

## ASSOCIATION BETWEEN MULTIPLE CARDIOVASCULAR RISK FACTORS AND ATHEROSCLEROSIS IN CHILDREN AND YOUNG ADULTS

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### ABSTRACT

**Background** In adults, cardiovascular risk factors reinforce each other in their effect on cardiovascular events. However, information is scant on the relation of multiple risk factors to the extent of asymptomatic atherosclerosis in young people.

**Methods** We performed autopsies on 204 young persons 2 to 39 years of age, who had died from various causes, principally trauma. Data on antemortem risk factors were available for 93 of these persons, who were the focus of this study. We correlated risk factors with the extent of atherosclerosis in the aorta and coronary arteries.

**Results** The extent of fatty streaks and fibrous plaques in the aorta and coronary arteries increased with age. The association between fatty streaks and fibrous plaques was much stronger in the coronary arteries ( $r=0.60$ ,  $P<0.001$ ) than in the aorta ( $r=0.23$ ,  $P=0.03$ ). Among the cardiovascular risk factors, body-mass index, systolic and diastolic blood pressure, and serum concentrations of total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol, as a group, were strongly associated with the extent of lesions in the aorta and coronary arteries (canonical correlation [a measure of the association between groups of variables]:  $r=0.70$ ;  $P<0.001$ ). In addition, cigarette smoking increased the percentage of the intimal surface involved with fibrous plaques in the aorta (1.22 percent in smokers vs. 0.12 percent in nonsmokers,  $P=0.02$ ) and fatty streaks in the coronary vessels (8.27 percent vs. 2.89 percent,  $P=0.04$ ). The effect of multiple risk factors on the extent of atherosclerosis was quite evident. Subjects with 0, 1, 2, and 3 or 4 risk factors had, respectively, 19.1 percent, 30.3 percent, 37.9 percent, and 35.0 percent of the intimal surface covered with fatty streaks in the aorta ( $P$  for trend=0.01). The comparable figures for the coronary arteries were 1.3 percent, 2.5 percent, 7.9 percent, and 11.0 percent, respectively, for fatty streaks ( $P$  for trend=0.01) and 0.6 percent, 0.7 percent, 2.4 percent, and 7.2 percent for collagenous fibrous plaques ( $P$  for trend=0.003).

**Conclusions** These findings indicate that as the number of cardiovascular risk factors increases, so does the severity of asymptomatic coronary and aortic atherosclerosis in young people. (N Engl J Med 1998;338:1650-6.)

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**A** THEROSCLEROSIS leading to coronary heart disease is complex in origin. Involved in the pathogenesis of atherosclerosis are hemodynamic, thrombotic, and carbohydrate-lipid metabolic variables, along with intrinsic characteristics of the arterial wall.<sup>1</sup> These physiologic and biochemical factors underlie the clinical events that may eventually occur. Environmental factors such as smoking or a sedentary lifestyle also contribute to this process. The progression of atherosclerotic disease and the increasing severity of atherosclerosis relate not only to the presence and extent of cardiovascular risk factors but also to the persistence of risk factors over time.<sup>2,3</sup> Sudden death may occur in a young person with only a single lesion complicated by a coronary thrombus, without extensive vessel disease. Consequently, the extent of vascular lesions may not be directly related to the occurrence of clinical events, such as myocardial infarction. Morbidity due to coronary artery disease, however, is generally related to the extent of vascular lesions.<sup>4</sup> In this regard, clinical risk factors are considered to be useful in predicting the severity of atherosclerosis.<sup>5</sup>

Epidemiologic studies have established that multiple risk factors increase the probability of cardiovascular events, since cardiovascular risk factors tend to reinforce each other in their influence on morbidity and mortality.<sup>6</sup> Although a specific risk factor influences the risk that a person will have cardiovascular disease, risk factors tend to aggregate and usually appear in combination. Furthermore, since clustering of risk factors is evident in childhood and persists into young adulthood,<sup>7-10</sup> the presence of multiple risk factors could indicate the acceleration of atherosclerosis in young people.

Coronary arteriography has contributed considerably to elucidating the relation of the severity of coronary artery disease to cardiovascular risk factors. Unfortunately, assessing the extent of atherosclerotic coronary lesions by this invasive method in asymptomatic young people is not practical, and its

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value is limited as compared with that of actual anatomical observations.<sup>11</sup> Autopsy data from epidemiologic studies have shown a relation between coronary artery disease and cardiovascular risk factors; for example, high serum total cholesterol concentrations and cigarette smoking are important contributors to the development of coronary atherosclerosis.<sup>6</sup> Autopsy studies from the Bogalusa Heart Study have demonstrated a strong association of specific antemortem risk factors with vascular lesions in children and young adults.<sup>12,13</sup> These observations have been extended by the findings in a larger, multicenter postmortem study, Pathobiological Determinants of Atherosclerosis in Youth.<sup>14-17</sup> Multiple risk-factor data collected ante mortem in the Bogalusa Heart Study can be applied further to autopsy data. In this study we examined the influence of multiple risk factors on the extent of atherosclerosis in the aorta and coronary arteries in young people.

## METHODS

### Study Population

The Bogalusa Heart Study is a long-term epidemiologic study of cardiovascular risk factors from birth through the age of 38 years in a biracial population (65 percent white and 35 percent black).<sup>18,19</sup> Seven cross-sectional surveys, each including more than 3500 children, have been carried out since 1973. Since 1978, five follow-up surveys have been conducted among young adults who participated in previous cross-sectional surveys as children. Participation rates ranged from approximately 80 percent for school-age children to approximately 60 percent for the adult cohort. To date, data have been collected on approximately 14,000 people.

For the autopsy studies, a local information system was established in 1978 to obtain the family's or coroner's consent to conduct an autopsy after the death of a young person. For practical and logistic reasons, an autopsy was conducted on any resident of Washington Parish in Bogalusa, Louisiana, or adjacent parishes who died between the ages of 2 and 39 years. Not all the young people who died in this area had been eligible for the Bogalusa Heart Study's survey of cardiovascular risk factors, which was restricted to ward 4 of Washington Parish. Most deaths were due to accidents or homicide; only about 10 percent were due to renal, neoplastic, or infectious diseases or suicide. Autopsies were conducted in local funeral homes or in hospitals in adjacent communities, and selected tissues (including the heart and coronary arteries, aorta, and kidneys) were brought to the Department of Pathology at Louisiana State University Medical Center in New Orleans for study.

As of January 1996, specimens had been collected at autopsy from 86 white males, 52 black males, 36 white females, and 30 black females, representing more than 60 percent of all known eligible deaths. The mean ( $\pm$ SD) age at death ranged from 20.4 $\pm$ 6.6 years among white females to 21.8 $\pm$ 6.8 years among black males. Of the 204 persons examined at autopsy, 93 had previously been surveyed as part of the Bogalusa Heart Study and therefore had provided data on antemortem risk factors. Among these 93 persons, the mean age at death was 19.6 $\pm$ 5.7 years for the 41 white males, 20.4 $\pm$ 6.2 years for the 19 white females, 21.7 $\pm$ 5.2 years for the 23 black males, and 22.4 $\pm$ 6.0 years for the 10 black females.

### Characterization of Cardiovascular Risk Factors

Essentially the same protocols were used in all surveys. The methods used to measure each risk factor have been described in

detail previously.<sup>19</sup> Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. Body-mass index (the weight in kilograms divided by the square of the height in meters) was used as a measure of obesity.

Blood pressure was measured in the right arm, with the subject in a relaxed, sitting position. The average of six measurements (three taken by each of two examiners) with a mercury sphygmomanometer was used in all analyses. The fourth Korotkoff phase was considered the diastolic blood pressure. Cigarette-smoking status, which was assessed by a questionnaire beginning at the age of eight and continuing through adulthood, was measured in terms of the number of cigarettes smoked per week.<sup>20</sup> Serum total cholesterol, triglycerides, and high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were measured by standardized procedures,<sup>21</sup> which met the performance requirements of the lipid-standardization program of the Centers for Disease Control and Prevention.

### Evaluation of Atherosclerotic Lesions

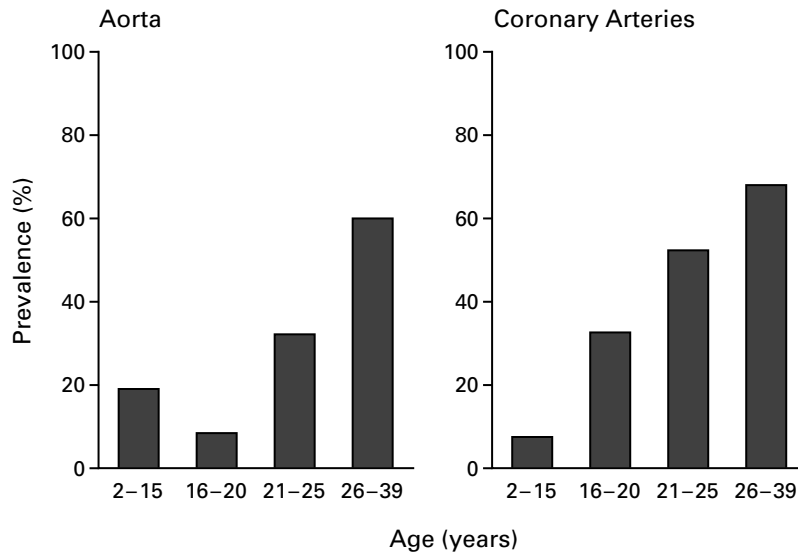
At autopsy, the aorta and coronary arteries were opened longitudinally and stained with Sudan IV to localize lipid deposition. The extent of the intimal surface that was covered with fatty streaks and raised fibrous plaques in the vessels was graded visually according to procedures developed in the International Atherosclerosis Project<sup>22</sup>; these procedures are currently used by the Department of Pathology at Louisiana State University Medical Center. The pathologists grading the lesions were unaware of the subjects' risk-factor data. Briefly, the grader first estimated the percentage of the total intimal surface area involved with any atherosclerotic lesion and then estimated the percentage distribution of fatty streaks, fibrous plaques, complicated lesions (those with evidence of hemorrhage, ulceration, necrosis, or thrombosis, with or without calcification), and calcified lesions within this lesion-covered area. The recorded percentages of individual types of lesions within the lesion-covered area were converted to percentages of the total intimal surface area by multiplying each estimate by the fraction of intimal surface area covered with atherosclerotic lesions.

Three pathologists evaluated the vessels independently; the extent of atherosclerosis was expressed as the mean of the three values assigned by these pathologists for the percentage of the intimal surface covered by lesions. The prevalence of atherosclerotic lesions was defined as the percentage of persons studied who had at least minimal sudanophilic intimal deposits.

### Statistical Analysis

We used z scores (standardized values) specific for the study period, race, sex, and age to eliminate the effects of age, race, sex, and potential variations in laboratory measurements on the antemortem risk-factor variables. For the 65 persons whose risk-factor status was assessed more than once, we used the average of the adjusted levels. Risk factors were defined as values above the 75th percentile (specific for study period, race, age, and sex) for the group as a whole. Antemortem values for very-low-density lipoprotein cholesterol and triglyceride values in nonfasting subjects were not included in the analyses.

Spearman correlation analysis was used to examine the association between the extent of fatty-streak or fibrous-plaque lesions in the aorta and coronary arteries and age at death and the z scores of individual risk-factor variables. A multivariate technique, referred to as canonical correlation analysis, was then used to examine the association between the two sets of variables — that is, the antemortem risk-factor variables and the extent of fatty-streak and fibrous-plaque lesions in the aorta and coronary arteries. The prevalence of atherosclerosis in various age groups was evaluated with a chi-square test. The influence of cigarette smoking on the extent of atherosclerosis and the effect of multiple risk factors on the extent of atherosclerosis were evaluated with analysis of covariance after the extent of lesions was adjusted for race, sex, and age at death; subjects with no risk factors were



**Figure 1.** The Prevalence of Fibrous-Plaque Lesions in the Aorta and Coronary Arteries in 204 Children and Young Adults, According to Age. There is a consistent trend toward a greater prevalence of coronary-artery lesions with increasing age ( $P=0.001$ ).

compared with those with one, two, and three or four risk factors. All statistical tests were two-sided. SAS software was used for all analyses.<sup>23</sup>

## RESULTS

### Prevalence, Extent, and Interrelations of Lesions

Essentially all persons in the age groups we studied had fatty streaks in the aorta. In contrast, the prevalence of fatty streaks in the coronary arteries increased with age from approximately 50 percent at 2 to 15 years of age to 85 percent at 21 to 39 years ( $P=0.01$ ). The prevalence of raised fibrous-plaque lesions in the aorta and coronary arteries is shown in Figure 1. In the aorta, there was a trend toward increasing prevalence with age ( $P=0.001$ ), especially after the age of 15 years; prevalence increased to 60 percent by the age of 26 to 39 years. In the coronary vessels, this age-related trend was even more consistent ( $P=0.001$ ), with the prevalence increasing from 8 percent at 2 to 15 years to 69 percent at 26 to 39 years.

For each type of lesion, there was a trend toward involvement of an increasing percentage of the intimal surface with increasing age. In the aorta, the mean ( $\pm$ SD) percentage of the surface involved with fatty streaks increased from  $13.8\pm 15.5$  percent at 2 to 15 years of age to  $28.8\pm 15.3$  percent at 26 to 39 years ( $P<0.001$ ), and the percentage involved with fibrous plaques increased from  $0.2\pm 0.5$  percent to  $4.0\pm 7.4$  percent, respectively ( $P<0.001$ ). In the coronary arteries, the percentage of the surface involved with fatty streaks increased from  $0.5\pm 0.7$

percent to  $7.1\pm 8.2$  percent ( $P<0.001$ ), and the percentage involved with fibrous plaques increased from  $0.2\pm 0.9$  percent to  $6.9\pm 11.4$  percent ( $P<0.001$ ).

With respect to the interrelation of types of lesions in the aorta and coronary arteries, the correlation of the extent of fatty streaks and fibrous plaques in the aorta with the extent of lesions of the same type in the coronary arteries was only moderate ( $r=0.36$  to  $0.37$ ,  $P=0.001$ ). Furthermore, the correlation between the extent of fatty streaks and that of fibrous plaques was much greater in the coronary arteries ( $r=0.60$ ,  $P<0.001$ ) than in the aorta ( $r=0.23$ ,  $P=0.03$ ).

### Relation of Lesions to Specific Risk Factors

Correlations between the extent of lesions and specific antemortem risk factors are shown in Table 1. The extent of atherosclerotic lesions correlated positively and significantly with body-mass index, systolic blood pressure (except in the case of fibrous plaques in the aorta), diastolic blood pressure (this was true only for fibrous plaques in the coronary arteries), serum total cholesterol concentrations (except for fibrous plaques in the aorta and coronary artery), serum LDL cholesterol concentrations (except for fibrous plaques in the aorta), and serum triglyceride concentrations (except for fatty streaks in the aorta). Furthermore, canonical correlation analysis showed that the extent of fatty-streak and fibrous-plaque lesions in the aorta and coronary vessels as a group were associated moderately strongly with body-mass index ( $r=0.48$ ), systolic blood pressure

**TABLE 1.** CORRELATION BETWEEN THE EXTENT OF LESIONS IN THE AORTA AND CORONARY ARTERIES AND ANTEMORTEM RISK-FACTOR VARIABLES.\*

RISK-FACTOR VARIABLE	AORTA		CORONARY ARTERIES	
	FATTY STREAKS	FIBROUS PLAQUES	FATTY STREAKS	FIBROUS PLAQUES
Body-mass index	0.33†	0.24‡	0.41§	0.29†
Systolic blood pressure	0.31†	0.17	0.47§	0.41§
Diastolic blood pressure	0.14	0.10	0.18	0.24‡
Total cholesterol	0.54§	0.15	0.26‡	0.23
LDL cholesterol	0.54§	0.16	0.29‡	0.32†
HDL cholesterol	-0.03	0.05	-0.14	-0.12
Triglycerides	0.23	0.26‡	0.32†	0.37†

\*Values shown are Spearman correlation coefficients. In this analysis, we used average z scores for risk factors in subgroups, defined by age, race, and sex, of all participants in the cross-sectional surveys. Although there was a total of 93 participants, because of missing data, the numbers used varied from 65 to 86, depending on the variables.

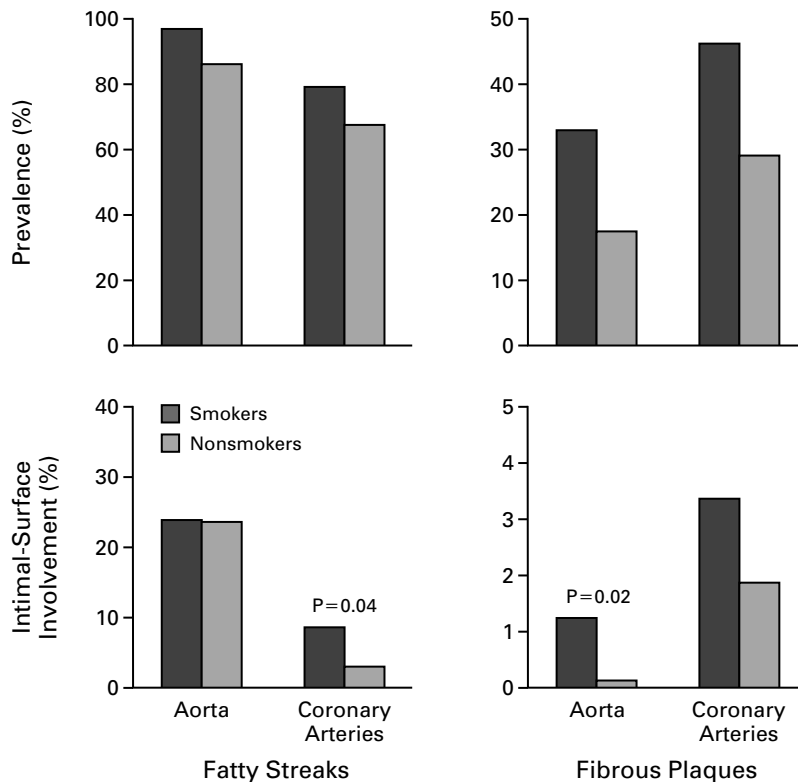
†P<0.01.

‡P<0.05.

§P<0.001.

( $r=0.55$ ), serum triglyceride concentrations ( $r=0.50$ ), and LDL cholesterol concentrations ( $r=0.43$ ) and associated weakly with diastolic blood pressure ( $r=0.22$ ) and HDL cholesterol concentrations ( $r=-0.16$ ). On the other hand, antemortem risk-factor variables as a group were most strongly associated with the extent of fatty streaks in the coronary arteries ( $r=0.55$ ), followed by the extent of fibrous plaques in the coronary arteries ( $r=0.52$ ), fibrous plaques in the aorta ( $r=0.40$ ), and fatty streaks in the aorta ( $r=0.38$ ). Overall, the highest canonical correlation between antemortem risk-factor variables and the extent of lesions in the aorta and coronary arteries was 0.70 ( $P<0.001$ ).

The influence of cigarette smoking on the prevalence and extent of aortic and coronary-artery lesions is shown in Figure 2. The prevalence of lesions in these vessels was similar in the 15 smokers and the 34 nonsmokers (for the remaining subjects, smoking status was unknown). The mean ( $\pm$ SE) percentage of the intimal surface involved with fibrous-plaque



**Figure 2.** The Influence of Cigarette Smoking on the Prevalence (Top Panels) and Extent (Bottom Panels) of Atherosclerosis in the Aorta and Coronary Arteries in Children and Young Adults.

There were 34 nonsmokers and 15 smokers among the 93 subjects; for the remaining subjects, smoking status was unknown. Even though the lifetime amount of smoking may be relatively low at young ages, its adverse effects are obvious.

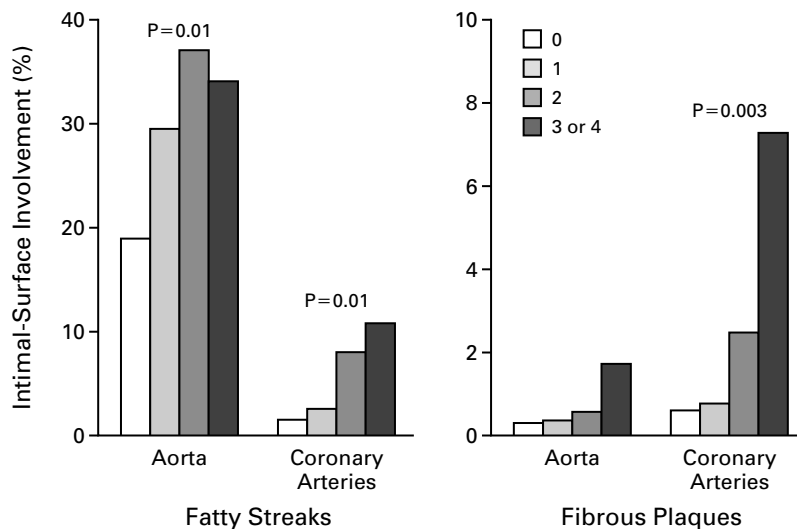
lesions in the aorta was higher in smokers than in nonsmokers ( $1.22 \pm 0.62$  percent vs.  $0.12 \pm 0.07$  percent,  $P=0.02$ ), as was the percentage involved in fatty-streak lesions in the coronary vessels ( $8.27 \pm 3.43$  percent vs.  $2.89 \pm 0.83$  percent,  $P=0.04$ ).

#### Relation of Lesions to Multiple Risk Factors

The mean percentage of the intimal surface covered by lesions in patients with different numbers of risk factors (0, 1, 2, and 3 or 4) is shown in Figure 3. The risk factors we evaluated included body-mass index, systolic blood pressure, serum triglyceride concentration, and serum LDL cholesterol concentration. In subjects with 0, 1, 2, and 3 or 4 risk factors, 19.1 percent, 30.3 percent, 37.9 percent, and 35.0 percent, respectively, of the intimal surface area was involved with fatty streaks in the aorta ( $P$  for trend=0.01). In the coronary arteries, 1.3 percent, 2.5 percent, 7.9 percent, and 11.0 percent, respectively, of the intimal surface was involved with fatty streaks ( $P$  for trend=0.01), and 0.6 percent, 0.7 percent, 2.4 percent, and 7.2 percent was involved with collagenous fibrous plaques ( $P$  for trend=0.003). The extent of fatty-streak lesions in the coronary arteries was 8.5 times as great in persons with three or four risk factors as in those with none ( $P=0.03$ ), and the extent of fibrous-plaque lesions in the coronary arteries was 12 times as great ( $P=0.006$ ).

#### DISCUSSION

Observations from autopsy studies by the Bogalusa Heart Study and the multicenter Pathobiological Determinants of Atherosclerosis in Youth study clearly documented a strong relation between coronary atherosclerosis and cardiovascular risk factors in young people.<sup>12-17</sup> Our observation that specific antemortem risk factors such as elevations in body-mass index, systolic blood pressure, serum LDL cholesterol concentration, and serum triglyceride concentration and cigarette smoking are significantly related to the extent of atherosclerotic lesions in young people is in agreement with the findings in those studies. Furthermore, the prevalence and extent of lesions in the coronary arteries, especially fibrous-plaque lesions that encroach on the lumen, increased with age in the young people we studied. Previous studies of the natural history of atherosclerosis indicated that in populations with high rates of premature coronary artery disease, advanced lesions begin to appear with greater frequency during childhood and young adulthood.<sup>24</sup> Although there has been some question about the clinical significance of fatty streaks in the aorta, which some suggest are evanescent, their presence in association with fibrous plaques in coronary vessels is considered to indicate that atherosclerosis is progressive and severe.<sup>25</sup> In the current study, the correlation between the extent of fatty streaks and



**Figure 3.** The Effect of Multiple Risk Factors on the Extent of Atherosclerosis in the Aorta and Coronary Arteries in Children and Young Adults.

Values shown are the percentages of the intimal surface covered with lesions in subjects with 0, 1, 2, and 3 or 4 risk factors. Risk factors were elevated values for body-mass index, systolic blood pressure, and serum triglyceride and LDL cholesterol concentrations, defined as values above the 75th percentile for the study group (specific for study period, race, sex, and age). There were 52 subjects with no risk factors, 20 with one, 14 with two, and 7 with three or four. The  $P$  value is based on the analysis of trend. A marked increase in the percentage of the intimal surface covered by fibrous plaques is evident in the coronary vessels of subjects with multiple risk factors.

that of fibrous plaques was much greater in the coronary arteries than in the aorta. Also, the proportion of collagenous fibrous plaques in relation to fatty streaks was greater in the coronary vessels than in the aorta.

We found that the extent of atherosclerotic lesions in the coronary vessels increased markedly in young people with multiple risk factors. This finding supports the concept that multiple risk factors have a synergistic effect on morbidity and mortality from coronary heart disease in middle age and later, as has been demonstrated by epidemiologic studies such as the Framingham Study.<sup>26</sup> We could not examine the effect of multiple risk factors on the extent of atherosclerosis separately according to race and sex because of the small numbers of persons in each group within our sample.

The multiple risk factors we evaluated included high values for body-mass index, systolic blood pressure, and LDL cholesterol and triglycerides in serum. Cardiovascular risk factors such as dyslipidemia, hypertension, hyperinsulinemia or insulin resistance, and obesity often coexist in both children and young adults.<sup>9,10</sup> Since the clustering of these conditions — termed syndrome X,<sup>27</sup> the deadly quartet,<sup>28</sup> or insulin-resistance syndrome<sup>29</sup> — is seen so frequently, a common pathophysiologic mechanism involving insulin resistance has been suggested. Although we did not measure plasma insulin and glucose concentrations as indicators of carbohydrate-lipid metabolism, it is reasonable to suggest that these variables may be part of the cluster of risk factors in the study population, as we have shown previously.<sup>9,10,30</sup> In this regard, the effects of elevated glycosylated hemoglobin concentrations and of obesity on atherosclerosis are evident throughout the group of 15-to-34-year-old subjects in the Pathobiological Determinants of Atherosclerosis in Youth study.<sup>16</sup>

Our observation that the extent of fatty-streak lesions in the coronary vessels of children and young adults was higher in cigarette smokers than in non-smokers is in agreement with the findings of the Pathobiological Determinants of Atherosclerosis in Youth study.<sup>14,17</sup> Therefore, it is to be expected that cigarette smoking by young people who have multiple other risk factors will adversely influence the extent of coronary atherosclerosis.

The effects of multiple risk factors on coronary atherosclerosis give further justification for the evaluation of cardiovascular risk in young people and provide a rationale for both prevention and intervention. It may be important to focus on multiple cardiovascular risk factors early in life, rather than on a specific risk factor, such as hypercholesterolemia. Interventions related to modifiable risk factors, such as the prevention of smoking, weight control, and

encouragement of physical exercise and a prudent diet, if undertaken early in life, may retard the development of atherosclerosis.

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