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Carotid Plaque, Aging, and Risk Factors

A Study of 457 Subjects

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Background and Purpose The aim of this study was to assess the prevalence of extracranial carotid artery atherosclerosis and its relation to principal cardiovascular risk factors at different ages in a sample of the general population.

Methods B-mode ultrasonography was used to investigate the carotid district in 457 subjects (231 men and 226 women; mean age, 55.4±18.7 years; range, 18 to 97 years) in the metropolitan area. The ultrasonographic findings were then related to risk factors.

Results Carotid plaques were found in 178 subjects (38.9%). The prevalence of atherosclerosis, number of plaques, and severity of stenosis were observed to increase with age. Age ($P<.0001$), cigarette smoking ($P<.0001$), male sex ($P<.001$), total cholesterol ($P<.05$), and, inversely, the ratio of high-density lipoprotein cholesterol to total cholesterol ($P<.05$) were found to be independently associated with carotid atherosclerosis. Stratified analysis by sex and age showed effect modifications by age on cigarette smoking, total cholesterol, and the ratio of high-density lipoprotein cholesterol to total cholesterol. After multivariate analysis including interaction terms, cigarette smoking and cholesterol levels were no longer found to be associated with carotid atherosclerosis in elderly subjects. Age ($P<.01$), total cholesterol ($P<.05$), and diabetes ($P<.05$) were positively related to the severity of vascular narrowing.

Conclusions There is a high prevalence of asymptomatic carotid atherosclerosis in the general population, particularly among the very old. The association between risk factors and carotid atherosclerosis is less pronounced in the elderly than in younger subjects. (***Stroke.* 1994;25:1133-1140.**)

Key Words • aging • atherosclerosis • carotid arteries • risk factors

High-resolution B-mode ultrasound scan, a valid noninvasive technique for the assessment of extracoronary atherosclerosis, has been widely used to study carotid atherosclerosis.[1-3] Carotid atherosclerosis is important in view of its relation to cerebrovascular ischemic diseases and to coronary atherosclerosis.[4-6] However, most of the information available on this topic refers to patients with clinical signs of atherosclerosis or those selected according to different criteria.[5,7-9] Few studies have been performed to investigate the prevalence of asymptomatic extracranial carotid atherosclerosis and its relation to risk factors among the general population.[10-12] Moreover, less information, often conflicting, is available regarding unselected elderly subjects, those who are most affected by the atherosclerotic process.[13-15]

To investigate the prevalence of extracranial carotid artery atherosclerosis and its relation to risk factors at different ages, we conducted a survey of a random sample of unselected individuals living on their own in the metropolitan area, using sonographic noninvasive methods.

Subjects and Methods

The study population comprised a sample of the general population, consisting of subjects taken from the records of a general practitioner in Turin, Italy. This sample is representative of a metropolitan district because the choice of a physician is usually made according to proximity to the subject's residence. The general practitioner, randomly selected from among those practicing in the hospital's district, was informed of the aims and the procedures of the study. Four-hundred sixty-two subjects aged 18 or older were registered; they were invited to participate in the study by the physician himself by means of a telephone call followed by a letter. Five persons were unable to attend; 457 gave their informed consent. The high rate of participation (98.9%) may well be due to the personal invitation by the general practitioner. The reasons for nonparticipation were temporary different residence (2), unsuitable working hours (2), and transportation difficulties in an elderly subject (1). Participants were invited to our department between June and December 1991. A standardized questionnaire was administered to each patient to investigate personal or family history of cardiovascular and cerebrovascular disease, and an accurate medical history was compiled by a physician. Finally, a complete physical examination was performed; height and weight were measured, and the body mass index (BMI) was calculated as weight (kilograms) divided by height squared (square meters). Systolic and diastolic blood pressure levels were measured twice, and the average of the two readings was used.

Detailed questionnaires were also used to assess significant cardiovascular risk factors. Subjects were defined as hypertensive according to World Health Organization criteria[16] or if they were receiving any antihypertensive medication. Subjects with a history of diabetes or those receiving any antidiabetic medication were considered diabetic. All hypertensive and diabetic patients were receiving therapy. Subjects were deemed hypercholesterolemic or hypertriglyceridemic if they had total cholesterol of 240 mg/dL or greater or triglycerides of 200 mg/dL or greater, respectively. Only three patients were receiving hypocholesterolemic drugs. Overweight was defined as BMI greater than 25 kg/m^2.

Blood glucose, total cholesterol, and triglyceride concentrations were enzymatically determined in the morning after a

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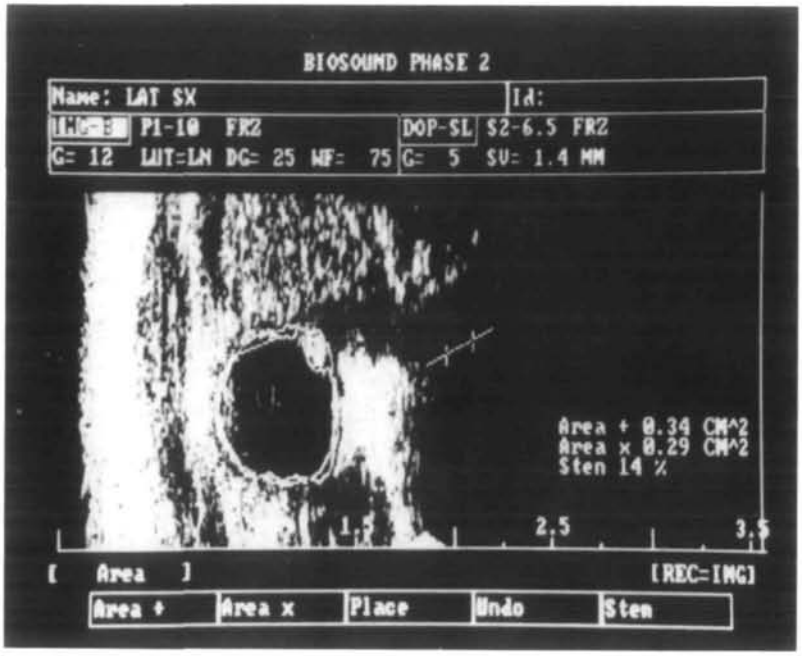

Duplex ultrasound scan shows small plaque at the common carotid artery (transverse scanning plane). The percentage of stenosis was automatically calculated by the apparatus after the operator outlined area of plaque and residual lumen using the trackball.

12-hour fast (Boehringer Mannheim). High-density lipoprotein (HDL) cholesterol was enzymatically assayed after lipoprotein precipitation. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula.

Participants underwent a duplex scanning examination at the Noninvasive Vascular Diagnostic Laboratory in our department. The ultrasonographic examinations were performed by two qualified physicians certified by the Italian Group of Vascular Ultrasonography. With the subject in the supine position the common, internal, and external carotid arteries and the carotid bifurcation of both sides were examined with longitudinal (anterior, lateral, and posterior) and transverse scans. A high-resolution duplex ultrasound system (Biosound Phase 2) was used, with 7.5-MHz scanning frequency in B-mode and 5-MHz scanning frequency in pulsed-Doppler mode. The axial resolution of this system is approximately 0.3 mm. The atherosclerotic lesion was defined as plaque when a distinct area with more than 50% greater intimal plus medial thickness (usually >2 mm) compared with neighboring sites could be identified.[9,10,17,18] The intimal-medial thickness was evaluated as the distance between the lumen-intima interface and the media-adventitia interface, measured by using two cursors during the scanning from a frozen frame of longitudinal B-scan.[9,10] The degree of stenosis was calculated as a percentage ratio between the area of the plaque and that of the lumen using the formula (Lumen Area−Residual Lumen)×100. Both the areas were automatically measured by the system on a frozen transverse scanning plane at the site of maximal narrowing, after the operator outlined the area of the plaque and the residual lumen using the trackball (Figure).[18] When two or more plaques were present in the same vessel, only that causing the greatest degree of stenosis was considered for analysis. The severity of carotid atherosclerosis was classified as no lesion, minimal plaques (<25%), mild stenosis (25% to 49%), moderate stenosis (50% to 75%), severe stenosis (76% to 99%), or occlusion (100%). The entire scanning procedure was recorded on a videocassette recorder. The evaluations recorded on videotape were analyzed at the end of each day's examination by the same physician, who checked the original classification from images of the most affected sites. Reproducibility of the estimated severity of stenosis was evaluated in 30 randomly selected subjects who were invited to undergo a repeated carotid examination by both physicians 15 days after the original assessment. The mean coefficient of variation for the difference between degree of stenosis obtained in repeated examinations evaluated by the same physician was 5%; the mean coefficient of variation for differences between different physicians was 7.4%.

Statistical Analysis

The SPSS-PC statistical package was used to process the data collected. The sample was divided into four groups according to age (18 to 44, 45 to 64, 65 to 74, and ≥75 years). The age- and sex-specific prevalence of atherosclerosis, number of plaques, and percentage of stenosis were calculated, and differences among groups were analyzed using the χ^2 test. Age standardization was performed by the direct method, using the metropolitan population in 1989 as standard.

The following risk factors were analyzed as dichotomous variables: sex, cigarette smoking, hypertension, and diabetes mellitus. Age, BMI, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and ratio of HDL to total cholesterol were analyzed as continuous variables. The normal distribution of each variable was evaluated by "eyeballing" with a normal probability plot (observed versus expected). The association between carotid atherosclerosis and risk factors was assessed using odds ratios (OR) and 95% confidence intervals (CI) for dichotomous variables, ANOVA for continuous variables with normal distribution, and the Mann-Whitney test for continuous variables not normally distributed (triglyceridemia and ratio of HDL to total cholesterol). Risk factors were stratified by age (<65 and ≥65 years) and sex, and a forward stepwise multiple logistic regression analysis was performed, in which the previously significant risk factors were entered as independent variables. Finally, the interaction terms, corresponding to effect modifications by age and sex on variables independently associated with carotid atherosclerosis, were introduced in the logistic model.[19]

The association between severity of maximum vascular narrowing and risk factors was evaluated using linear regression analysis (univariate and forward stepwise multivariate methods). Maximum percentage of stenosis was normalized by rank transformation according to Blom. Dichotomous variables were coded 0 if absent and 1 if present.

Results

Four-hundred fifty-seven subjects (231 men and 226 women) participated in the study (mean age, 55.4±18.7

TABLE 1. Age- and Sex-Specific Prevalence of Carotid Atherosclerosis in 457 Subjects

	Men		Women		Total		No Plaque	
Age, y	No.	(%*)	No.	(%†)	No.	(%‡)	No.	(%‡)
18-44 (n=121)	4	(6.3)	...		4	(3.3)	117	(96.7)
45-64 (n=162)	46	(48.9)	13	(19.1)	59	(36.4)	103	(63.6)
65-74 (n=101)	30	(69.8)	29	(50.0)	59	(58.4)	42	(41.6)
≥75 (n=73)	25	(80.6)	31	(73.8)	56	(76.7)	17	(23.3)
	$P<.001$		$P<.001$		$P<.001$		$P<.001$	

*Percentage of all men (with and without plaque) in each age group.
†Percentage of all women (with and without plaque) in each age group.
‡Percentage of all subjects in each age group.

years; range, 18 to 97 years). Carotid plaques were found in 178 subjects (38.9%). The prevalence of carotid lesions in the overall sample was 45.4% for men and 32.3% for women. The estimated age-adjusted rates for the metropolitan area of Turin were 25.3% for men and 17.6% for women.

The prevalence of atherosclerosis, greater in men than in women in all age groups, increased progressively with age (Table 1), as did the number of plaques and the severity of vascular narrowing (Table 2). No occlusion was found.

Table 3 shows the age-specific prevalence of risk factors and the mean values of certain continuous variables in the total series. All the cardiovascular risk factors, with the exception of cigarette smoking and BMI, were significantly associated with carotid atherosclerosis in the overall sample (Table 4). Results of the stratification by age and sex are shown in Table 5. Using multiple logistic regression analysis on all the subjects (Table 6), age ($P<.0001$), cigarette smoking ($P<.0001$), male sex ($P<.001$), total cholesterol ($P<.05$), and, inversely, ratio of HDL to total cholesterol ($P<.05$) were found to be independently associated with carotid atherosclerosis. Stratification by sex did not show effect modifications on any of these variables (Table 5); in contrast, the effect modifications by age on cigarette smoking, total cholesterol, and ratio of HDL to total cholesterol were considered for analysis. Multiple logistic regression analysis, including the interaction terms, showed a significant effect modification by age on cigarette smoking and a relevant, nonsignificant interaction with total cholesterol (Table 6).

The prevalence and the mean values of risk factors according to increasing severity of vascular narrowing are shown in Table 7. Age ($P<.01$), diabetes ($P<.05$), and total cholesterol ($P<.05$) were independently related to the severity of vascular narrowing in patients with carotid atherosclerosis (Table 8).

Discussion

A number of studies[8,20-23] have investigated cerebrovascular ischemic diseases and determined that some risk factors are still predictive even in later life.[20,24-26] In contrast, only a few studies have investigated carotid atherosclerotic disease itself, which usually develops years or even decades before symptoms appear. In this cross-sectional study we used a reliable, noninvasive ultrasonographic method to investigate carotid atherosclerosis and

TABLE 2. Age-Specific Distribution of Subjects by Number of Plaques and Percentage of Stenosis

	Age Group, y							
	18-44 (n=121)		45-64 (n=162)		65-74 (n=101)		≥75 (n=73)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Plaque, No.								
1 (n=54)	2	(1.7)	18	(10.5)	21	(20.8)	13	(17.8)
2-3 (n=92)	2	(1.7)	35	(21.0)	27	(26.7)	28	(38.4)
>3 (n=32)	...		6	(3.7)	11	(10.9)	15	(20.5)
Stenosis, %								
<25 (n=83)	3	(2.5)	32	(19.8)	27	(26.7)	21	(28.8)
25-49 (n=77)	...		24	(14.8)	27	(26.7)	26	(35.6)
50-75 (n=14)	...		3	(1.9)	5	(5.0)	6	(8.2)
76-99 (n=4)	1	(0.8)	...		...		3	(4.1)

$P<.001$ for number of plaques and percentage of stenosis.

TABLE 3. Age-Specific Prevalence of Risk Factors and Age-Specific Values (Mean±SD) of Certain Continuous Variables in the Total Population

	Age Group, y				
	18-44 (n=121)	45-64 (n=162)	65-74 (n=101)	≥75 (n=73)	*P*
Overweight	5 (4.1%)	16 (9.9%)	12 (11.9%)	8 (11.0%)	NS
BMI, kg/m²	22.8±3.3	25.2±3.8	25.0±3.6	24.2±3.9	<.001*
Cigarette smoking	49 (40.5%)	60 (37.0%)	22 (21.8%)	8 (11.0%)	<.001†
Hypertension	2 (1.7%)	37 (22.8%)	31 (30.7%)	24 (32.9%)	<.001†
SBP, mm Hg	121.7±11.2	139.0±17.4	144.9±17.6	150.6±14.8	<.001*
DBP, mm Hg	77.5±6.7	84.1±8.4	83.3±7.8	83.9±8.1	<.001*
Diabetes	...	10 (6.2%)	8 (7.9%)	4 (5.5%)	<.05†
Glucose, mg/dL	97.5±82.5	98.1±30.3	102.7±30.8	99.1±16.6	NS
Hypercholesterolemia	16 (13.2%)	62 (38.3%)	48 (47.5%)	29 (39.7%)	<.001†
Cholesterol, mg/dL	201.5±39.1	228.3±50.4	235.6±55.5	223.7±54.3	<.001*
Hypertriglyceridemia	7 (5.8%)	18 (11.1%)	8 (7.9%)	7 (9.6%)	NS
Triglycerides, mg/dL	110.9±50.8	142.9±75.8	126.7±47.1	131.5±48.5	<.001*

BMI indicates body mass index; SBP, systolic blood pressure; and DBP, diastolic blood pressure. Values are number and (percentage) unless otherwise indicated.
*F (ANOVA).
†*r* (Pearson's correlation coefficient).

its relation to cardiovascular risk factors in a random sample of the general population.

In accordance with data from the literature,[13,26-28] our results indicate that there is a high prevalence of carotid atherosclerosis in healthy, free-living subjects (up to 59.9% in subjects aged 65 to 74 years and 76.7% in the oldest age group). This finding is particularly relevant because of the very low prevalence of symptomatic patients in our series (only eight subjects [1.8%] suffered from previous minor cerebral ischemic accidents). In all age groups, men are more prone to atherosclerosis than women, but this difference is markedly less in the group aged 65 to 74 years and nearly disappears in the oldest age group. This may be due to postmenopausal hormonal modifications in women, which increase their susceptibility to the atherosclerotic process, and to the incidence of premature death among men suffering from extensive severe atherosclerosis.

Not only the prevalence of atherosclerosis but also the extention of the disease (expressed as the number of carotid artery lesions) and the severity of vascular narrowing appear to increase with advancing age. The number of carotid plaques rises progressively with age, averaging two in subjects aged older than 74 years, 20.5% of whom had more than three plaques. The severity of stenosis also increased: the mean percentage of narrowing at the site of maximum stenosis was 9.1% in those aged 45 to 64 years, 17.3% in subjects aged 65

TABLE 4. Univariate Association Between Carotid Atherosclerosis and Risk Factors

	With CA	Without CA	OR (95% CI)	F*	z*
Male sex, %	59.0	45.2	1.34 (1.09-1.64)	...	...
Cigarette smoking, %	33.7	28.3	1.19 (0.92-1.57)	...	...
Hypertension, %	30.9	14.0	2.21 (1.53-3.18)	...	...
Diabetes, %	9.6	1.8	5.33 (2.01-14.2)	...	...
Age, y	68.3±10.4	47.1±18.2	...	200.4‡	
BMI, kg/m²	24.7±3.8	24.1±3.7	...	2.3	
TC, mg/dL	238.5±58.7	211.6±42.4	...	32.3‡	
HDL-C, mg/dL	50.8±14.9	54.5±12.4	...	7.8†	
LDL-C, mg/dL	159.7±54.7	132.7±39.9	...	37.3‡	
Triglycerides, ranks	256.9	211.2	...		3.61‡
HDL-C/TC ratio, ranks	198.3	277.1	...		6.21‡

CA indicates carotid atherosclerosis; OR, odds ratio; CI, confidence interval; BMI, body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.
*F by ANOVA; *z* by Mann-Whitney test.
†$P<.01$.
‡$P<.001$.

TABLE 5. Stratified Analysis of Risk Factors by Age (<65 and ≥65 Years) and Sex

	<65 y	≥65 y	Men	Women
Male sex§	2.49	1.29	. . .	. . .
	(1.51-4.11)	(1.01-1.66)		
Cigarette smoking§	1.86	1.41	1.29	0.89
	(1.41-2.46)	(0.67-2.97)	(0.94-1.56)	(0.73-1.09)
Hypertension§	2.69	1.14	2.07	1.77
	(1.53-4.75)	(0.71-1.85)	(1.02-4.22)	(1.29-2.42)
Diabetes§	5.23	5.64	4.30	8.00
	(1.52-17.9)	(0.76-42.7)	(1.15-16.1)	(1.62-39.6)
Age‖	75.82‡	11.50‡	112.45‡	102.75‡
BMI‖	9.77†	3.64*	1.23	0.06
TC‖	39.45‡	0.80	10.11†	28.01†
HDL-C‖	15.68‡	0.50	0.13	9.29†
LDL-C‖	41.67‡	1.01	9.19†	34.54†
Triglycerides¶	3.43‡	1.05	1.04	4.05‡
HDL-C/TC ratio¶	6.87‡	1.09	2.48*	5.87‡

BMI indicates body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.
*$P<.05$, †$P<.01$; ‡$P<.001$.
§Odds ratio (95% confidence interval).
‖F (ANOVA).
¶z (Mann-Whitney test).

to 74 years, and 27.1% in those aged older than 74 years. However, most of the subjects aged 75 or older showed minimal (28.8%) or mild (35.6%) stenosis, whereas only three patients (4.1%) had severe vascular narrowing. In the Framingham Study,[29] 8% of the 1189 members of the cohort aged 66 to 93 years had stenosis of 50% or greater. O'Leary et al,[13] in their survey of 5201 subjects aged 65 or older, observed, as we did, that maximum stenosis increased with age, but the prevalence of severe stenosis (75% to 100%) was quite low in both men (2.3%) and women (1.1%). Pujia et al[28] reported a prevalence of 5% of flow-reducing stenosis (lumen reduction ≥50%) in subjects aged 75 or older. Jungquist et al[14] found stenosis of 60% or greater in 4.5% of men aged 69 examined in his study. Prati et al[12] reported a very low prevalence of stenotic plaque (>40%) in subjects aged 80 years or older (7.1% in men and 12.1% in women). These data, derived from cross-sectional studies, do not allow speculation as to the natural history of atherosclerotic disease in elderly subjects.

TABLE 6. Risk Factors for Carotid Atherosclerosis in the Total Population: Multiple Logistic Regression Model Analysis, Forward Stepwise Method

	β	SE (β)	*P*	OR	95% CI
Without interaction terms					
Age, y	0.1288	0.0134	.0000	1.13	1.10-1.16
Male sex	0.9839	0.2804	.0004	2.67	1.54-4.63
Cigarette smoking	1.2240	0.3215	.0001	3.40	1.81-6.39
TC, mg/dL	0.0063	0.0029	.0313	1.006	1.001-1.012
HDL-C/TC ratio	−4.5977	2.1890	.0357	0.01	0.001-0.73
Including interaction terms					
Age, y	0.1517	0.0197	.0000	1.16	1.12-1.21
Male sex	0.9366	0.2833	.0009	2.55	1.46-4.44
Cigarette smoking	1.6058	0.3828	.0002	4.98	2.35-10.5
TC, mg/dL	0.0076	0.0031	.0137	1.007	1.001-1.014
HDL-C/TC ratio	−4.7768	2.1931	.0294	0.01	0.001-0.61
Age×TC	−0.0025	0.0017	.1338	0.99	0.99-1.00
Age×cigarette smoking	−1.1486	0.5808	.0480	0.32	0.10-0.99

OR indicates odds ratio; CI, confidence interval; TC, total cholesterol; and HDL-C, high-density lipoprotein cholesterol.

TABLE 7. Prevalence of Dichotomous Risk Factors and Values (Mean±SD) of Continuous Risk Factors According to Percent Stenosis

	Percent Stenosis				
	0 (n=279)	1%-24% (n=83)	25%-49% (n=77)	50%-75% (n=14)	76%-99% (n=4)
Male sex	126 (45.2)	47 (56.6)	43 (55.8)	12 (85.7)	3 (75.0)
Hypertension	39 (14.0)	23 (27.7)	21 (27.3)	10 (71.4)	1 (25.0)
Cigarette smoking	79 (28.3)	29 (34.9)	20 (26.0)	9 (64.3)	2 (50.0)
Diabetes	5 (1.8)	6 (7.2)	6 (7.8)	4 (28.6)	1 (25.0)
Age, y	47.2±18.2	66.3±10.7	70.2±9.0	69.7±10.4	68.4±18.2
BMI, kg/m^2	24.1±3.7	24.7±4.1	24.4±3.5	25.4±3.6	23.7±3.3
TC, mg/dL	211.6±42.4	231.3±59.3	242.6±52.6	242.9±62.2	279.6±100.2
HDL-C, mg/dL	54.5±12.9	47.8±13.2	54.8±15.9	49.4±15.3	51.6±19.2
LDL-C, mg/dL	132.7±39.9	154.6±55.9	162.1±47.6	163.1±56.0	195.7±108.5
Triglycerides, mg/dL	122.1±54.9	144.3±78.6	128.6±43.2	151.9±84.0	164.0±82.1
HDL-C/TC ratio	0.26±0.07	0.22±0.07	0.23±0.07	0.21±0.07	0.20±0.10

BMI indicates body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol. Values in parentheses are percentages.

However, it can certainly be stated that in aged subjects the progression of atherosclerosis is more likely to appear as an extensive, multisegmental vascular involvement rather than as a severely narrowing process. On the other hand, age ($P<.01$), with total cholesterol ($P<.05$) and diabetes ($P<.05$), was found to be independently related to the severity of vascular narrowing.

The prevalence of risk factors increases progressively up to the age of 65 to 74 years and then, with the exception of hypertension, declines in the oldest age group. This phenomenon in cross-sectional study design is most likely explained by the premature death from cardiovascular disease of high-risk subjects. The physiological trend toward a reduction in total and LDL cholesterol in later life, or the lower number of smokers among elderly women, may also contribute to this decline.

In regard to the relation between carotid atherosclerosis and risk factors, evidence from the literature is quite discordant.* Of all risk factors investigated, age has by far the strongest independent association with carotid atherosclerosis. Aging influences the pathogenesis of atherosclerosis both in terms of physiological vascular changes and by increasing exposure to tradi-

*References 6, 8-10, 12, 14, 15, 17, 28, 30-33.

TABLE 8. Relation Between Severity of Vascular Narrowing and Risk Factors

	Univariate Regression Coefficients			
	β	SE (β)	T	P
Age, y	0.0092	0.0039	2.381	.0184
Male sex	−0.0602	0.0830	−0.725	.4691
Cigarette smoking	0.0075	0.0865	0.087	.9311
Hypertension	0.0962	0.0882	1.090	.2770
Diabetes	0.2641	0.1347	1.961	.0499
BMI, kg/m^2	−0.0007	0.0108	−0.065	.9485
TC, mg/dL	0.0012	0.0006	1.970	.0486
HDL-C, mg/dL	0.0029	0.0027	1.060	.2906
LDL-C, mg/dL	0.0010	0.0007	1.354	.1774
Triglycerides, ranks	0.0004	0.0006	0.656	.5130
HDL-C/TC, ranks	−0.1622	0.5681	−0.286	.7756
Multivariate linear regression analysis				
Age, y	0.0111	0.0039	2.860	.0048
TC, mg/dL	0.0016	0.0006	2.354	.0197
Diabetes	0.2881	0.1343	2.144	.0335

BMI indicates body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

TABLE 9. Odds Ratios (95% Confidence Intervals) of Cigarette Smoking and Total Cholesterol in Subjects Aged <65 and ≥65 Years: Multiple Logistic Regression Analysis Including Interaction Terms

	<65 y	≥65 y
Cigarette smoking	4.98	1.59
	(2.35-10.54)	(0.75-3.37)
Total cholesterol	1.0076	1.0051
	(1.0017-1.0135)	(0.998-1.011)

tional risk factors. Male sex is strongly and independently associated with carotid atherosclerosis. This association is still evident in later life, although the prevalence of carotid atherosclerosis increases in women after menopause, reaching 73.8% in women aged 75 and older.

In addition to these two irreversible risk factors, total cholesterol, cigarette smoking, and, inversely, the ratio of HDL to total cholesterol were independently associated with carotid atherosclerosis. Several population studies have indicated that cigarette smoking is one of the most concordant independent risk factors for carotid atherosclerosis,[7,10-15,17,30-32] although other studies failed to confirm this association.[9,32] There are contrasting opinions regarding the relation between carotid atherosclerosis and hyperlipidemia; most evidence seems to suggest that high blood total or LDL cholesterol levels[7,10,17,30,34-36] or low HDL cholesterol or ratio of HDL to total cholesterol[33,35-38] are independent risk factors for extracranial carotid atherosclerosis that are restricted to young adults. To assess whether the associations observed in the overall sample are modified in elderly subjects, we evaluated the effect modifications by age and sex, and the interaction terms of interest were then introduced in the multiple logistic model. Age has a significant effect modification on cigarette smoking but not on total cholesterol. This finding, which is in contrast to results in other reports,[39,40] cannot easily be explained. However, the relevant modification of the β-coefficient of cholesterol (15.8%) suggests that there is an effect modification by age, so that this interaction can be forced in the analysis.[41] The multivariate analysis, including these interaction terms, shows that neither cigarette smoking (OR, 1.59; 95% CI, 0.75 to 3.37) nor total cholesterol (OR, 1.005; 95% CI, 0.998 to 1.011) are associated with carotid atherosclerosis in subjects aged 65 and older (Table 9). Other investigators[13,14,17] have reported that some risk factors continue to be related to carotid atherosclerosis in the later decades of life. However, Jungquist et al[14] did not find any statistically significant relation between risk factors and the extent of carotid atherosclerosis in subjects aged 69 years. Pujia et al,[28] in their study on elderly patients living in retirement homes, did not find any statistically significant relation between cardiovascular risk factors and the presence of carotid lesions. Although hypertension, cigarette smoking, and diabetes mellitus are considered important risk factors for atherosclerosis, we failed to confirm this relation in elderly patients. This absence of any association between carotid atherosclerosis and reversible risk factors in subjects aged 65 and older is chiefly explained by the cross-sectional study design. In the most advanced age groups there is an underrepresentation of high-risk subjects, who have high rates of premature cardiovascular death. Moreover, hypertension and diabetes appear to affect the intracranial more than the extracranial arteries. However, whereas atherosclerosis increases with age, the association with traditional risk factors declines. Among the elderly, despite the predictive role of some precipitating conditions, those risk factors that have a purely atherogenic effect seem to have little bearing on atherosclerotic disease.

Our conclusion is that there is a high prevalence of asymptomatic carotid atherosclerosis in the general population and that this prevalence is noticeably elevated in elderly subjects. At an advanced age the association between risk factors and carotid atherosclerosis seems to be less relevant than at a younger age.

References

1. Spencer MP, Reid JM. Quantitation of carotid stenosis with continuous wave (CW) Doppler ultrasound. *Stroke.* 1979;10:326-330.
2. O'Leary DH, Polak JF, Wolfson SK, Bond MG, Bonner W, Sheth S, Psaty BM, Sharret AR, Manolio TA. Use of sonography to evaluate carotid atherosclerosis in the elderly. *Stroke.* 1991;22: 1155-1163.
3. Sutton-Tyrrell K, Wolfson SK, Thompson T, Kelsey SF. Measurement variability in duplex scan assessment of carotid atherosclerosis. *Stroke.* 1992;23:215-220.
4. Hennerici M, Hulsbomer HM, Hefter H, Lammerts D, Rautenberg W. Natural history of asymptomatic extracranial arterial disease. *Brain.* 1987;110:777-791.
5. Admani AK, Mangion DM, Ndik DR. Extracranial carotid artery stenosis: prevalence and associated risk factors in elderly stroke patients. *Atherosclerosis.* 1991;86:31-37.
6. Craven TE, Ryu JE, Espeland MA, Kahl FR, McKinney WM, Toole JF, McMahan MR, Thompson CJ, Heiss G, Crouse JR III. Evaluation of the associations between carotid artery atherosclerosis and coronary artery stenosis: a case control study. *Circulation.* 1990;82:1230-1242.
7. Duncan GW, Lees RS, Ojemann RG, David SS. Concomitants of atherosclerotic artery stenosis. *Stroke.* 1977;8:665-669.
8. Ellekjaer EF, Wyller TD, Suerre JM, Holmen J. Lifestyle factors and risk of cerebral infarction. *Stroke.* 1992;23:829-834.
9. Giral P, Filitti V, Levenson J, Phitos Merli I, Plainfosse MC, Mainardi C, Gold A, Simon A. Relation of risk factors for cardiovascular disease to early atherosclerosis detected by ultrasonography in middle-aged normotensive hypercholesterolemic men. *Atherosclerosis.* 1990;85:151-159.
10. Salonen R, Seppanen K, Raharamar R, Salonen JT. Prevalence of carotid atherosclerosis and serum cholesterol levels in eastern Finland. *Arteriosclerosis.* 1988;8:788-792.
11. Gomstomzyk JG, Heller WD, Gerhardt P, Lee PN, Keil U. B-scan ultrasound examination of the carotid arteries within a representative population (Monica Project Augsburg). *Klin Wochenschr.* 1988;66(suppl 11):58-65.
12. Prati P, Vanuzzo D, Casaroli M, Di Chiara A, De Biasi F, Feruglio GA, Touboul P. Prevalence and determinants of carotid atherosclerosis in a general population. *Stroke.* 1992;23:1705-1711.
13. O'Leary DM, Polar JF, Kronmal RA, Kittner SJ, Bond MG, Wolfson SR, Bommer W, Price TR, Gardin JM, Savage PJ. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. *Stroke.* 1992;23: 1752-1760.
14. Jungquist G, Hansson BS, Isacsson SO, Janzon L, Steen B, Lindell SE. Risk factors for carotid artery stenosis: an epidemiological study of men aged 69 years. *J Clin Epidemiol.* 1991;44:347-353.
15. Aronow WS, Schoenfeld MR, Paul P. Risk factors for extracranial internal or common carotid arterial disease in persons aged 60 years and older. *Am J Cardiol.* 1989;63:881-882.
16. World Health Organization Expert Committee on Arterial Hypertension. *Report.* Geneva, Switzerland: World Health Organization; 1978. WHO Technical Report Series 231.
17. Salonen R, Salonen JT. Progression of carotid atherosclerosis and its determinants: a population based ultrasonographic study. *Atherosclerosis.* 1990;81:33-40.

18. Fabris F, Poli L, Zanocchi M, Bo M, Fiandra U, Fonte G. A four year clinical and echographic follow-up of asymptomatic carotid plaque. *Angiology.* 1992;43:590-598.
19. Matthews DE, Farewell WT. *Using and Understanding Medical Statistics.* 2nd ed, revised. Basel, Switzerland: S Karger, AG; 1988: 207-222.
20. Welin L, Svardsudd K, Wilhelmsen L, Larsson B, Tibblin G. Analysis of risk factors for stroke in a cohort of men born in 1913. *N Engl J Med.* 1987;317:521-526.
21. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke.* 1991;22: 312-318.
22. Harmsen P, Rosengren A, Tsipogianni A, Wilhelmsen L. Risk factors for stroke in middle-aged men in Goteborg, Sweden. *Stroke.* 1990;21:223-229.
23. Iso H, Jacobs DR, Wentworth D, Neaton JD, Cohen JA. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the Multiple Risk Factor Intervention Trial. *N Engl J Med.* 1989;320:904-910.
24. Wolf PA, Abbott RA, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991;22:983-988.
25. Aronow WS. Risk factors for geriatric stroke: identification and follow-up. *Geriatrics.* 1990;45:37-44.
26. McGill H, Arias Stella J, Carbonell L. General findings of the International Atherosclerosis Project. *Lab Invest* 1968;18:498-502.
27. Josse M, Toubool P, Mas J, Laplane D, Bouser M. Prevalence of asymptomatic internal carotid artery stenosis. *Neuroepidemiology.* 1987;6:150-152.
28. Pujia A, Rubba P, Spencer MP. Prevalence of extracranial carotid artery disease detectable by echo-Doppler in an elderly population. *Stroke.* 1992;23:818-822.
29. O'Leary DH, Anderson KM, Wolf PA, Evans JC, Pohelman HW. Cholesterol and carotid atherosclerosis in older persons: the Framingham Study. *Ann Epidemiol.* 1992;2:147-153.
30. Tell G, Howard G, McKinney WH. Risk factors for site specific extracranial carotid artery plaque as measured by B-mode ultrasound. *J Clin Epidemiol.* 1989;42:551-559.
31. Dempsey RJ, Moore RW. Amount of smoking independently predicts carotid artery atherosclerosis severity. *Stroke.* 1992;23: 693-696.
32. Whisnant JP, Homer D, Ingall TJ, Baker HL, O'Fallon WM, Wiebers DO. Duration of cigarette smoking is the strongest predictor of severe extracranial carotid artery atherosclerosis. *Stroke.* 1990;21:707-714.
33. Crouse JR, Toole JF, McKinney WM, Dignan MB, Howard G, Kahl FR, McMahan MR, Harpold GM. Risk factors for extracranial carotid artery atherosclerosis. *Stroke.* 1987;18:990-996.
34. Postiglione A, Rubba P, De Simone B, Patti L, Cicerano U, Mancini M. Carotid atherosclerosis in familial hypercholesterolemia. *Stroke.* 1985;16:658-661.
35. Ford SC, Crouse JR, Howard G, Toole JF, Ball MR, Fraye J. The role of plasma lipids in carotid bifurcation atherosclerosis. *Ann Neurol.* 1985;17:301-303.
36. Terrence CF, Rao GR. Triglycerides as risk factor in extracranial atherosclerotic cerebrovascular disease. *Angiology.* 1983;34: 452-460.
37. Vitale E, Zuliani G, Baroni L, Bicego L, Grego F, Valerio G, Fellin R. Lipoprotein abnormalities in patients with extracoronary atherosclerosis. *Atherosclerosis.* 1990;81:95-102.
38. Van Merode T, Hick P, Hoeks APG, Reneman RS. Serum HDL/total cholesterol ratio and blood pressure in asymptomatic atherosclerotic lesions of the cervical carotid arteries in men. *Stroke.* 1985;16:34-38.
39. Jacobsen SJ, Freedman DS, Hoffmann RG, Gruchow HW, Anderson AJ, Barboriak JJ. Cholesterol and coronary artery disease: age as an effect modifier. *J Clin Epidemiol.* 1992;45:1053-1059.
40. Kronmal RA, Zain KC, Ye Z, Omenn GS. Total serum cholesterol levels and mortality risk as a function of age: a report based on the Framingham data. *Arch Intern Med.* 1993;153:1065-1073.
41. Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health.* 1989;79:340-349.