

# Associations of Coronary Heart Disease Risk Factors With the Intermediate Lesion of Atherosclerosis in Youth

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**Abstract**—The raised fatty streak (fatty plaque) is the gross term for the lesion intermediate between the juvenile (flat) fatty streak and the raised lesion of atherosclerosis. We measured the percentage of intimal surface involved with flat fatty streaks, raised fatty streaks, and raised lesions in the aortas and right coronary arteries of 2876 autopsied persons aged 15 through 34 years who died of external causes. Raised fatty streaks were present in the abdominal aortas of  $\approx 20\%$  of 15- to 19-year-old subjects, and this percentage increased to  $\approx 40\%$  for 30- to 34-year-old subjects. Raised fatty streaks were present in the right coronary arteries of  $\approx 10\%$  of 15- to 19-year-old subjects, and this percentage increased to  $\approx 30\%$  for 30- to 34-year-old subjects. The percent intimal surface involved with raised fatty streaks increased with age in both arteries and was associated with high non-high density lipoprotein (HDL) and low HDL cholesterol concentrations in the abdominal aorta and right coronary artery, with hypertension in the abdominal aorta, with obesity in the right coronary artery of men, and with impaired glucose tolerance in the right coronary artery. Associations of risk factors with raised fatty streaks became evident in subjects in their late teens, whereas associations of risk factors with raised lesions became evident in subjects aged  $>25$  years. These results are consistent with the putative transitional role of raised fatty streaks and show that coronary heart disease risk factors accelerate atherogenesis in the second decade of life. Thus, long-range prevention of atherosclerosis should begin in childhood or adolescence. (*Arterioscler Thromb Vasc Biol.* 2000;20:1998-2004.)

**Key Words:** atherosclerosis ■ intermediate lesion ■ raised fatty streaks ■ fatty plaque ■ risk factors

Atherosclerotic lesions commonly classified as “fatty streaks” are grossly and microscopically heterogeneous.<sup>1</sup> The typical fatty streak of childhood and adolescence (the “juvenile” fatty streak)<sup>2</sup> is not elevated above the intimal surface and contains predominantly foam cells of mononuclear or smooth muscle cell origin with minimal extracellular lipid or connective tissue.<sup>3</sup> In adolescents and young adults, some fatty streaks are elevated above the surrounding surface and contain, in addition to lipid-filled foam cells, aggregates of extracellular lipid in acellular areas.<sup>2,3</sup> They have been called fatty plaques or raised fatty streaks, descriptive terms that do not imply any particular pathogenetic relationship with other lesions. However, because raised fatty streaks possess features of both the flat fatty streak and the more advanced fibrous plaque, many observers have suggested that they represent juvenile fatty streaks in the process of becoming fibrous plaques and, therefore, have called them transitional or intermediate lesions.<sup>1,4</sup>

In 1985, investigators organized a multicenter cooperative study, Pathobiological Determinants of Atherosclerosis in

Youth (PDAY), to examine more intensively the lesions of atherosclerosis in 15- to 34-year-old autopsied individuals.<sup>5</sup> We previously have reported associations of the risk factors for adult coronary heart disease (CHD) with fatty streaks (flat and raised combined) and with raised lesions.<sup>6–8</sup> Preliminary analyses of a limited number of PDAY cases showed that raised fatty streaks are frequent in this age group and are associated with CHD risk factors.<sup>9</sup> In the present study, we report a more extensive analysis of the prevalence, extent, and risk factor associations of raised fatty streaks in almost 3000 individuals. Raised fatty streaks are associated with CHD risk factors, and these results have important implications for the long-range prevention of CHD.

## Methods

### Study Design

Fifteen cooperating centers adopted a Standard Operating Protocol and Manual of Procedures to collect specimens and data and to submit them to central laboratories for analysis. A statistical coordinating center received all data pertaining to each case.

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**TABLE 1. Risk Factors, Samples, Analyses, Classification, and Prevalence in the PDAY Study**

Risk Factor	Sample	Analysis	Classification	Prevalence, %
High non-HDL cholesterol	Serum	Total cholesterol less HDL cholesterol	≥4.14 mmol/L (≥160 mg/dL)	28.0
Low HDL cholesterol	Serum	Cholesterol after precipitation of apoB lipoproteins	<0.91 mmol/L (<35 mg/dL)	18.7
Smoking	Serum	Thiocyanate	≥90 μmol/L	44.0
Hypertension	Renal arteries	Intimal thickness and algorithm to estimate mean arterial pressure	≥110 mm Hg	15.5
Obesity	Measured at autopsy	BMI=weight (kg)/height (m) <sup>2</sup>	≥30 kg/m <sup>2</sup>	14.3
Impaired glucose tolerance	Red blood cells	% Glycohemoglobin	≥8%	4.3

**Subjects**

Study subjects were persons aged 15 through 34 years who died of external causes (accidents, homicides, or suicides) within 72 hours of injury and were autopsied within 48 hours of death in one of the cooperating forensic laboratories. Age and race were obtained from the death certificate. We collected 2876 acceptable cases from June 1, 1987, to August 31, 1994. The Institutional Review Board of each cooperating center approved the present study.

**Dissecting and Preserving Arteries**

PDAY investigators bisected the aorta longitudinally and fixed the left half in 10% neutral buffered formalin. They opened the right coronary artery longitudinally and fixed it in the same manner as the aorta. Collection centers shipped each aorta and coronary artery in a plastic bag to a central laboratory, which stained the arteries with Sudan IV and packaged them in plastic bags for storage and grading.

**Grading of Fatty Streaks and Raised Lesions**

Three pathologists independently graded the stained right coronary arteries and left halves of the aortas. They visually estimated the extent of intimal surface area involved with fatty streaks and raised lesions by procedures developed in the International Atherosclerosis Project.<sup>10</sup> The intraclass correlations among the 3 pathologists in grading the extent of involvement with fatty streaks were 0.813 for the thoracic aorta, 0.777 for the abdominal aorta, and 0.796 for the right coronary artery. In grading the extent of involvement with raised lesions, the coefficients were 0.593 for the thoracic aorta, 0.726 for the abdominal aorta, and 0.827 for the right coronary artery. The averages of the 3 independent grades of fatty streaks and of raised lesions were the consensus grades used in previous PDAY publications.<sup>6-8</sup>

Four graders independently estimated the fraction of fatty streaks that were raised in each aortic segment. The intraclass correlation coefficients among the 4 pathologists in grading the fraction of fatty streaks that were raised were 0.538 for the thoracic aorta and 0.585 for the abdominal aorta. We multiplied the average of the 4 fractions by the consensus extent of fatty streaks to obtain the percent surface involvement with raised fatty streaks and obtained the surface area involvement with flat fatty streaks by subtraction.

If the consensus extent of fatty streaks in the right coronary artery was >2%, the 4 graders independently estimated the fraction of fatty streaks that were raised. The intraclass correlation coefficient among the 4 pathologists in grading the fraction of fatty streaks that were raised was 0.648. We multiplied the average of the 4 fractions by the consensus extent of fatty streaks to obtain the percent surface involvement with raised fatty streaks and obtained the surface area involvement with flat fatty streaks by subtraction.

If the consensus extent of fatty streaks in the right coronary artery was ≤2% and at least 2 of the 3 pathologists had scored the specimen as positive for fatty streaks, the 4 graders independently scored the specimen as negative or positive for the presence of raised fatty streaks. The 4 graders agreed in the classification of presence or absence of raised fatty streaks in 89.9% (κ=0.694, P=0.0001)<sup>11</sup> of 484 right coronary arteries. If only 1 of the pathologists had scored

the specimen as positive for fatty streaks, we considered the specimen as negative for raised fatty streaks.

For estimating the prevalence of lesions, we considered a case as positive for a particular lesion classification if at least 2 graders scored the case as positive for that lesion type.

**Microscopic Confirmation of Gross Identification of Raised Fatty Streaks**

To examine the histological characteristics of raised fatty streaks identified grossly, we excised flat and raised fatty streaks from 36 arteries and stained microscopic sections with hematoxylin and eosin and with oil red O. Lesions classified as raised fatty streaks showed features typical of American Heart Association (AHA) type III lesions:<sup>4</sup> numerous intimal macrophage foam cells with ≥1 pool of extracellular lipid but no well-defined core of extracellular lipid and no thick fibrous cap. Flat fatty streaks were almost exclusively AHA type II lesions.

**Risk Factor Measurements**

Methods of measuring CHD risk factors and the limitations of these measurements were presented in previous publications<sup>6-8</sup> and are summarized in Table 1, which also shows the prevalence of each risk factor in PDAY subjects.

**Statistical Analyses**

The extent of involvement with flat fatty streaks, raised fatty streaks, and raised lesions in the aorta and the extent of raised lesions in the right coronary artery were analyzed by multiple linear regression.<sup>12</sup> The percent intimal surface area involved with lesions was transformed with a logit transformation, with a small constant added to avoid the logarithm of zero.<sup>13</sup> The extent of raised fatty streaks in cases for which the consensus grade of fatty streaks was >0% and ≤2% and the consensus of the 4 graders was that raised fatty streaks were present was regarded as a censored observation. The mean extent of raised fatty streaks, after transformation with a logit transformation, was assumed to be a linear function of the predictor variables. The likelihood function was constructed as described by Shumway et al<sup>14</sup> for a combination of censored and uncensored observations. Estimates of the parameters were obtained by the method of maximum likelihood, and large sample standard errors were obtained from the inverse of the estimated information matrix. Tests of hypothesis made use of the large sample likelihood ratio test. The extent of raised fatty streaks in censored observations was estimated, and the extent of flat fatty streaks was obtained by subtraction. Prevalence of lesions was analyzed by multiple logistic regression.<sup>15</sup>

**Results**

**Presentation of Results**

The following text describes the significant differences in prevalence and extent of each type of lesion (flat fatty streaks, raised fatty streaks, and raised lesions) by age, sex, race, and

**TABLE 2. Ratio of Percent Intimal Surface Area Involved for High Level of Risk Factor to Involvement for Low Level of Risk Factor by Age, Adjusted for Race and Sex**

Risk Factor and Group	Abdominal Aorta		Right Coronary Artery	
	15–24 y	25–34 y	15–24 y	25–34 y
<b>High non-HDL cholesterol*</b>				
All				
Flat fatty streaks	1.24±0.06†	1.25±0.04†	1.33±0.18†	1.72±0.18†
Raised fatty streaks	1.93±0.26†	2.39±0.24†	1.39±0.17†	1.91±0.18†
Raised lesions	0.96±0.15	1.44±0.14†	1.30±0.18	1.79±0.19†
<b>Low HDL cholesterol*</b>				
All				
Flat fatty streaks	1.09±0.06	1.22±0.05†	1.19±0.17	1.27±0.17
Raised fatty streaks	1.27±0.17	1.63±0.20†	1.10±0.14	1.56±0.19†
Raised lesions	0.89±0.15	1.05±0.14	1.02±0.15	1.20±0.16
<b>Smoking*</b>				
All				
Flat fatty streaks	1.16±0.05†	1.08±0.04†	1.15±0.14	1.01±0.11
Raised fatty streaks	1.00±0.12	1.27±0.11†	1.08±0.12	0.93±0.10
Raised lesions	1.11±0.14	2.92±0.25†	1.02±0.13	1.12±0.11
<b>Hypertension‡</b>				
Whites				
Flat fatty streaks	0.94±0.07	1.00±0.06	0.79±0.15	0.96±0.15
Raised fatty streaks	1.00±0.16	1.33±0.20	0.86±0.13	0.92±0.14
Raised lesions	0.66±0.15†	1.07±0.16	0.96±0.16	1.58±0.23†
Blacks				
Flat fatty streaks	0.98±0.06	1.03±0.04	0.79±0.13	0.96±0.12
Raised fatty streaks	0.90±0.13	1.21±0.14	1.03±0.13	1.10±0.12
Raised lesions	1.29±0.19	1.90±0.21†	1.27±0.18	2.07±0.25†
<b>Obesity§</b>				
Men				
Flat fatty streaks	1.02±0.07	1.13±0.06†	1.53±0.21†	1.44±0.17†
Raised fatty streaks	1.49±0.21†	1.29±0.15†	1.95±0.25†	1.58±0.18†
Raised lesions	1.02±0.16	1.01±0.13	1.88±0.26†	2.22±0.26†
Women				
Flat fatty streaks	0.92±0.10	1.02±0.07	1.23±0.29	1.17±0.23
Raised fatty streaks	1.09±0.26	0.95±0.20	1.17±0.25	0.95±0.18
Raised lesions	0.88±0.25	0.88±0.20	1.15±0.28	1.43±0.27
<b>Elevated glycohemoglobin*</b>				
All				
Flat fatty streaks	0.92±0.09	0.91±0.07	1.33±0.29	1.32±0.26
Raised fatty streaks	1.18±0.26	1.00±0.20	1.36±0.27	1.34±0.24
Raised lesions	0.90±0.22	1.36±0.25	1.18±0.27	2.43±0.46†

Values are ratio±SE.

\*Results adjusted for sex and race.

†Ratios significantly different from 1.00 ( $P<0.05$ ).

‡Results adjusted for sex.

§Results adjusted for race.

the significant associations of the extent of each lesion with the risk factors. The effect of each risk factor is presented quantitatively as the ratio of the high level of the risk factor to the low level of that risk factor by arterial segment and 10-year age group in Table 2. The effects of the major risk

factors combined, designated “risk level,” are summarized quantitatively as the ratio of the extent of involvement for the high-risk group to the extent of involvement for the low-risk group by arterial segment and 5-year age group (adjusted for race and sex) in Table 3. The extent of involvement with

**TABLE 3. Ratio of Percent Intimal Surface Area Involved in High-Risk Group to Percent Surface Area Involved in Low-Risk Group**

Artery and Lesion Type	Age			
	15–19 y	20–24 y	25–29 y	30–34 y
<b>Abdominal aorta</b>				
Flat fatty streaks	1.66±0.25*	1.62±0.13*	1.61±0.11*	1.66±0.17*
Raised fatty streaks	2.38±0.90*	3.62±0.79*	5.40±0.99*	8.10±2.07*
Raised lesions	0.63±0.39	1.73±0.44	4.29±0.85*	8.48±1.91*
<b>Right coronary artery</b>				
Flat fatty streaks	2.91±1.08*	2.75±0.63*	2.58±0.53*	2.41±0.72*
Raised fatty streaks	3.45±1.17*	3.32±0.69*	3.18±0.60*	3.02±0.84*
Raised lesions	1.53±0.62	2.91±0.67*	5.26±1.03*	8.68±2.18*

Values are ratio±SE.

\*Ratios significantly different from 1.00 ( $P<0.05$ ).

lesions in the high- and low-risk groups (adjusted for sex and race) is given in the Figure.

### Age, Race, and Sex Effects

#### Thoracic Aorta

Flat fatty streaks were present in almost all thoracic aortas. Raised fatty streaks increased in prevalence from  $\approx 10\%$  in the 15- to 19-year age group to  $\approx 30\%$  in the 30- to 34-year age group ( $P=0.0001$ ), were more frequent in men than in women ( $P=0.0001$ ), and were more frequent in blacks than in whites ( $P=0.0348$ ).

Raised fatty streaks increased in percentage of surface involvement with age ( $P=0.0001$ ), were more extensive in men than in women ( $P=0.0130$ ), and were more extensive in blacks than in whites ( $P=0.0001$ ). However, the average percentage of surface involved with raised fatty streaks was very low ( $<2\%$ ) throughout all age groups as was the percentage of involvement with raised lesions ( $<3\%$ ). Because clinically significant raised lesions were rare in the thoracic aorta, analyses of their relationships with risk factors were not performed.

#### Abdominal Aorta

Flat fatty streaks were present in almost all abdominal aortas. The prevalence of raised fatty streaks rose from  $\approx 20\%$  in the 15- to 19-year age group to  $\approx 40\%$  in the 30- to 34-year age group ( $P=0.0001$ ) in whites and blacks; prevalence was greater in men than in women ( $P=0.0001$ ). The prevalence of raised lesions increased  $>10$ -fold between the 15- to 19- and 30- to 34-year age groups ( $P=0.0001$ ), and prevalence was greater in whites than in blacks ( $P=0.0213$ ).

The percent surface area involved with flat fatty streaks increased with age until 25 to 29 years and did not increase further, presumably because these lesions are replaced by more advanced lesions ( $P=0.0001$ ). Women had more extensive flat fatty streaks than did men ( $P=0.0001$ ), and blacks had more than whites ( $P=0.0001$ ). The extent of raised fatty streaks and raised lesions increased with age ( $P=0.0001$ ). There were no significant sex or race differences for raised fatty streaks and no sex differences for raised lesions; but whites had more extensive raised lesions than did blacks ( $P=0.0401$ ).

#### Right Coronary Artery

The prevalence of flat and raised fatty streaks increased with age ( $P=0.0001$ ) throughout the 15- to 34-year age span, and the prevalence of raised lesions increased with age in subjects aged  $>25$  years ( $P=0.0001$ ). Prevalence of all 3 types of lesions was greater in men than in women ( $P=0.0022$ ). The prevalence of flat fatty streaks was greater in blacks than in whites ( $P=0.0125$ ), and the prevalence of raised lesions was greater in whites than in blacks ( $P=0.0168$ ).

The percent intimal surface involved for all 3 types of lesions increased with age ( $P=0.0001$ ). Black women had more extensive flat fatty streaks than did white women ( $P=0.0117$ ), but white men and black men were similar in the extent of flat fatty streaks ( $P=0.6061$ ). White men had more extensive raised fatty streaks than did white women ( $P=0.0009$ ), but black men and black women had about the same extent of raised fatty streaks ( $P=0.8515$ ). Men, both black and white, had much more extensive raised lesions than did black or white women ( $P=0.0001$ ).

### Risk Factor Effects

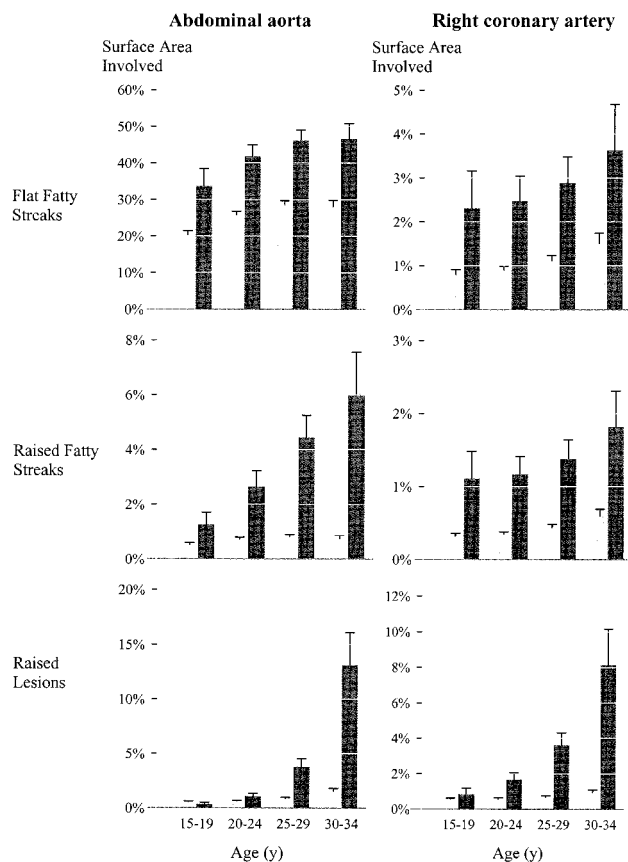
#### Non-HDL Cholesterol

In the abdominal aorta, high non-HDL cholesterol ( $\geq 4.14$  mmol/L [ $\geq 160$  mg/dL]) was associated with more extensive flat fatty streaks ( $P=0.0001$ ) and raised fatty streaks ( $P=0.0001$ ) and with more extensive raised lesions in subjects aged  $>25$  years (non-HDL cholesterol by age interaction,  $P=0.0228$ ).

In the right coronary artery, high non-HDL cholesterol was associated with more extensive flat fatty streaks ( $P=0.0001$ ), raised fatty streaks ( $P=0.0001$ ), and raised lesions ( $P=0.0001$ ). The effect of high non-HDL cholesterol on raised fatty streaks (non-HDL cholesterol by age interaction,  $P=0.0438$ ) and raised lesions (non-HDL cholesterol by age interaction,  $P=0.0597$ ) increased with age.

Table 2 shows the effect of the non-HDL cholesterol concentration as a ratio of the extent of lesions in high non-HDL cholesterol subjects to the extent of lesions in low non-HDL cholesterol subjects (see Table 1 for definitions). This ratio was higher for raised fatty streaks than for raised lesions in both arteries. The ratio was  $>1.0$  for flat and raised fatty streaks beginning in the 15- to 24-year age group. The ratio for raised lesions was significantly  $>1.0$  only for those





Mean percent intimal surface area involved with lesions in the abdominal aorta (left panels) and right coronary artery (right panels) by 5-year age group and risk status, adjusted for sex and race. Low-risk subjects (light gray bars) have non-HDL cholesterol concentration  $<4.14$  mmol/L ( $<160$  mg/dL), HDL cholesterol concentration  $\geq 0.91$  mmol/L ( $\geq 35$  mg/dL), and BMI  $<30$  kg/m<sup>2</sup> and are nonsmokers and normotensive. High-risk subjects (dark gray bars) have non-HDL cholesterol concentration  $\geq 4.14$  mmol/L ( $\geq 160$  mg/dL), HDL cholesterol concentration  $<0.91$  mmol/L ( $<35$  mg/dL), and BMI  $\geq 30$  kg/m<sup>2</sup> and are smokers and hypertensive. Only subjects with normal glycohemoglobin ( $<8\%$ ) are included. Extension over each bar represents standard error.

aged  $>25$  years, an observation suggesting that elevated non-HDL cholesterol affects flat fatty streaks and raised fatty streaks before it affects raised lesions.

#### HDL Cholesterol

In the abdominal aorta, low HDL cholesterol ( $<0.91$  mmol/L [ $<35$  mg/dL]) was associated with more extensive flat fatty streaks ( $P=0.0002$ ) and raised fatty streaks ( $P=0.0003$ ) but not with raised lesions.

In the right coronary artery, low HDL cholesterol was associated with more extensive flat fatty streaks ( $P=0.0524$ ) and with more extensive raised fatty streaks in the older age groups (HDL cholesterol by age interaction,  $P=0.0419$ ). There was a slight but nonsignificant trend for low HDL cholesterol subjects to have more extensive raised lesions after the age of 25 years.

As shown in Table 2, the ratio of the extent of raised fatty streaks in low HDL cholesterol subjects to that in high HDL cholesterol subjects was higher than the ratios for raised lesions. The pattern of effects was similar to that for non-HDL cholesterol, but the effects were weaker.

#### Smoking

In the abdominal aorta, smoking was associated with more extensive flat fatty streaks ( $P=0.0006$ ). Smoking also was associated with raised lesions after the age of 25 years (smoking by age interaction,  $P=0.0001$ ). Smokers in the 30- to 34-year age group had 3-fold more extensive raised lesions in the abdominal aorta than did nonsmokers.

There were no significant associations of smoking with lesions in the right coronary artery.

Table 2 shows the ratio of the extent of each type of lesion in smokers to that in nonsmokers. The ratio for flat fatty streaks is significantly  $>1.0$  in the abdominal aorta in the 15- to 24-year age group and in all 3 types of lesions in the 25- to 34-year age group.

#### Hypertension

In the abdominal aorta, hypertension was associated with increased raised fatty streaks in subjects aged  $>30$  years (age by hypertension interaction,  $P=0.0386$ ). Hypertension was also associated with raised lesions in the abdominal aortas of blacks (race by hypertension interaction,  $P=0.0006$ ) aged  $>25$  years (age by hypertension interaction,  $P=0.0051$ ).

In the right coronary artery, hypertension was associated with more extensive raised lesions in those aged  $>25$  years (age by hypertension interaction,  $P=0.0016$ ).

The ratios of the extent of lesions in hypertensive subjects to that in normotensive subjects (Table 2) show that hypertension affected raised lesions but not flat or raised fatty streaks. We believe that the ratio of 0.66 for raised lesions in the abdominal aorta of younger whites is due to the low prevalence of hypertension in the younger age group and does not represent a real effect of hypertension.

#### Obesity

In the abdominal aorta, obesity (body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>) was associated with more extensive flat fatty streaks in men aged  $>25$  years ( $P=0.0198$ ) and with more extensive raised fatty streaks in men in all age groups ( $P=0.0016$ ). In the right coronary artery, obesity was associated with more extensive flat fatty streaks in men ( $P=0.0002$ ), raised fatty streaks in men ( $P=0.0001$ ), and raised lesions in men ( $P=0.0001$ ). There was no effect of obesity on raised fatty streaks or raised lesions in women.

The effects of obesity are summarized as ratios in Table 2. Obesity nearly doubled the extent of raised fatty streaks in the right coronary arteries of 15- to 24-year-old men and doubled the extent of raised lesions in 25- to 34-year-old men. There were smaller effects on flat and raised fatty streaks in the abdominal aortas of men. In contrast, none of the ratios in women was significantly different from 1.0.

#### Impaired Glucose Tolerance

No significant differences in atherosclerotic lesions were associated with elevated glycohemoglobin ( $\geq 8\%$ ) in the abdominal aorta. In the right coronary artery, elevated glycohemoglobin was associated with more extensive flat fatty streaks ( $P=0.0637$ ) and raised fatty streaks ( $P=0.0339$ ) and with more extensive raised lesions in the older age groups (age by glycohemoglobin interaction,  $P=0.0103$ ).

In Table 2, the ratios of the extent of flat and raised fatty streaks in right coronary arteries of subjects with elevated glycohemoglobin to that in subjects with normal glycohemoglobin

globin tended to be  $>1.0$  but were not significantly greater, probably because of the low prevalence of elevated glycohemoglobin. The ratio for raised lesions in the right coronary arteries of 25- to 34-year-old subjects was substantial.

#### Combined Risk Factors

We defined low-risk subjects as normotensive nonsmokers having non-HDL cholesterol concentration  $<4.14$  mmol/L ( $<160$  mg/dL), HDL cholesterol  $\geq 0.91$  mmol/L ( $\geq 35$  mg/dL), and BMI  $<30$  kg/m<sup>2</sup>; we defined high-risk subjects as hypertensive smokers having non-HDL cholesterol concentration  $\geq 4.14$  mmol/L ( $\geq 160$  mg/dL), HDL cholesterol  $<0.91$  mmol/L ( $<35$  mg/dL), and BMI  $\geq 30$  kg/m<sup>2</sup>. Subjects with elevated glycohemoglobin were excluded. With the exception of the abdominal aorta in the 15- to 19- and 20- to 24-year age groups and the right coronary artery in the 15- to 19-year age group, the high-risk level was associated with more extensive flat fatty streaks, raised fatty streaks, and raised lesions in the abdominal aorta and the right coronary artery in all age groups ( $P<0.05$ , Figure). The effect of the combined risk factors on raised fatty streaks and on raised lesions increased with increasing age in the abdominal aorta (age by risk factor level interaction,  $P<0.0420$ ), and the effect on raised lesions in the right coronary artery increased with increasing age (age by risk factor level interaction,  $P=0.0050$ ).

Table 3 shows the ratios of the extent of lesions in high-risk subjects to that in low-risk subjects by lesion type and 5-year age group. Both sexes and both races showed the same patterns of relationships. The ratios for raised fatty streaks in the 2 youngest age groups (15 to 19 and 20 to 24 years) were  $\approx 1.5$  times greater than those for flat fatty streaks and  $\approx 2$  times greater than those for raised lesions. The ratios between high- and low-risk subjects aged  $>25$  years were higher for raised lesions than for flat or raised fatty streaks.

## Discussion

### Summary of Results

Raised fatty streaks can be reproducibly identified and quantified in gross specimens of fixed and Sudan IV-stained abdominal aortas and right coronary arteries. Their prevalence increases with age. With a few exceptions, the extent of raised fatty streaks is associated with the major established risk factors for CHD, and these risk factor effects appear in the mid-teens, whereas the effects of the risk factors on raised lesions do not appear until  $>25$  years of age. The effects of risk factors on raised fatty streaks are greater than their effects on raised lesions in 15- to 24-year-old subjects.

### Raised Fatty Streak as the Intermediate or Transitional Lesion

Fatty streaks occur in young persons around the world, regardless of race, sex, environment, diet, or incidence of CHD in older persons from the same populations.<sup>16</sup> This observation has generated skepticism as to whether the fatty streak is the initial lesion of atherosclerosis. Pathologists have long known, however, that the grossly defined fatty streak was heterogeneous when examined microscopically. By identifying and quantifying the raised fatty streak, we have shown that this variety of fatty streak increases with age in preva-

lence and extent in adolescence and young adulthood and that its extent is associated with CHD risk factors.

These results, based on gross observations, are consistent with the microscopic,<sup>3</sup> chemical,<sup>17</sup> and physicochemical<sup>18</sup> observations that characterize a lesion having features of the simple fatty streak and the fibrous plaque. Additional evidence indicating the transitional role of this lesion was reviewed by the AHA Committee on Lesions,<sup>4</sup> and the intermediate lesion was incorporated into the AHA classification system on the basis of histological characteristics as the type III lesion.<sup>19</sup>

### Association of Raised Fatty Streaks With Risk Factors

These results are also consistent with the results of previous analyses of a limited number of PDAY cases that indicated an association of raised fatty streaks (fatty plaques) with total serum cholesterol concentration, smoking, hypertension, and glycohemoglobin.<sup>9</sup> Previous PDAY reports showed that CHD risk factors predominantly affect raised lesions after  $\approx 25$  years of age.<sup>6-8</sup> The results reported in the present study show that the risk factors begin to affect the precursors of raised lesions, raised fatty streaks, as early as 15 to 19 years of age.

As would be expected if raised fatty streaks represent a juvenile fatty streak progressing to a raised lesion (as demonstrated in Table 3), the proportional effects of risk factors on raised fatty streaks in the 15- to 19- and 20- to 24-year age groups are greater than their effects on raised lesions. Thus, the risk factors begin to accelerate the progression of atherosclerosis at least by the middle of adolescence, and perhaps even earlier.

These results also suggest that in studies of atherosclerosis in youth, raised fatty streaks should be differentiated from all fatty streaks because they are more sensitive to the effects of risk factors at a younger age than are the raised lesions.

### Implications for Primary Prevention of Atherosclerotic Diseases

Although skeptics might still argue that the flat fatty streak is not the initial lesion of atherosclerosis, the totality of evidence is compelling that the raised fatty streak is a lesion of atherosclerosis. Our results support the contention that control of this lesion through risk factor modification should begin at least by mid-adolescence. On the other hand, if one accepts the premise that the flat fatty streak is the initial lesion of atherosclerosis, risk factor control should begin earlier than mid-adolescence as the strategy for the long-range prevention of atherosclerosis and its sequelae.<sup>20-22</sup>

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