth date be identical in each data set for a match to be identified. Of the 4,023 members in the ARIC cohort, 2,884 (71.7%) were linked to the 1975 private census. This degree of linkage is consistent with the participation in the 1975 census, the low emigration rate of adults, and the degree of immigration into the county since 1975.

Of the 2,884 persons linked to the 1975 census, a total of 811 were excluded from the final study group. Three hundred forty-two persons were excluded due to incomplete or inconsistent information on smoking status. These included 185 never smokers with missing information on passive smoking, either in 1975 (133 individuals), or in 1987–1989 (52 individuals). In addition, 157 individuals had missing or inconsistent smoking status at one or both times. For example, among 122 never smokers in 1987–1989, 104 were reported as former smokers in 1975. An additional 469 persons were excluded due to incomplete information on wall thickness (389 persons) or other risk factors (80 persons). The final study population was thus composed of 2,073 persons.

Study Variables

Carotid artery intimal–medial wall thickness was measured using high-resolution B-mode ultrasound imaging based on the technique developed by Pignoli *et al.* (17). The ultrasound reading process includes the measurement of the intimal–medial thickness (in mm) at the far wall of designated 1-cm lengths of the common carotids, the carotid bifurcations, and the internal carotids. The average intimal–medial wall thickness over the six sites (three for the left and three for the right carotid arteries), was used in this study. Details of the scanning and reading procedures and their reliability have been described elsewhere (18, 19). Ultrasonic images were recorded and standardized readings were performed at the ultrasound reading center by trained readers. Between-reader reliability coefficients ranged from 0.78 to 0.92 for the different carotid sites. Within-reader variability was found to be significantly smaller than between-reader variability (19).

Persons were classified as current, former, or never smokers on the basis of cigarette smoking histories in 1975 and 1987–1989. In addition, persons were considered to be exposed to environmental tobacco smoke in 1975 (passive smokers) if one or more persons in their household were smokers of cigarettes, pipe, or cigars at that time. Information on smoke exposure outside of the household was not collected in the 1975 census. In the ARIC examinations in 1987–1989, persons were considered to be passive smokers if they reported regularly spending 1 hr or more per week around smokers. This information was collected only for those who claimed not to be current smokers in 1987–1989.

Individuals who claimed to be never smokers at both times were classified into four categories of passive smoking: exposed to environmental tobacco smoke in 1975 only, in 1987–1989 only, in both, or in neither time period. Current and former smokers in 1987–1989 were each classified into three categories based on their 1975 smoking status (current, former, or never smokers in 1975). Among both former and current smokers in 1987–1989, only 49 persons claimed to be never smokers in 1975; these were therefore combined with the 1975 former smokers. Thus, eight smoking categories were included in the analyses (see Table 2). Additional information on possible confounding variables, including age, gender, systolic blood pressure, body mass index, low density lipoprotein cholesterol concentration (LDL cholesterol), presence of diabetes, dietary fat (Key's score), physical activity, alcohol intake, and education (highest grade completed), was obtained from the ARIC interview, examination, and laboratory studies (16). Systolic blood pressure was calculated as the average of the second and third of three

consecutive measurements with a random zero sphygmomanometer. Body mass index was calculated as weight(kg)/height(m)^2. LDL cholesterol concentration was estimated using the Friedewald formula (20). Persons were considered diabetic if they reported having diabetes or taking blood-glucose lowering medications, or if they had a fasting blood glucose level of at least 140 mg/100 ml or a nonfasting blood glucose of at least 200 mg/100 ml. Key's score is a measure of the serum cholesterol elevating potency of the dietary pattern of an individual (21). It was constructed by combining information on percentage of energy from saturated and polyunsaturated fat, and dietary cholesterol, obtained using an interviewer-administered version of the food frequency questionnaire developed by Willett *et al.* (22). Physical activity was assessed using a modified version of Baecke *et al.*'s questionnaire and summarized in three indices: physical activity during leisure, physical activity during sport, and physical activity during work (23, 24). Ethanol intake in grams per week was estimated based on participants' answers to interview questions on amounts of beer, wine, and liquor drank per week.

Statistical Analysis

The smoking categories were compared in regard to age, gender, race, pack–years of smoking, hours per week around smokers in 1987–1989, and intimal–medial wall thickness using χ^2 tests and analysis of variance. Mean intimal–medial wall thickness measurements for each of the smoking categories were adjusted for age, gender, systolic blood pressure, LDL cholesterol, diabetes, body mass index, Key's score, physical activity, alcohol intake, and education using multiple linear regression. The smoking categories were included in the regression equations as dummy variables. Analysis of variance was used to compare 1975 former or never smokers to 1975 current smokers. Among never smokers, two-way ANOVA was used to investigate the independent effects of passive smoking in both time periods and their interaction. The possibility of a dose–response effect of environmental tobacco smoke on intimal–medial carotid wall thickness among never smokers was investigated using multiple linear regression and including packs of cigarettes/day smoked in the household (1975) and hours per week around smokers (1987–1989) as continuous covariates.

RESULTS

Among the 4,023 Washington County ARIC cohort participants, the 2,884 who were linked to the 1975 Washington County census were slightly older, included a larger proportion of females, whites, and never smokers, and had slightly higher systolic blood pressures than those not linked to the census. Differences in other risk factors were small and not statistically significant ($P > 0.05$) (Table 1). Overall the final study group, composed of 2,073 persons, was generally similar in demographic characteristics and cardiovascular risk factors to the 2,884 ARIC cohort participants linked to the 1975 census. (see Table 1).

Table 2 shows variations in age, gender, pack–years of smoking, and hours around smokers as reported in 1987–1989 for the different smoking categories. Overall, differences in age and gender across the eight categories were statistically significant ($P \leq 0.0001$). Differences in age were of small magnitude. Never smokers in 1975 and 1987–1989, particularly those exposed to environmental tobacco smoke (ETS) in 1975 only and in both 1975 and 1987–1989, included larger proportions of females than the remaining categories. The lowest proportions of females were found among former smokers in 1987–1989. Pertinent categories were also significantly different in pack–years of smoking and hours around smokers ($P \leq 0.0001$). In never smokers, the mean number of hours per week around smokers (ascertained in 1987–1989) among those exposed to environmental tobacco smoke in both periods was higher than that among those exposed only in 1987–1989. In former smokers in 1987–1989, pack–years of smoking and hours around smokers were greater in current smokers in 1975 than in never and former smokers in 1975. Among current smokers in 1987–1989, those who were also current smokers in 1975 were slightly older and had more pack–years of smoking than never or former smokers in 1975.

Table 3 shows unadjusted and adjusted mean intimal–medial carotid wall thickness according to smoking category, stratified by gender. Overall, adjusted mean thickness differed significantly across categories ($P \leq 0.0001$ for men and $P = 0.001$ for women). Because patterns were similar across genders, Table 3 also shows mean intimal–medial wall thickness in the entire study sample adjusted for age, gender, and risk factors. The lowest mean intimal–medial wall thickness was found among never smokers in both time periods who in addition had never been exposed to environmental tobacco smoke. Adjusted mean thicknesses were higher for all three categories of exposure to ETS than for the never smokers with no recorded exposure to environmental tobacco smoke at either time. When the independent effects of exposure to ETS in 1975 and in 1987–1989 among never smokers was investigated using analysis of variance, exposure to ETS in 1987–1989 was found to be associated with a statistically significant increase in intimal–medial wall thickness vis-a-vis no ETS, after adjustment for age, gender, and cardiovascular risk factors (adjusted mean difference (95% confidence interval): 0.035 mm (0.008–0.062)). Exposure to ETS in 1975 and exposure to ETS in both periods were also associated with increased wall thickness vis-a-vis no ETS after adjustment, although these increases did not achieve statistical significance (dif-

TABLE 1

Description of Washington County ARIC Cohort Participants Not Linked and Linked to the 1975 Washington County Census and Final Study Group by Demographic Characteristics and Selected Risk Factors for Atherosclerosis

		ARIC participants not linked to 1975 Washington County Census		ARIC participants linked to 1975 Census		Final study group[a]	
Total number		1139[b]		2884[b]		2073	
Age in years mean (standard deviation)		51.4	(5.7)	54.9	(5.5)	54.9	(5.5)
Females (percentage)		48.0		55.1		55.6	
White (percentage)		98.2		99.1		99.3	
Complete high school education (percentage)		72.4		70.8		70.5	
Systolic blood pressure (mmHg) mean (standard deviation)		117.3	(16.7)	119.8	(17.4)	119.3	(17.6)
LDL cholesterol (mg/dl) mean (standard deviation)		138.3	(35.9)	140.1	(38.5)	139.6	(38.6)
Body mass index (kg/m^2) mean (standard deviation)		27.9	(5.3)	27.8	(5.3)	27.4	(5.1)
Diabetes (percentage)		9.1		9.4		8.7	
Usual ethanol intake (g/week)[c] mean (standard deviation)		102.1	(112.3)	104.4	(117.5)	104.4	(111.9)
Key's score[d] mean (standard deviation)		42.4	(10.3)	42.8	(9.7)	42.6	(9.7)
Physical activity scores[d] mean (standard deviation)	Leisure	2.4	(0.5)	2.4	(0.5)	2.4	(0.5)
	Sport	2.5	(0.8)	2.4	(0.8)	2.5	(0.8)
	Work	2.2	(1.0)	2.1	(1.0)	2.2	(1.0)
Mean intimal–medial carotid wall thickness (mm) mean (standard deviation)		0.746[e]	(0.188)	0.757[f]	(0.209)	0.758	(0.212)
Cigarette smoking status in 1987–1989 (percentage)	Never	40.1		45.7		40.0	
	Former	35.5		32.0		35.9	
	Current	24.4		22.3		24.1	

[a] Excluding 342 persons with missing or inconsistent information on smoking status and 469 persons with missing information on carotid wall thickness or cardiovascular risk factors (see text).
[b] Actual numbers on which statistics are based may vary slightly due to missing information.
[c] Among persons reporting ethanol intake.
[d] See text for definition of Key's score and physical activity scores.
[e] Based on only 974 persons due to missing information.
[f] Based on only 2438 persons due to missing information.

ference for ETS 1975: 0.023 mm (−0.016–0.062), difference for ETS both: 0.022 mm (−0.005–0.049)). Contrary to the expectation exposure to ETS in both periods was not consistently associated with greater wall thickness than exposure to ETS in only one period. Among former smokers in 1987–1989, adjusted mean wall thickness was greater in 1975 current smokers than in 1975 former or never smokers (0.017 mm (−0.012–0.046)). Current smokers in both 1975 and 1987–1989 had much larger intimal–medial wall thickness than persons who were current smokers in 1987–1989 but were never or former smokers in 1975 (0.051 (−0.022–0.124)). Current smokers in both periods had the largest mean intimal–medial wall thickness value of all smoking categories. Adjusted mean intimal–medial wall thicknesses and their 95% confidence intervals are shown in Fig. 1.

Due to missing information, only 421 of the 829 never smokers could be included in the analyses for dose–response. Packs/day smoked in household in 1975 and hours/week around smokers in 1987–1989 were found to be independently and positively associated with intimal–medial thickness among never smokers after adjustment for age and gender, but confidence intervals for the difference in wall thickness per unit change in exposure to ETS were wide and overlapped 0 (not shown in a table or figure). In nonsmokers, each pack/day smoked in the household in 1975 was associated with a 0.002-mm increase in wall thickness (95% confidence interval: −0.03 mm–0.03 mm), and each hour/week around smokers in 1987–1989 was associated with a 0.0003-mm increase in wall thickness (95% confidence interval: −0.0005 mm–0.001 mm), after adjustment for age and gender. Both effects were greatly reduced, and even inverted in the case of packs/day smoked in household in 1975, after adjustment for systolic blood pressure, body mass index, LDL cholesterol, diabetes, Key's score, physical activity, alcohol intake, and education (−0.004 mm per pack/day and 0.00001 mm per hour/week).

TABLE 2

Selected Characteristics of Study Group by Active Smoking Status and Exposure to Environmental Tobacco Smoke (ETS) in 1975 and 1987–1989

	N	Age mean (standard deviation)	Females (percentage)	Pack–years of smoking 1987–1989 mean/median (*n*)[a]	Hours per week around smokers 1987–1989[b] mean/median (*n*)[a]
			Never smokers in 1975 and 1987–1989		
No ETS	211	54.9 (5.6)	68.2	—	—
ETS 1975 only	77	55.6 (5.7)	88.3	—	—
ETS 1987–1989 only	282	54.0 (5.5)	57.1	—	10.0/3.0
ETS 1975 and 1987–1989	259	54.1 (5.5)	89.2	—	22.2/9.0
			Former smokers in 1987–1989		
Never/former smokers in 1975	448	56.0 (5.6)	35.3	17.5/12 (434)	12.1/2.0 (376)
Current smokers in 1975	296	55.7 (5.6)	38.2	38.6/34 (292)	14.4/4.0 (227)
			Current smokers in 1987–1989		
Never/former smokers in 1975	44	52.7 (5.0)	56.8	24.5/18.5 (43)	—
Current smokers in 1975	456	54.5 (5.3)	55.5	39.6/37.0 (451)	—

Note. Overall differences in age, gender, pack–years of smoking, and hours per week around smokers are statistically significant ($P < 0.01$).
[a] Information on number of individuals for each measurement is provided when it does not coincide with total *N* in group.
[b] Only collected for individuals who were not current smokers in 1987–1989.

DISCUSSION

ARIC is one of the first population-based studies to examine the relationship of suspected risk factors to atherosclerosis defined on the basis of carotid intimal–medial wall thickness determined by B-mode ultrasound. Although the precise relationship between carotid intimal–medial thickness and future atherosclerotic disease has yet to be firmly established, intimal–medial carotid wall thickness has been related to traditional cardiovascular risk factors (7, 10, 25) and to risk of acute coronary events (26–28). These findings suggest that carotid intimal–medial thickness may be a valid indicator of early atherosclerotic disease.

Associations of active smoking with carotid atherosclerosis (assessed by the presence of plaques, stenosis,

TABLE 3

Crude and Adjusted Mean Intimal–Medial Wall Thickness by Active Smoking Status and Exposure to Environmental Tobacco Smoke (ETS) in 1975 and 1987–1989

	Females			Males			Total		
	N	Mean	Adjusted mean[a] ± standard error	*N*	Mean	Adjusted mean[a] ± standard error	*N*	Mean	Adjusted mean[b] ± standard error
				Never Smokers in 1975 and 1987–1989					
No ETS	144	0.662	0.669 ± 0.013	67	0.735	0.733 ± 0.027	211	0.685	0.706 ± 0.013
ETS 1975 only	68	0.697	0.686 ± 0.019	9	0.798	0.745 ± 0.072	77	0.709	0.731 ± 0.022
ETS 1987–1989 only	161	0.706	0.703 ± 0.013	121	0.765	0.789 ± 0.020	282	0.731	0.738 ± 0.011
ETS 1975 and 1987–1989	231	0.688	0.684 ± 0.011	28	0.804	0.780 ± 0.041	259	0.701	0.734 ± 0.012
				Former smokers in 1987–1989					
Never/former smokers in 1975	158	0.691	0.695 ± 0.013	290	0.840	0.821 ± 0.013	448	0.788	0.757 ± 0.009
Current smokers in 1975	113	0.721	0.714 ± 0.015	183	0.843	0.834 ± 0.016	296	0.796	0.768 ± 0.011
				Current smokers in 1987–1989					
Never/former smokers in 1975	25	0.689	0.704 ± 0.032	19	0.753	0.801 ± 0.050	44	0.717	0.744 ± 0.028
Current smokers in 1975	253	0.739	0.741 ± 0.011	203	0.872	0.895 ± 0.016	456	0.798	0.807 ± 0.009

[a] Mean wall thickness was adjusted for age, systolic blood pressure, LDL cholesterol, presence of diabetes, Key's score, physical activity scores, alcohol intake, and education using multiple linear regression. Gender, presence of diabetes, and years of education (categorized into six levels) were included as dummy variables. Age, LDL cholesterol, body mass index, alcohol intake in grams per week, systolic blood pressure, Key's score, and physical activity scores were included as continuous covariates.
[b] Adjusted for gender, in addition to risk factors listed in footnote[a].

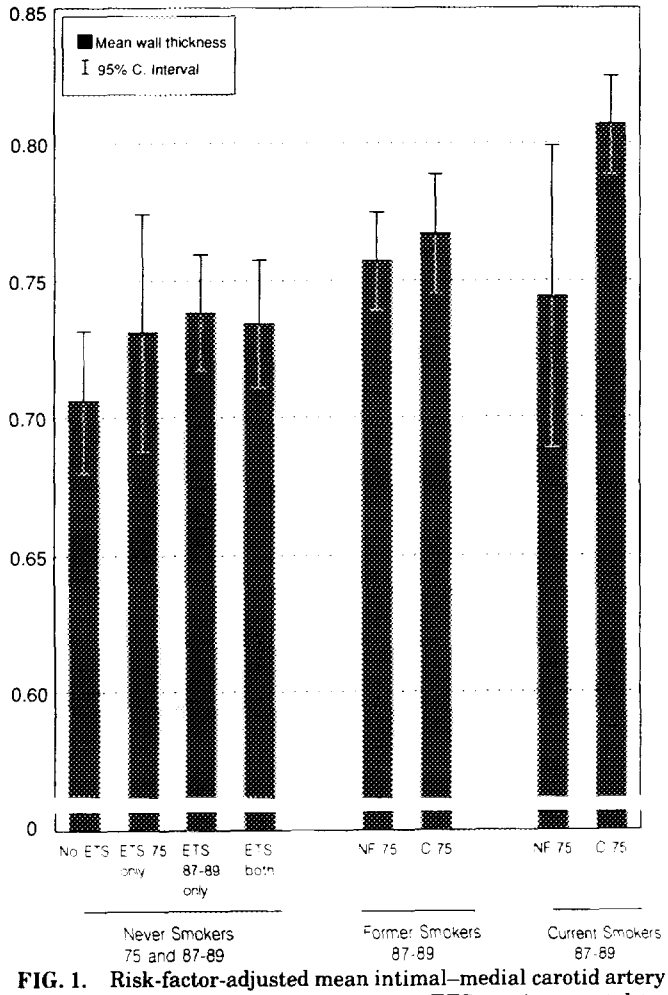

FIG. 1. Risk-factor-adjusted mean intimal–medial carotid artery wall thickness (mm) by smoking category. ETS, environmental tobacco smoke; NF 75, never or former smokers in 1975; C 75, current smokers in 1975. Adjusted for age, gender, systolic blood pressure, LDL cholesterol, diabetes, Key's score, body mass index, physical activity, alcohol intake, and education using multiple linear regression.

or occlusion in angiography or ultrasound) and with progression of carotid atherosclerotic lesions have been reported previously (2–6, 8, 9). Cigarette smoking has also been found to be associated with intimal–medial carotid wall thickness (7, 10, 25). Several studies have also documented associations of passive household smoking with coronary heart disease deaths or events (11, 12). However, to our knowledge, only in ARIC has the relationship of passive smoking to a potential indicator of carotid atherosclerosis been investigated: a previous cross-sectional analysis based on the entire ARIC cohort strongly suggested that there is a relationship of environmental tobacco smoke to carotid intimal–medial wall thickness (15).

By introducing a longitudinal design component, the present study provides additional evidence of a relationship between active smoking and intimal–medial wall thickness. Former and current smokers in 1987–1989 generally had greater intimal–medial wall thicknesses than never smokers at both times. In addition, among both former and current smokers in 1987–1989, smokers in 1975 had greater adjusted mean wall thickness than never or former smokers in 1975, although these differences did not achieve statistical significance. Due to the small numbers of never smokers in 1975, this group had to be combined with the more numerous former smokers. We were unable to compare current smokers in 1975 to never smokers in 1975 and may therefore have underestimated the association of smoking in 1975 with wall thickness. In fact, among 1987–1989 former smokers, when current smokers in 1975 were compared to the 43 persons who were never smokers in 1975, the magnitude of the difference in wall thickness was considerable (0.052 mm).

The association of smoking in 1975 with intimal–medial wall thickness in 1987–1989 may be attributable to increased pack–years of exposure. Both in former and current smokers in 1987–1989, total pack–years of smoking assessed in 1987–1989 was greater in 1975 current smokers than in 1975 never or former smokers. The wall thickness effect may also be due to differences in years since quitting smoking between the 1975 smoking categories, although Howard *et al.* (15) found no evidence of decreased wall thickness with increasing years since quitting smoking in cross-sectional analyses.

Although our study is not entirely conclusive regarding the effects of passive smoking, our results suggest that exposure to environmental tobacco smoke may also be associated with increased carotid artery intimal–medial wall thickness. Mean wall thickness was found to be lowest among never smokers who had never been exposed to environmental tobacco smoke, and passive smoking in one or both time periods was associated with an increase in wall thickness ranging from 0.023 to 0.035 mm, after adjustment for other risk factors. All three exposure to environmental tobacco smoke groups had consistently greater wall thickness than the no exposure group. Estimates also suggest that exposure to environmental tobacco smoke in 1975 is associated with increased wall thickness in 1987–1989 even among those not exposed to environmental tobacco smoke in the latter period; however, since only 77 persons were included in the ETS 1975 only group, the confidence interval on adjusted mean wall thickness is wide. Contrary to expectation, among females, the effect of exposure to environmental tobacco smoke in both time periods was similar to the effects of exposure in either time period. Another finding inconsistent with the passive smoking hypothesis is that a predicted linear "dose–response" effect could not be documented.

The characterization of exposure to environmental tobacco smoke is a potential limitation in our study. Measures of exposure to environmental tobacco smoke

were not strictly comparable in both time periods. In addition, individuals exposed to environmental tobacco smoke at work in 1975 (possibly a substantial source of exposure) were classified as not exposed if all other household members are nonsmokers. This type of misclassification may have biased our estimates toward the null hypothesis, and may explain our failure to document a "statistically significant" or a dose–response effect of exposure to environmental tobacco smoke. The smoking categories used are crude measures of exposure and many include individuals with considerable variation in exposure to environmental tobacco smoke, amount smoked, or years since quitting smoking. We were also unable to use biochemical markers to validate self-reports.

Although a possible limitation of our study is the exclusion of a relatively large number of individuals due to missing or inconsistent information, differences between those included and not included in the analyses were of small magnitude and not statistically significant for most variables. In addition, it is unlikely that excluded subjects were selected on the basis of both exposure and outcome (a necessary condition for our estimates to be biased). Potential confounders of the association, like blood pressure, LDL cholesterol, diabetes, body mass index, Key's score, physical activity, and ethanol intake, were measured in 1987 and not in 1975. Associations of 1975 exposures with 1987 wall thickness could thus be partly due to unmeasured 1975 confounders. Finally, it is also possible that the observed associations are partly due to residual confounding by socioeconomic status or other factors, which may persist even after adjustment for education and the main cardiovascular risk factors.

In spite of its limitations, however, several aspects of the study design strengthen the possibility of an association of passive and active smoking with carotid intimal–medial wall thickness. Our study is based on a relatively large, population-based sample. The association of exposure in 1975 with atherosclerosis 12–14 years later suggests that exposure is likely to have preceded wall thickening, although the absence of wall thickness measurements in 1975 makes it impossible to firmly establish a temporal relationship between smoking and wall thickening. Atherosclerosis is a chronic disease which is likely to develop over a long period of time as a result of past and persistent exposures. Associations with past exposures, such as those documented by our study, are more consistent with a biologically plausible process of atherogenesis than associations with current exposures. In addition, the use of noninvasively determined intimal–medial carotid wall thickness rather than clinically defined atherosclerotic disease as the outcome measure makes selection bias less likely.

The use of ultrasonically determined intimal–medial carotid artery wall thickness as an indicator of carotid atherosclerosis is relatively new in epidemiologic studies, and the public health importance of small differences in carotid intimal–medial thickness is still unclear. A recent preliminary analysis based on the entire ARIC cohort found that an increase of 0.16 mm in intimal–medial wall thickness (one standard deviation) was associated with a 24% increase in risk of coronary heart disease events in men and a 44% increase in risk among women, over a 2.2 year follow-up period (28). Among Finnish men, for each 0.1 mm increase in intimal–medial wall thickness the risk of acute myocardial infarction increased by 11% over a follow-up ranging from 1 month to 3 years for individual men (26). Therefore, although the magnitude of the differences in carotid wall thickness associated with active and passive smoking in our study appears small, their impact on the risk of future cardiovascular events over time may be significant.

In summary, both past and current active and passive smoking were found to be associated with increased carotid intimal–medial wall thickness. Although differences in mean wall thickness between categories frequently did not achieve statistical significance (possibly due in part to reduced sample size), the consistency of the associations observed suggests a relationship between active and passive smoking and carotid artery intimal–medial wall thickness. Within both former and current smokers in 1987–1989, those who smoked in 1975 had greater intimal–medial wall thickness than those who did not. All three groups of never smokers exposed to environmental tobacco smoke had greater wall thickness than the unexposed group. These differences were observed after adjustment for risk factors, and in spite of potential misclassification of exposure to ETS, which, as mentioned, is likely to have biased our estimates toward the null. These findings suggest that past and current exposure to environmental tobacco smoke may also be associated with increased carotid intimal–medial wall thickness. The additional follow-up of the ARIC cohort will allow assessment of the relationship of the detailed environmental tobacco data available from the baseline visit to intimal–medial wall thickness changes.

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