CUMULATIVE EFFECTS OF HIGH CHOLESTEROL LEVELS, HIGH BLOOD PRESSURE, AND CIGARETTE SMOKING ON CAROTID STENOSIS

PETER W.F. WILSON, M.D., JEFFREY M. HOEG, M.D., RALPH B. D'AGOSTINO, PH.D., HALIT SILBERSHATZ, PH.D., ALBERT M. BELANGER, M.A., HAROLD POEHLMANN, M.S., DANIEL O'LEARY, M.D., AND PHILIP A. WOLF, M.D.

ABSTRACT

Background Single measurements of cardiovascular risk factors may not accurately reflect a person's past exposure to those risk factors. We therefore studied the long-term associations of cardiovascular risk factors such as high serum cholesterol levels, high blood pressure, and cigarette smoking with the prevalence of carotid stenosis.

Methods We studied cross-sectional and longitudinal information from a sample of 429 men and 661 women in the Framingham Heart Study who underwent B-mode ultrasound measurements of the carotid artery. Their mean age was 75 years, and each had attended most of the biennial clinic examinations over the 34 years before the carotid ultrasound study. We used time-integrated measurements to assess the associations between various cardiovascular risk factors and the degree of carotid stenosis.

Results Moderate carotid stenosis (≥25 percent) was present in 189 men and 226 women. We assessed the odds ratios for this degree of stenosis as compared with minimal stenosis (<25 percent) according to increases in risk factors. In the men, the odds ratio for moderate carotid stenosis associated with an increase of 20 mm Hg in systolic blood pressure was 2.11 (95 percent confidence interval, 1.51 to 2.97). The odds ratio for an increase of 10 mg per deciliter (0.26 mmol per liter) in the cholesterol level was 1.10 (95 percent confidence interval, 1.03 to 1.16), and for an increase of five pack-years of smoking it was 1.08 (95 percent confidence interval, 1.03 to 1.13). The results were similar in the women. Time-integrated measurements of diastolic blood pressure showed significant associations with carotid stenosis in men and insignificant associations in women.

Conclusions Over the long term, high systolic blood pressure, high cholesterol levels, and smoking were associated with an increased risk of carotid stenosis in this elderly population. (N Engl J Med 1997; 337:516-22.)

THE effect of risk factors such as high levels of serum cholesterol and high-density lipoprotein (HDL) cholesterol, high blood pressure, and cigarette smoking on the incidence of coronary disease in middle-aged people has been well described.[1-3] Less certain, however, is the role of these risk factors in older people and the degree to which they are associated with vascular abnormalities detected by noninvasive techniques.[4-6] Cross-sectional studies of these traditional risk factors, accompanied by assessments of carotid stenosis by ultrasound techniques, are beginning to delineate the effect of these biochemical, biologic, and behavioral factors on the atherosclerotic process.

Interest in screening carotid arteries has increased as studies have demonstrated that carotid endarterectomy can prevent stroke in symptomatic persons with more than 70 percent stenosis[7,8] and in asymptomatic persons with at least 60 percent stenosis.[9] Data from most cross-sectional studies have shown that clinical factors measured at the time of noninvasive testing, such as blood pressure, total cholesterol, HDL cholesterol, and smoking, are not highly associated with stenosis,[10,11] although reports based on data from middle-aged adults suggest that abnormal levels of traditional risk factors are associated with greater thickness of the intima of the carotid artery.[5,12-16] Authors have noted that the measurement of a risk factor at a single point in time may not accurately reflect a person's past exposure to that factor. This may be particularly important for older people, among whom weight loss, declining health, and a decline in some risk factors are prevalent.[17,18]

Since total cholesterol levels typically peak in middle age and decline in the elderly, single evaluations of risk factors may underestimate associations with clinical or subclinical vascular disease in older people.[17] With these issues in mind, we undertook the present study, in which we compared current measurements, using summary time-integrated estimates of risk factors, with the degree of carotid stenosis as determined by B-mode ultrasonography.

METHODS

Subjects and Measurement of Risk Factors

Subjects considered for this investigation were surviving members of the original cohort of the Framingham Heart Study who participated in examination 20 (1988–1989) and had carotid ultrasound examinations performed. During the clinic visit, a history was obtained and a physical examination was performed. Persons who reported having smoked cigarettes during the previous

From the Framingham Heart Study, National Heart, Lung, and Blood Institute, Framingham, Mass. (P.W.F.W.); the National Heart, Lung, and Blood Institute, Bethesda, Md. (J.M.H.); and the Department of Mathematics, Boston University (R.B.D., H.S., A.M.B.), the Department of Neurology, Boston University School of Medicine (H.P., P.A.W.), and the Department of Radiology, Tufts University Medical Center (D.O.) — all in Boston. Address reprint requests to Dr. Wilson at the Framingham Heart Study, National Heart, Lung, and Blood Institute, 5 Thurber St., Framingham, MA 01701.

year were classified as smokers and were asked a follow-up question about the number of cigarettes they smoked per day on a regular basis. Blood pressure was measured after subjects had been seated for at least five minutes. Two blood-pressure measurements were taken, and the average values were used in the analyses. Blood was drawn from nonfasting subjects, and cholesterol and HDL cholesterol were measured by enzymatic assays.[19]

Over the course of the previous 34 years (biennial examinations 3 through 19), the cholesterol levels of the study participants were measured at 11 examinations. Nonenzymatic laboratory methods were used until examination 20.[20] The third biennial examination was used as the base line for this study because of previously reported regression to the mean in risk-factor measurements, which was particularly evident for blood pressure shortly after the study's inception.[21] Of the subjects whose cholesterol was measured and whose carotid arteries were evaluated at examination 20 (1189 subjects), only those who had attended six or more of the examinations at which cholesterol was measured were considered for this study (1090 subjects). Nonfasting cholesterol levels were determined at all but the 11th examination,[20] HDL cholesterol was measured at the 11th and 15th examinations, and blood pressure and the number of cigarettes smoked daily were recorded at all examinations. Each subject's exposure to each of these factors before the carotid evaluation was determined on the basis of the mean levels for that subject over the course of the study; antecedent averages for blood pressure, smoking, and total cholesterol were calculated from examinations 3 to 19, and averages for HDL cholesterol and the ratio of total to HDL cholesterol from examinations 11 and 15. The summary variable for smoking was determined by calculating the number of pack-years each subject smoked during the observation period.

Ultrasonography

A total of 1090 subjects underwent ultrasonography with an Ultrasonix high-resolution, real-time scanner with a 7.5-MHz imaging transducer, a 4-MHz pulse-wave Doppler transducer, and a 4-MHz continuous-wave transducer.[4] Projections of the carotid bifurcation were obtained on each side at three locations: the distal 1 cm of the common carotid artery, the carotid bulb, and the proximal 1 cm of the internal carotid artery. Frozen images, captured on a Mitsubishi page printer, and short segments of real-time scanning to demonstrate motion were recorded on videotape for later interpretation. Continuous-wave Doppler recording of the external carotid artery and both pulse-wave and continuous-wave recording of the carotid bifurcation exclusive of the external carotid artery were obtained at the site of maximal disturbance of flow.

Plaque thickness was measured with hand-held calipers in the near and far walls, exclusive of the external carotid artery, at the site of maximal disease in each view. The total plaque thickness was calculated by combining the measurements for the near and far walls. The residual lumen was measured at the site of maximal luminal narrowing, and the unobstructed lumen was measured just distal to the site of any wall abnormality. Peak systolic velocities and frequencies were recorded at the sites of maximal flow disturbance. The degree of vascular stenosis was estimated by a composite of both Doppler spectral criteria and assessment of gray-scale images. The maximal percent stenosis of the two arteries was used for this report.[4]

Quality control for the carotid measurements included second examinations and readings for 25 subjects within three months of their original evaluations. After estimation of the degree of maximal carotid stenosis in increments of 5 percent, the Pearson correlation coefficient for the method was 0.89. When the maximal carotid stenosis was categorized according to percentage (0, 1 to 24, 25 to 49, and ≥50 percent), the intraclass correlation coefficient was 0.86 (95 percent confidence interval, 0.72 to 0.93).

Statistical Analysis

Statistical methods included a general linear regression model, with adjustment for age, to compare mean levels of the risk factors[22] and age-adjusted logistic regression to test for associations between moderate (≥25 percent) and minimal (<25 percent) carotid stenosis.[23] Similar age-adjusted logistic-regression analyses were also undertaken to compare severe (≥50 percent) with less severe (<50 percent) carotid stenosis. The adult average levels of cholesterol, HDL cholesterol, blood pressure, and smoking at earlier examinations were calculated for each subject within each carotid-stenosis category, and separate analyses were performed for men and women.

RESULTS

Mean (±SE) risk-factor levels are shown in Table 1 according to the degree of stenosis. The relative frequency of specific current risk-factor levels is

TABLE 1. AGE-ADJUSTED MEAN LEVELS OF RISK FACTORS ACCORDING TO THE DEGREE OF CAROTID STENOSIS, 1987 TO 1989.*

DEGREE OF STENOSIS	NO. OF SUBJECTS	AGE	SYSTOLIC BP	DIASTOLIC BP	CHOLESTEROL	HDL CHOLESTEROL	TOTAL:HDL RATIO	SMOKING
		yr	mm Hg		mg/dl†			%
Men (n=429)								
0	90	75.0	145.1±2.3	78.9±1.2	198.6±4.0	39.1±1.3	5.4±0.2	5.3
1–24%	150	74.8	144.9±1.8	78.1±1.0	205.1±3.1	41.3±1.0	5.3±0.1	8.3
25–49%	149	75.5	146.5±1.8	77.3±1.0	202.8±3.1	42.1±1.0	5.2±0.2	9.6
≥50%	40	76.9	152.8±3.5	77.1±1.9	210.8±6.0	38.7±1.9	5.9±0.3	13.6
Overall			146.2	77.9	203.4	40.8	5.4	9.1
Women (n=661)								
0	213	74.6	145.0±1.5	76.4±0.7	223.1±2.7	53.8±1.1	4.5±0.1	6.0
1–24%	222	76.1	147.9±1.5	75.9±0.7	220.4±2.6	53.8±1.1	4.4±0.1	10.3
25–49%	182	76.7	148.3±1.6	73.7±0.8	223.0±2.9	53.1±1.2	4.6±0.1	16.6
≥50%	44	76.2	157.6±3.3	72.2±1.6	241.1±6.1	46.5±2.5	5.4±0.2	18.8
Overall			147.7	75.2	223.3	53.2	4.6	11.0

*BP denotes blood pressure, and HDL high-density lipoprotein. Blood pressure and cholesterol levels were adjusted for age by means of linear regression, and smoking was adjusted for age by means of logistic regression. Values for continuous variables are means ±SE.

†To convert values for cholesterol and HDL cholesterol to millimoles per liter, multiply by 0.02586.

TABLE 2. DISTRIBUTION OF CURRENT RISK-FACTOR CATEGORIES ACCORDING TO THE DEGREE OF CAROTID STENOSIS, 1987 TO 1989.*

DEGREE OF STENOSIS	NO. OF SUBJECTS	SYSTOLIC BP ≥140 mm Hg	DIASTOLIC BP ≥90 mm Hg	CHOLESTEROL ≥200 mg/dl (5.2 mmol/liter)	LOW HDL CHOLESTEROL†	TOTAL:HDL RATIO >4.5	CURRENT SMOKING
				percent			
Men (n=429)							
0	90	54	23	48	36	60	5
1–24%	150	60	16	55	32	63	10
25–49%	149	59	17	56	37	60	10
≥50%	40	71	17	63	37	66	12
Women (n=661)							
0	213	57	16	68	36	42	7
1–24%	222	64	11	71	33	42	9
25–49%	182	66	8	70	39	46	16
≥50%	44	78	7	69	56	60	18

*BP denotes blood pressure, and HDL high-density lipoprotein. Blood pressure and cholesterol levels were adjusted for age by means of linear regression, and smoking was adjusted for age by means of logistic regression.

†For men, the risk-factor category was defined as an HDL value of <35 mg per deciliter (0.9 mmol per liter). For women the value was <45 mg per deciliter (1.2 mmol per liter).

TABLE 3. AGE-ADJUSTED ODDS RATIOS FOR ≥25 PERCENT VERSUS <25 PERCENT CAROTID STENOSIS, ACCORDING TO CURRENT AND TIME-INTEGRATED RISK-FACTOR LEVELS.*

LEVEL	SYSTOLIC BP	DIASTOLIC BP	CHOLESTEROL†	HDL†	TOTAL:HDL RATIO	SMOKING
	EXAM 20: 20 mm Hg INCREASE		EXAM 20: 10 mg/dl INCREASE	EXAM 20: 5 mg/dl INCREASE	EXAM 20: 1 UNIT INCREASE	EXAM 20: CURRENT SMOKING
Current						
Men	1.12 (0.94–1.32) P=0.19	0.85 (0.62–1.17) P=0.31	1.01 (0.96–1.06) P=0.62	1.03 (0.95–1.12) P=0.43	1.01 (0.91–1.13) P=0.86	1.44 (0.74–2.78) P=0.28
Women	1.16 (1.02–1.35) P=0.044	0.60 (0.44–0.82) P=0.002	1.03 (0.99–1.07) P=0.14	0.96 (0.90–1.02) P=0.15	1.10 (0.99–1.22) P=0.07	2.60 (1.57–4.30) P<0.001
	EXAMS 3–19: 20 mm Hg INCREASE		EXAMS 3–19: 10 mg/dl INCREASE	EXAMS 11 AND 15: 5 mg/dl INCREASE	EXAMS 11 AND 15: 1 UNIT INCREASE	EXAMS 3–19: 5 PACK-YEAR INCREASE
Time-integrated						
Men	2.11 (1.51–2.97) P<0.001	2.22 (1.27–3.94) P=0.006	1.10 (1.03–1.16) P=0.002	1.04 (0.96–1.13) P=0.32	1.07 (0.95–1.21) P=0.29	1.08 (1.03–1.13) P=0.002
Women	1.98 (1.55–2.55) P<0.001	1.32 (0.83–2.07) P=0.23	1.08 (1.03–1.14) P=0.002	0.96 (0.90–1.02) P=0.13	1.19 (1.05–1.34) P=0.005	1.20 (1.13–1.28) P<0.001

*BP denotes blood pressure, and HDL high-density lipoprotein. Values in parentheses are 95 percent confidence intervals.

†To convert values for cholesterol and HDL cholesterol to millimoles per liter, multiply by 0.02586.

shown in Table 2. For instance, there were 90 men with 0 percent stenosis, of whom 54 percent had systolic pressures of 140 mm Hg or higher and 23 percent had diastolic pressures of 90 mm Hg or higher.

The associations of risk factors with the presence of at least 25 percent carotid stenosis as compared with less than 25 percent stenosis are shown in Table 3. The values in the tables represent the estimated age-adjusted effects of specified differences in given variables. For instance, among women the estimated odds ratio for at least 25 percent carotid stenosis associated with an increase of 20 mm Hg in systolic blood pressure was 1.16 (95 percent confidence interval, 1.02 to 1.35); for an increase of 20 mm Hg in diastolic pressure it was 0.60 (95 percent confidence interval, 0.44 to 0.82), and for current smoking it was 2.60 (95 percent confidence interval, 1.57 to 4.30). A positive association with systolic pressure and an inverse association with diastolic pressure were evident in women when current blood-pressure levels were used in the analysis. None of the current

risk-factor levels were associated with carotid stenosis of at least 25 percent in men.

Associations between the time-integrated risk-factor levels and moderate carotid stenosis appear in Table 3. There were significant associations among men and women for systolic pressure and total cholesterol. For instance, among men the odds ratio for at least 25 percent carotid stenosis that was associated with an increase of 20 mm Hg in systolic blood pressure was 2.11 (95 percent confidence interval, 1.51 to 2.97), and for an increase of 10 mg per deciliter in cholesterol it was 1.10 (95 percent confidence interval, 1.03 to 1.16). The time-integrated measurements of systolic pressure and cholesterol generally showed higher degrees of association with carotid stenosis than were evident for the levels that had been measured at the time of the carotid evaluations. The degree of association between the time-integrated measurement of cigarette smoking and moderate carotid stenosis was generally similar to the result obtained with the measurement of current smoking. The associations between moderate carotid stenosis and time-integrated measurements of diastolic pressure were generally positive, in contrast to what was observed for current levels of diastolic pressure. Time-integrated measurements of the ratio of total cholesterol to HDL cholesterol were associated with moderate carotid stenosis in women, for whom the odds ratio associated with a one-unit increase was 1.19 (95 percent confidence interval, 1.05 to 1.34), but the result was not significant in men, for whom the corresponding odds ratio was 1.07 (95 percent confidence interval, 0.95 to 1.21).

In an analysis restricted to subjects who had not smoked during the 10 years before the ultrasound evaluation, a history of smoking 10 or more years before the evaluation was associated with at least 25 percent carotid stenosis as compared with less than 25 percent stenosis in men ($P = 0.038$ for smoking 10 years earlier and $P = 0.042$ for smoking more than 10 years earlier) and women ($P < 0.001$ and $P = 0.065$, respectively) (data not shown).

Additional age-adjusted logistic-regression analyses were undertaken to test for factors associated with carotid stenosis of ≥50 percent as compared with <50 percent. The results for ≥50 percent and ≥25 percent stenosis tended to be similar in men. On the other hand, the odds ratios in the current and time-integrated analyses for ≥50 percent carotid stenosis were generally stronger for lipid factors in women. For instance, the odds ratio associated with an increase of 10 mg per deciliter in cholesterol for women was 1.12 (95 percent confidence interval, 1.04 to 1.21) for current levels and 1.22 (95 percent confidence interval, 1.13 to 1.32) for time-integrated levels. Similarly, the odds ratio associated with a one-unit increase in the ratio of total cholesterol to HDL cholesterol for women was 1.34 (95 percent confidence interval, 1.13 to 1.59) for current levels and 1.50 (95 percent confidence interval, 1.25 to 1.80) for time-integrated levels.

Mean levels of systolic blood pressure in men and women who had carotid evaluations at examination 20 are shown in Figure 1. Men and women with greater degrees of stenosis tended to have higher systolic blood pressures throughout the 34 years of observation. Analogous figures for mean diastolic blood pressure are shown in Figure 2, and the corresponding data for mean cholesterol levels are shown in Figure 3. As with systolic blood pressure, higher mean cholesterol levels were associated with greater degrees of carotid stenosis. At biennial examination 20, however, these distributions were attenuated dramatically.

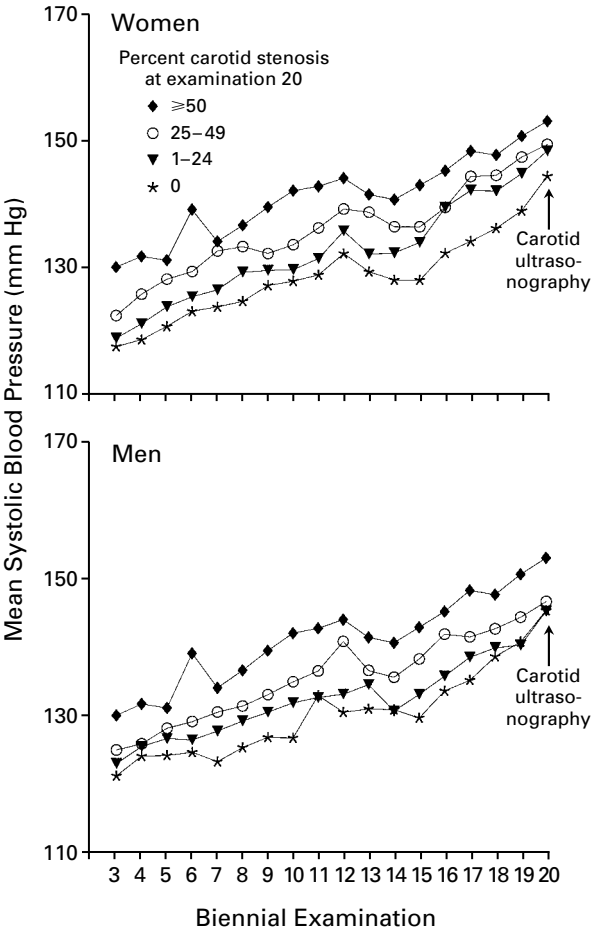

Figure 1. Mean Systolic Blood Pressure in Men and Women at 17 Biennial Examinations, According to the Severity of Carotid Stenosis as Determined by B-Mode Ultrasonography at the 20th Biennial Examination (1988).

Subjects were categorized according to the degree of carotid stenosis, and mean levels of systolic blood pressure are shown for the corresponding biennial examination.

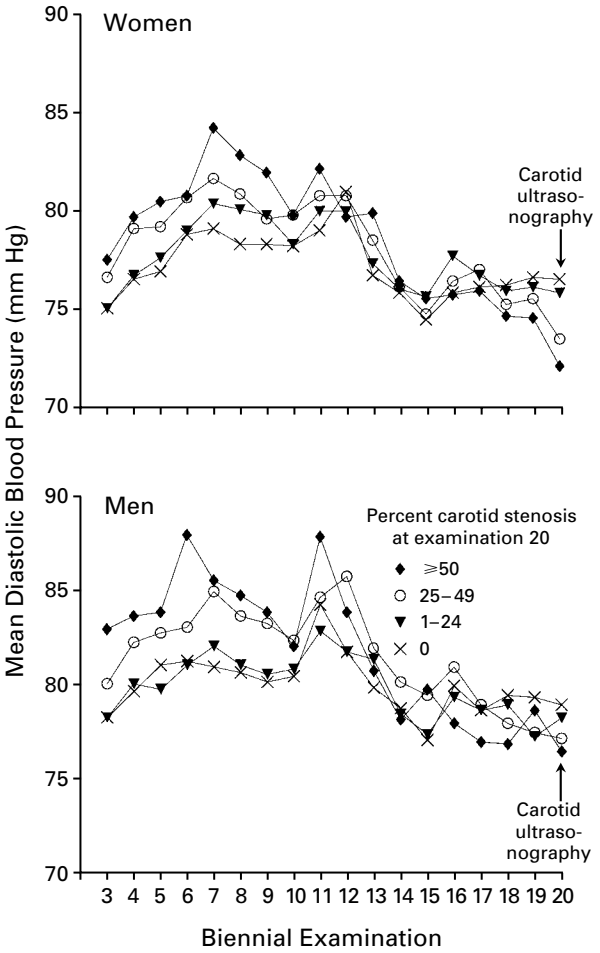

Figure 2. Mean Diastolic Blood Pressure in Men and Women at 17 Biennial Examinations, According to the Severity of Carotid Stenosis as Determined by B-Mode Ultrasonography at the 20th Biennial Examination (1988).

Subjects were categorized according to the degree of carotid stenosis, and mean levels of diastolic blood pressure are shown for the corresponding biennial examination.

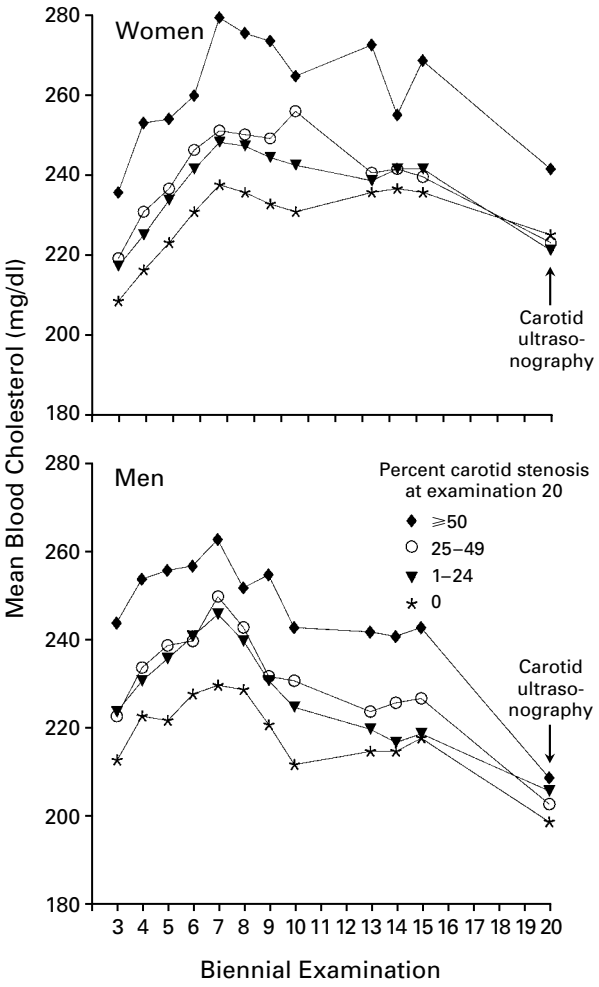

Figure 3. Mean Cholesterol Levels in Men and Women at 12 Biennial Examinations Spanning 34 Years, According to the Severity of Carotid Stenosis as Determined by B-Mode Ultrasonography at the 20th Biennial Examination (1988).

Subjects were categorized according to the degree of carotid stenosis, and mean levels of cholesterol are shown for the corresponding biennial examination. To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

DISCUSSION

Several investigators have reported that the association between risk factors and clinical coronary heart disease grows weaker in the elderly.[17,18,24-26] For instance, young adults and middle-aged people with vascular disease commonly have higher total cholesterol levels, but the apparent effect of cholesterol on vascular disease wanes after the age of 50 years and almost disappears after 65.[27] On the other hand, associations between HDL cholesterol and coronary heart disease tend to persist.[26,28]

Reports have also focused on associations between risk factors and carotid abnormalities detected by ultrasonography.[13-15,29-31] Results often differ, and it is important to know the population being studied, the age group, and the carotid abnormality described. For instance, among Finns 42 to 60 years of age, there were strong associations between carotid stenosis and lipids (low-density lipoprotein and HDL cholesterol) but no significant association with blood pressure.[29] On the other hand, the Atherosclerosis Risk in Communities investigators, studying more than 7000 American men and women 45 to 64 years of age, found relatively little stenosis in their population sample. Those researchers focused on significant correlations between preclinical disease, the intimal medial thickness of the carotid artery — a diagnostic measure not available in the current study — and a large

variety of risk factors, such as high lipoprotein levels, smoking, high blood pressure, high glucose levels, hematologic measures, and genetic markers.[12-14] It is now accepted that the intimal medial thickness of the distal common carotid artery is an indicator of early atherosclerotic disease,[32] although the zone of thickening is distinct from the plaques that form in the proximal internal carotid artery.[33] The findings for moderate carotid stenosis were emphasized in this report, although comparable findings were available on the smaller number of people with severe stenosis.

This study emphasizes that contemporaneous measurements of systolic pressure, diastolic pressure, and smoking appear to be associated with moderate carotid stenosis in women but not in men. Associations between risk factors and carotid stenosis were more consistent for both sexes when time-integrated measurements of exposure over a period of 34 years were used. Similar dose–duration concepts have been used to study familial hypercholesterolemia and vascular disease in young adults. A person's lifetime cholesterol level has been highly associated with the width of his or her Achilles' tendon as determined by computed tomography and with calcified stenoses of coronary-vessel ostia as seen on ultrafast computed tomography.[34-36] Recent reports have also demonstrated that intimal medial thickening of the carotid bulb was present in approximately 75 percent of middle-aged men and women with familial hypercholesterolemia.[37]

Carotid stenosis appears to be positively associated with current systolic pressure and inversely associated with current diastolic pressure in women (Table 3). Similar trends, though not statistically significant, were observed in men. Such findings must be interpreted with caution, because the time-integrated analyses of diastolic pressure tended to be positively associated with moderate carotid stenosis, although the results did not reach statistical significance. It is probable that elderly persons with known vascular disease are more likely to be receiving therapy for hypertension, and the inverse effect of diastolic blood pressure may simply reflect intervention.

The strongly positive association between the time-integrated measurement of systolic pressure and carotid stenosis is a reminder of the importance of systolic pressure in determining the risk of vascular disease. For instance, the systolic pressure was more highly associated with coronary heart disease and stroke than the diastolic pressure in the Framingham Heart Study.[38,39] Although clinical practice typically emphasizes the role of diastolic pressure, this finding underscores the importance of systolic pressure and its role in increasing the risk of clinical and subclinical sequelae of vascular disease.

The relation between vascular disease and the time-integrated measurement of a risk factor can be expected to be stronger than the association with a single measurement for a variety of reasons. Multiple measurements of the same variable may classify persons more accurately, because there may be significant laboratory or biologic variation in the factor under consideration and risk-factor levels may change unpredictably among older persons.[40-42] Laboratory methods were relatively uniform over the course of the study. Cholesterol and HDL cholesterol were generally measured in the nonfasting state, and the reported difference between measurements of these analytes in the fasting and nonfasting states is minimal.[41,43] Laboratory methods also evolved over time, but quality control of the enzymatic measurements of lipoprotein cholesterol was linked to the Abell–Kendall methods that were in use during the study.[41,44]

This study was based on the survivors of a long-term observational investigation. Cholesterol levels often decline in the elderly, and single measurements in an older subject may misrepresent exposure.[45] The importance of multiple measurements and time-integrated effects may be particularly evident when levels or habits change. The association of cigarette smoking with carotid stenosis is more complex, because long-term exposure is highly associated with stenosis and smoking cessation 10 years before the carotid evaluation was still associated with carotid stenosis in these analyses.

There are preventive implications of the significant associations between carotid stenosis and time-integrated measurements of traditional risk factors. Lower blood pressure, lower cholesterol levels, and abstention from smoking in middle adulthood might lead to less carotid stenosis in the elderly, along with less coronary heart disease and stroke.

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