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Coronary Risk Factors Measured in Childhood and Young Adult Life Are Associated With Coronary Artery Calcification in Young Adults: The Muscatine Study

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Objectives. **This study was designed to estimate the prevalence of coronary artery calcification in young adult men and women and to examine the association between the presence of coronary artery calcification and coronary risk factors measured in childhood and young adult life.**

Background. **Electron beam computed tomography is a sensitive, noninvasive method for detecting coronary artery calcification, a marker of the atherosclerotic process. Coronary artery calcification is associated with coronary risk factors in older adults.**

Methods. **Subjects (197 men, 187 women) had coronary risk factors measured in childhood (mean age 15 years) and twice during young adult life (mean ages 27 and 33 years). Each underwent an electron beam computed tomographic study at their second young adult examination.**

Results. **The prevalence of coronary artery calcification was 31% in men and 10% in women. Increased body size, increased blood pressure and decreased high density lipoprotein (HDL) cholesterol levels were the coronary risk factors that showed the strongest association with coronary artery calcification. Significant odds ratios for coronary artery calcification, using standardized risk factor measurements at a mean age of 33 years in men and women, respectively, were 6.4 and 13.6 for the highest decile of body mass index, 6.4 and 6.4 for the highest decile of systolic blood pressure and 4.3 and 4.7 for the lowest decile of HDL cholesterol.**

Conclusions. **Coronary artery calcification is more prevalent in men in this young adult population. Coronary risk factors measured in children and young adults are associated with the early development of coronary artery calcification. Increased body mass index measured during childhood and young adult life and increased blood pressure and decreased HDL cholesterol levels measured during young adult life are associated with the presence of coronary artery calcification in young adults.**

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Cardiovascular diseases are the leading causes of death in both men and women in the United States. Each year ~1,250,000 Americans suffer a myocardial infarction, and >500,000 die from coronary artery disease (1). Although >6 million patients have symptomatic coronary artery disease, many additional adults have a smaller degree of atherosclerosis affecting their coronary arteries (1). Because subjects with mild coronary artery disease may experience no symptoms, the total number of adults with coronary artery disease is unknown. Clearly, there is a need for a noninvasive method to detect the presence of the atherosclerotic process in asymptomatic subjects with coronary artery disease.

The relation between coronary artery calcification and atherosclerotic plaque has been established in postmortem heart specimens (2–4). Calcified deposits detected radiographically correlate with an identifiable atherosclerotic plaque on histologic examination, and these deposits occur almost exclusively when coronary artery disease is present, especially in younger populations (5). Electron beam computed tomography exhibits a high level of sensitivity in detecting calcium and provides additional information on anatomic localization and extent of calcification (6). Coronary artery calcification has been shown to be associated with coronary risk factors (3,4,7).

To our knowledge, the association between coronary artery calcification in young adults and coronary risk factors measured in childhood and young adult life has not been described. Therefore, the present study sought to estimate the prevalence of coronary artery calcification detected by electron beam computed tomography in a group of young adults (29 to 37 years old) and to examine the association between calcification

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and coronary risk factors measured during childhood and during young adult life.

Methods

Subjects and protocol. Subjects were eligible for study if they had previously participated during childhood in one of the biennial school surveys conducted in Muscatine, Iowa, between 1971 and 1981 and participated in one Muscatine Young Adult Follow-Up Survey between the ages of 20 and 34 years. We previously showed (8,9) that these subjects represent the longitudinal cohort by examination of the childhood age-, gender- and survey year-specific Z scores at the time of their last childhood examination. The mean Z scores were not significantly different from 0, which indicated that the adults in the longitudinal cohort represented the childhood population with respect to their weight, body mass index, triceps skinfold thickness, blood pressure, cholesterol and triglyceride levels without significant bias. During the previous examinations, body size, blood pressure and lipid levels were measured in each subject. If a subject participated in more than one childhood survey, the data from the time of the last survey were used in the analyses. Similarly, if a subject participated in more than one young adult survey, data from the most recent survey were used in the analyses. Of the 284 male and 272 female eligible subjects from this longitudinal cohort, 197 men and 187 women participated. The mean body weight, body mass index, blood pressure, lipid and lipoprotein Z scores from the Muscatine Young Adult Follow-Up Survey indicate that the coronary risk factors of participants versus nonparticipants did not differ between the two groups and that the participants are representative of the entire longitudinal cohort. For the 394 subjects who participated in all three surveys, the mean age was 15 years (range 8 to 18) at the childhood examination, 27 years (range 20 to 34) at the young adult examination and 33 years (range 29 to 37) at the most recent study.

Standardized body size measurements, blood pressure measurements and blood samples were obtained for all participants in the most recent study (8,9). Each subject completed a personal health and family history questionnaire. Subjects traveled from Muscatine, Iowa, to the University of Iowa Hospitals and Clinics in Iowa City, Iowa, for completion of the electron beam computed tomographic study. For all women, a serum pregnancy test was obtained the day before the scheduled study, and those with a positive result were excluded from further participation until after completion of their pregnancy.

The protocol was approved by the University of Iowa Institutional Review Board, and written informed consent was obtained from all subjects.

Body size, blood pressure and lipid and homocysteine levels. Height was recorded to the nearest 0.5 cm, and weight to the nearest 0.1 kg. Triceps skinfold thickness and waist and hip circumferences were recorded to the nearest 1 mm. Body mass index was calculated by dividing weight by height^2. Three random-zero blood pressure measurements were recorded for each subject after a 5-min seated rest period and measurement of pulse obliteration pressure. Cuff size was appropriate for arm size. First and fifth Karotkoff sounds were recorded as systolic and diastolic blood pressures, and the mean of the three measurements was the variable used for analysis.

Total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol, apolipoprotein A1 and B and lipoprotein(a) levels were measured in the core lipid laboratory located in the University of Iowa Hospitals and Clinics. This laboratory uses a Spectrum High Performance Diagnostic System (Abbott Laboratories), and quality control is maintained with a Centers for Disease Control standardization program. All previous childhood and young adult lipid samples were analyzed by this same laboratory. Low density lipoprotein (LDL) cholesterol was calculated using the equation LDL cholesterol = Total cholesterol − HDL cholesterol − Triglycerides/5.

Plasma homocysteine levels were measured at the Oregon Regional Primate Research Center by high pressure liquid chromatography and electrochemical detection (10).

Electron beam computed tomography. Studies were performed with an Imatron C-150 ultrafast computed tomographic scanner (Imatron). Each subject was positioned supine, head first, into the scanner aperture with no couch angulation. Data acquisition was triggered to a constant phase of the cardiac cycle during held inspiration while a standard eight-level localization scan was performed. Patient centering was verified, and the image showing the left main coronary artery or the first image showing either the left anterior descending or circumflex coronary artery was selected as the reference level. The subject was repositioned so that images would be taken beginning at a point 2 cm above the reference level. Coronary visualization was achieved without contrast medium by using the high resolution volume mode of the scanner in conjunction with a 100-ms scan time, 3-mm slice thickness and electrocardiographic triggering (to 80% of the RR interval) during held inspiration. Twenty contiguous 3-mm slices, cephalad to caudad, were obtained. An additional 20 contiguous slices were obtained, using the same technique, caudad to the last slice of the previous scan to examine the most distal regions of the coronary circulation. Thus, 40 contiguous slices were available for each subject. Total radiation dose to the skin was estimated to be 10 mGy (1.0 rad).

All scans were read at the central reading station jointly by two investigators (W.S. and B.H.T.). To determine the presence and quantity of coronary calcium, each of the 40 contiguous slices was evaluated sequentially. Scans were taken using a 30-cm^2 field of view and a 512 by 512 reconstruction matrix so that the area represented by 1 pixel was equal to 0.343 mm^2. All pixels with a density ≥130 Hounsfield units (HU) were displayed, and a region of interest manually encircled around each visible lesion, which was then confirmed to be within a coronary artery. Image-processing software computed the area of all pixels ≥130 HU within the region of interest. The threshold for a calcified lesion for this study was set at a tomographic density of 130 HU having an area ≥1.03 mm^2 (three or more contiguous pixels). Calcified lesions were

considered focal if 1 mm of tissue separated the calcium deposits. Calcific deposits closer than 1 mm were considered a single lesion.

Both readers of the ultrafast computed tomographic scans were unaware of the subject's coronary risk factor levels. Subjects with lesions that exceeded the threshold for coronary artery calcium were considered to have evidence of the atherosclerotic process present in their coronary arteries. For the analyses reported here, only the presence or absence of coronary artery calcification was evaluated. Calcium quantification data were not used because the lesions in this young age group were small.

Statistical analyses. The main objective of the present study was to characterize the association between childhood and young adult measures of body size, blood pressure and lipids and coronary artery calcification in the fourth decade of life. The dependent variable for the analyses was the presence (at least three contiguous pixels ≥130 HU) or the absence of coronary artery calcification as measured by ultrafast computed tomography. The independent variables were the coronary risk factors measured during childhood and young adult life. For each independent variable from the childhood, young adult and most recent examinations, age-, gender- and survey-specific Z scores were determined for each subject. Distributional assumptions were tested, and variables that were not normally distributed (triceps skinfold thickness; triglyceride, apolipoprotein A1 and B, lipoprotein(a) and homocysteine levels; total cholesterol/HDL cholesterol ratio) were transformed to near normality by taking the natural logarithm.

Mean Z scores for subjects with versus those without coronary artery calcification were compared by gender at each examination. The two-sample *t* test and the Wilcoxon rank sum test were used to analyze both the untransformed and transformed risk factors. The mean values of the measured risk factors, along with results from the parametric analysis of untransformed Z scores, are reported. Analytic results were consistent regarding the significance of group differences from both the parametric and nonparametric analyses of untransformed and transformed variables.

Age-adjusted risk odds ratios for coronary artery calcification associated with the upper decile of the risk factor distribution (lowest decile for HDL cholesterol and apolipoprotein A1) relative to the lower (upper) nine deciles were estimated, by gender, using logistic regression analysis. Multiple logistic regression analysis was used to investigate the association between coronary artery calcification and the multiple dichotomized (highest or lowest decile) coronary risk factors. All study participants were combined for these analyses; age and an indicator variable for gender were included in each logistic model. Three separate analyses were conducted, using 1) coronary risk factor measurements from the most recent school survey during childhood, 2) coronary risk factor information from the most recent young adult survey, and 3) coronary risk factor information from the calcium study examination.

A significance level of 0.05 was used for all analyses. Procedures from the Statistical Analysis System (SAS, version 6) were used for data analysis.

Results

Prevalence of coronary artery calcium. In the age group 29 to 37 years, the prevalence of coronary artery calcification was 31% (61 of 197) in men and 10% (18 of 187) in women. This gender difference was highly significant ($p < 0.0001$).

Association between coronary risk factors and coronary artery calcification. Tables 1 and 2 describe the coronary risk factor levels, measured during childhood and twice during young adult life, by coronary artery calcification status for the 197 men and 187 women, respectively. The data reported in Tables 1 and 2 are mean values. Because of the change with age and gender of the variables measured, all the associated hypotheses were tested using age-, gender- and survey-specific Z scores.

In young adult men, mean childhood measures of body habitus (weight, body mass index and triceps skinfold thickness) were significantly higher in those with than without coronary artery calcification (Table 1). In young adult women, no childhood measurements showed a significant mean difference between those with and without coronary artery calcification (Table 2), in part because of the lower prevalence of coronary artery calcification among women in this age group. Mean body habitus and blood pressure measures from the third and fourth decades of life (young adult and most recent measurements) were consistently higher for young adult men and women with than without coronary artery calcification. Apolipoprotein B levels and LDL/HDL cholesterol and total/HDL cholesterol ratios were also consistently higher in young adult men and women with coronary than without coronary artery calcification. Apolipoprotein A1 and HDL cholesterol levels were significantly lower in women with than without coronary artery calcification.

Table 3 presents the risk odds ratios for coronary artery calcification associated with the upper decile of the risk factor distribution (lower decile for HDL cholesterol and apolipoprotein A1) relative to the lower (upper) nine deciles. Upper decile values for body habitus and blood pressure measures from the third and fourth decades of life are associated with increased odds of coronary artery calcification, as are upper decile LDL cholesterol levels in men, lower decile HDL cholesterol levels in men and women and several other lipid variables. Self-reported current smoking and regular alcohol use were not associated with the presence of coronary artery calcification in men or women in this age group.

Table 4 presents the risk of coronary artery calcification from stepwise multiple logistic regression analysis of dichotomized age-, gender- and survey-standardized coronary risk factors. Each logistic model included age and a gender indicator variable. Analysis of childhood coronary risk factor information identified only high body weight as a significant predictor of coronary artery calcification in young adults. The odds of coronary artery calcification were 3.0 times higher for

Table 1. Serial Measurements (mean ± SD) During Childhood and Two Young Adult Examinations in 61 Male Subjects With and 136 Without Coronary Artery Calcification

	Childhood (8–18 yr old)		Young Adult (20–34 yr old)		Most Recent (29–37 yr old)	
	CAC Absent	CAC Present	CAC Absent	CAC Present	CAC Absent	CAC Present
Height (cm)	171.4 ± 10.2	170.8 ± 10.5	178.3 ± 6.5	178.3 ± 7.0	178.8 ± 6.5	178.5 ± 7.2
Weight (kg)	63.8 ± 12.3	67.7 ± 13.8*	79.6 ± 11.6	90.5 ± 15.8†	83.8 ± 13.0	95.8 ± 16.9†
BMI (kg/m^2)	21.6 ± 3.0	23.0 ± 3.2*	25.0 ± 3.4	28.4 ± 4.6†	26.2 ± 3.8	30.1 ± 4.9†
Waist/hip ratio			0.87 ± 0.1	0.90 ± 0.1‡	0.88 ± 0.1	0.93 ± 0.1†
TSF (mm)	7.6 ± 4.8	9.6 ± 4.8*	11.8 ± 6.4	14.4 ± 7.4‡	16.7 ± 6.9	20.3 ± 7.7‡
Systolic BP (mm Hg)	121.2 ± 11.6	121.0 ± 12.5	117.4 ± 12.0	123.0 ± 14.3*	116.9 ± 10.3	122.7 ± 13.0*
Diastolic BP (mm Hg)	77.1 ± 9.0	76.2 ± 9.3	70.7 ± 11.1	78.4 ± 10.2†	76.5 ± 8.6	82.0 ± 9.2†
Total chol (mg/dl)	146.6 ± 21.7	155.2 ± 32.5	173.2 ± 29.4	190.6 ± 43.8‡	185.2 ± 32.3	195.8 ± 39.1
Triglyderides (mg/dl)	77.9 ± 40.3	82.8 ± 35.2	98.0 ± 61.4	107.4 ± 59.7	125.8 ± 76.1	148.1 ± 92.4
HDL (mg/dl)			44.9 ± 11.6	42.2 ± 10.6	44.2 ± 11.3	41.3 ± 10.8
LDL (mg/dl)			108.6 ± 25.7	123.7 ± 35.1‡	115.9 ± 28.6	123.6 ± 36.5
LDL/HDL ratio			2.5 ± 0.8	3.1 ± 1.2*	2.7 ± 0.9	3.1 ± 1.2‡
Total chol/HDL ratio			4.1 ± 1.2	5.0 ± 2.6*	4.4 ± 1.3	5.2 ± 2.0‡
Apo A1 (mg/dl)					108.3 ± 17.3	103.2 ± 16.3
Apo B (mg/dl)					79.5 ± 30.0	91.7 ± 39.6‡
Lipoprotein(a) (mg/dl)					14.4 ± 18.7	13.5 ± 19.1
Homocysteine (nmol/ml)					9.0 ± 3.8	9.4 ± 3.4

p values reflect analyses of age-standardized data: *p < 0.01; †p < 0.001; ‡p < 0.05. Apo = apolipoprotein; BMI = body mass index; BP = blood pressure; CAC = coronary artery calcification; chol = cholesterol; HDL = high density lipoprotein; LDL = low density lipoprotein; TSF = triceps skinfold thickness.

young adults who were in the upper decile of age-, gender- and survey-specific weight than those in the lower nine deciles ($p < 0.01$). The model resulting from the analysis of the young adult coronary risk factor information included diastolic blood pressure (odds ratio [OR] 4.2, $p < 0.001$), body mass index (OR 5.3, $p < 0.0005$) and total/HDL cholesterol ratio (OR 4.3, $p < 0.005$). Finally, the model resulting from the analysis of the most recent coronary risk factor information included systolic blood pressure (OR 6.5, $p < 0.0001$), body mass index (OR 6.1, $p < 0.001$), LDL cholesterol level (OR 3.1, $p < 0.025$) and HDL cholesterol level (OR 5.5, $p < 0.001$).

Measures of body size were significantly associated with the presence of coronary artery calcification. To examine the additive effects of blood pressure on this association, subjects were divided into gender-specific tertiles of distribution for body mass index and systolic blood pressure. Figure 1 shows

Table 2. Serial Measurements (mean ± SD) During Childhood and Two Young Adult Examinations in 18 Female Subjects With and 169 Without Coronary Artery Calcification

	Childhood (8–18 yr old)		Young Adult (20–34 yr old)		Most Recent (29–37 yr old)	
	CAC Absent	CAC Present	CAC Absent	CAC Present	CAC Absent	CAC Present
Height (cm)	161.2 ± 7.4	160.5 ± 7.9	164.3 ± 6.1	166.4 ± 5.3	164.7 ± 6.1	166.3 ± 5.3
Weight (kg)	55.6 ± 9.3	58.3 ± 16.0	65.3 ± 12.8	83.0 ± 14.8*	70.3 ± 14.4	91.8 ± 18.0*
BMI (kg/m^2)	21.3 ± 3.1	22.4 ± 5.1	24.2 ± 4.7	29.9 ± 5.2*	25.9 ± 5.2	33.1 ± 6.2*
Waist/hip ratio			0.73 ± 0.1	0.80 ± 0.1	0.75 ± 0.1	0.79 ± 0.1†
TSF (mm)	13.6 ± 5.7	14.2 ± 4.5	20.8 ± 7.8	29.0 ± 8.2*	27.3 ± 9.2	35.1 ± 6.4*
Systolic BP (mm Hg)	113.7 ± 11.7	116.1 ± 11.9	109.8 ± 9.9	120.3 ± 10.6*	111.9 ± 11.9	125.8 ± 20.7†
Diastolic BP (mm Hg)	75.5 ± 8.3	76.8 ± 8.5	67.6 ± 8.2	74.3 ± 11.2‡	69.6 ± 10.2	78.5 ± 14.8†
Total chol (mg/dl)	159.5 ± 23.9	159.1 ± 42.1	173.0 ± 29.1	179.9 ± 38.0	180.1 ± 34.5	182.1 ± 33.8
Triglycerides (mg/dl)	76.3 ± 35.0	79.8 ± 39.0	92.8 ± 55.5	139.4 ± 74.8†	109.8 ± 85.2	146.0 ± 70.8
HDL (mg/dl)			50.2 ± 12.7	42.1 ± 12.3†	52.3 ± 15.2	40.5 ± 13.5‡
LDL (mg/dl)			104.7 ± 28.6	109.4 ± 37.7	106.6 ± 30.9	112.4 ± 30.7
LDL/HDL ratio			2.3 ± 0.9	2.9 ± 1.6	2.3 ± 1.1	3.1 ± 1.3‡
Total chol/HDL ratio			3.7 ± 1.1	4.7 ± 2.0†	3.8 ± 1.5	5.0 ± 1.7*
Apo A1 (mg/dl)					132.6 ± 27.0	111.7 ± 24.2‡
Apo B (mg/dl)					57.6 ± 23.0	68.0 ± 22.3†
Lipoprotein(a) (mg/dl)					14.3 ± 17.9	20.6 ± 27.8
Homocysteine (nmol/ml)					8.2 ± 3.7	9.5 ± 6.7

p values reflect analyses of age-standardized data: *p < 0.001; †p < 0.05; ‡p < 0.01. Abbreviations as in Table 1.

Table 3. Odds Ratios for Presence of Coronary Artery Calcification Using Measured Variables From Childhood, Young Adult and Most Recent Examinations

	Childhood (8–18 yr old)		Young Adult (20–34 yr old)		Most Recent (29–37 yr old)	
	Male	Female	Male	Female	Male	Female
Weight	2.9‡	2.1	4.9*	13.6†	8.7†	19.6†
BMI	1.7	2.1	6.5†	4.7‡	6.4†	13.6†
Waist/hip ratio					2.9‡	2.1
TSF	1.5	0.8	2.9‡	6.8*	1.5	3.2
Systolic BP	1.3	0.5	4.4*	4.2‡	6.4†	6.4*
Diastolic BP	1.0	1.2	3.4‡	4.5‡	4.2‡	3.2
Total chol	2.3	2.1	2.7‡	2.0	2.9‡	1.2
Triglycerides	0.8	1.2	1.8	4.7‡	1.4	2.1
HDL			2.7	8.9†	4.3*	4.7‡
LDL			3.7*	1.2	2.1	2.0
LDL/HDL ratio			3.4‡	3.4	3.6‡	3.1
Total chol/HDL ratio			6.4†	3.8‡	4.8*	3.2
Apo A1					2.6	5.0*
Apo B					1.3	2.0
Lipoprotein(a)					0.9	1.1
Homocysteine					1.3	1.2

*$p < 0.01$; †$p < 0.001$; ‡$p < 0.05$. Abbreviations as in Table 1.

the percent of men with coronary artery calcification in each combination of body mass index and systolic blood pressure tertiles. Within each blood pressure tertile there was a pattern of increase in the percent of subjects with coronary artery calcification with an increase in the body mass index tertile. There was also a general pattern of increase with systolic blood pressure, although it was not as consistent within each body mass index tertile. Thus, 62% of men and 30% of women (data not shown) who were in the upper tertile for both body mass index and systolic blood pressure, compared with only 10% of men and 0% of women in the lower tertile for both variables, had coronary artery calcium.

Table 4. Risk of Coronary Artery Calcification From Stepwise Multiple Logistic Regression Analysis of Coronary Risk Factors*

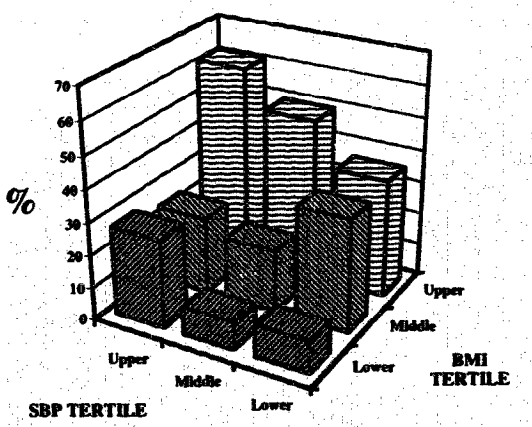
	Odds Ratio (95% CI)
Childhood	
Weight	3.0 (1.3–6.7)
Young adult	
DBP	4.2 (1.9–9.6)
BMI	5.3 (2.2–13.0)
Total chol/HDL ratio	4.3 (1.7–10.7)
Most recent	
SBP	6.5 (2.6–16.5)
BMI	6.1 (2.4–15.1)
LDL	3.1 (1.3–7.6)
HDL	5.5 (2.0–15.2)

*Adjusted for age group and gender; highest decile (lowest for high density lipoprotein [HDL]) versus other nine deciles. CI = confidence interval; other abbreviations as in Table 1.

Discussion

Prevalence and significance of coronary artery calcification. In the present study, the prevalence of coronary artery calcification detected by ultrafast computed tomography in the age group 29 to 37 years was 21% (30% in men, 10% in women). Using similar criteria for defining calcification Agatston et al. (11) studied 113 patients, ages 30 to 39 years, undergoing screening for coronary disease and found that 25% without and 100% with coronary disease had detectable cal-

Figure 1. Three-dimensional plot with percent of men with coronary artery calcification on the Y axis, tertile of systolic blood pressure (SBP) on the X axis and tertile of body mass index (BMI) on the Z axis. Sixty-two percent of men in the upper tertiles for both variables had coronary artery calcification versus only 10% in the lowest tertiles for both.



cium by electron beam computed tomography. Janowitz et al. (12), using only two adjacent pixels rather than our criterion of three, noted a prevalence of 21% in men and 11% in women 30 to 39 years old. No coronary risk factor data were provided in these studies for comparison. In a study of 215 consecutive necropsy studies of black and white male and female subjects, 30 to 39 years old, 15% to 25% of those who died as a result of natural causes or accidental death had radiographic evidence of coronary artery calcification, whereas 75% of those who died of atherosclerotic disease had radiographic evidence of coronary artery calcification (13).

Most studies investigating coronary artery calcification have documented a greater prevalence with increasing age and a greater prevalence in men than women in every age group (6,14–19). Differences in prevalence between men and women are most marked in the younger age groups, and this difference decreases with increasing age; these findings parallel the clinical incidence of coronary artery disease in women before and after menopause (12).

Calcium deposition usually indicates formation of complex plaques, but to our knowledge, no clinical studies have examined the interval between the formation of plaque and the deposition of calcium in the coronary arteries (20). Microcrystalline calcium in the lipid core has been detected in coronary arteries at autopsy in subjects as young as 23 years old (21).

Blankenhorn (2) established the relation between coronary calcification and atherosclerotic plaque in 3,500 arterial segments taken from 89 randomly selected postmortem heart specimens. He found no radiopaque lesions without concomitant atherosclerosis. Eggen et al. (13) noted a proportional increase in prevalence of advanced coronary lesions with the amount of coronary artery intimal surface area involved with calcium. When calcification exceeded 10% of the surface for any branch of the coronary arteries in the age group 30 to 39 years, the prevalence of ischemic myocardial lesions was 3.9 times greater, and that for stenotic lesions was 5 times greater. In fact, these investigators noted that the value of information concerning calcified coronary plaques in the differential diagnosis of clinically significant coronary artery disease was greatest in the fourth decade of life compared with that in the fifth, sixth and seventh decades.

Margolis et al. (14) followed 800 subjects over a 5-year period after they had undergone angiography and fluoroscopy and reported that 40% of the 250 subjects with coronary artery calcification had died compared with only 10% of the 550 without coronary artery calcification. They concluded that the prognostic significance of coronary artery calcification appeared to be independent of information obtained by cardiac catheterization and angiography.

Detection of coronary artery calcification. The presence of calcified deposits, detected in vivo, accurately predicts the presence of atherosclerotic plaque, and coronary calcific deposits occur almost exclusively when coronary atherosclerosis is present (5). The detection of coronary artery calcification with fluoroscopy has been shown to be of value in predicting not only the presence of obstructive coronary artery disease (22), but also future coronary events (14,23).

Computed tomography has a high level of sensitivity in detecting calcium, and the thin section scans can show added anatomic detail as well as better definition of the location and extent of any calcification (7,11). During conventional computed tomographic scanning, the heart and coronary arteries move, thus blurring and obscuring the presence of calcified deposits. Electron beam computed tomography has a 100-ms scan time and pixel resolution of 0.5 mm^2. The speed is sufficient to minimize cardiac motion, and pixel sizes are such that small deposits of calcium can be readily detected. Electron beam computed tomography has been shown to be an effective, noninvasive method to detect and localize the presence of anatomic coronary artery disease and to quantify the amount of calcium in coronary arteries; conversely, the absence of coronary artery calcification is highly specific for the absence of obstructive disease (4,11,12,16,24).

Coronary risk factors and coronary artery calcification. In the study reported herein, childhood weight, body mass index and triglyceride levels in men were significantly related to coronary artery calcification detected 15 to 20 years later in young adults. To our knowledge, these are the first data to link childhood coronary risk factors to evidence of advanced atherosclerosis in asymptomatic adults. In the Bogalusa Heart Study (25,26), postmortem identification of coronary artery fatty streaks in persons 6 to 30 years old was significantly correlated with serum triglyceride, very low density lipoprotein (VLDL) cholesterol and systolic and diastolic blood pressure levels and ponderal index (a measure of obesity). In a postmortem study of men 15 to 34 years old, the percent of intimal surface involved with atherosclerotic lesions in the right coronary artery was positively correlated with age, smoking and a combination of LDL and VLDL cholesterol levels and negatively associated with HDL cholesterol levels (27).

Our study shows that coronary risk factors measured in men and women during their third and fourth decades of life are significantly associated with the presence of coronary artery calcification that is detected by electron beam computed tomography. Measures of obesity (i.e., weight, body mass index and triceps skinfold thickness), blood pressure and decreased HDL cholesterol levels were consistently the most strongly associated risk factors in both men and women in our study. In addition, increased apolipoprotein B levels in both men and women and decreased apolipoprotein A1 levels in women measured during the most recent examination were associated with coronary artery calcification.

Lipoprotein(a) has been shown to be an independent risk factor for coronary heart disease in middle-aged, hyperlipidemic white men (28), although it may not be a risk factor in white men with normal lipid levels (29). To our knowledge, no prospective studies of other racial groups or women have been published. In our study, lipoprotein(a) was not associated with increased risk for coronary artery calcification in male or female young adults.

In a study of 675 men and 190 women, 22 to 85 years old,

Wong et al. (7) examined the association between the presence and extent of coronary artery calcification and self-reported coronary risk factor data. They demonstrated a significantly greater prevalence of coronary artery calcification in both men and women with a history of hypertension and hypercholesterolemia as well as in men with a history of diabetes, previous smoking, infrequent exercise and obesity than in those without these risk factors. There was a significant continuous graded relation between the prevalence and amount of calcium and the number of reported risk factors present in asymptomatic men and women. Our data did not show an association between smoking or alcohol use and the presence of coronary artery calcification.

Recently, a number of studies have shown that plasma concentration of homocysteine, an amino acid that results from the demethylation of methionine, is higher in patients with cerebrovascular, peripheral arterial and coronary heart disease than in control subjects (10,30–32). However, in our study, no significant difference was seen in this newly recognized risk factor in subjects with and without coronary artery calcification. This finding may in part relate to the lower mean age of our study participants than those in the cited studies. Additionally, it has been suggested that hypercoagulability as a result of increased production of both fibrinogen and thrombin may be one mechanism by which increased homocysteine levels increase coronary risk (33). Although a vascular plaque may provide a focus for subsequent thrombus formation, there would appear to be no identifiable relation between a higher homocysteine level and early calcific plaque formation in our young adult subjects.

Limitations of the study. Several studies have examined the sensitivity, specificity and predictive value of coronary artery calcification for clinically significant coronary artery disease identified by coronary angiography (5,11,15,16,34). The negative predictive value is highest in younger age groups and decreases with excessively high calcium scores and increasing age (11,16). Sensitivity is fairly high (85%) in subjects <50 years old (34), but because the presence of calcification dramatically increases as age exceeds 50 years, the sensitivity approaches 100% but the specificity becomes low (28%) (11). Sensitivity is lowest in subjects with only single-vessel disease and increases with involvement of two or more vessels, especially if the calcium score is elevated (15,35). Although specificity is low in younger adults, it is highest for excluding disease in those with multiple rather than a single coronary artery involved (15). The low specificity may result from the partial volume effect for identifying calcified pixels, especially if the lesions are small. However, it may also be related to the ability to detect atherosclerotic disease when there is minimal or no lumen narrowing on angiography.

In the present study, the presence of coronary artery calcification was used as an indicator of the ongoing atherosclerotic process. However, in the age group that we studied, it is likely that there are subjects with advancing atherosclerotic coronary artery disease but have not yet developed calcium deposits. Thus, our estimate of the prevalence of atherosclerosis is most likely underestimated. Similarly, the impact of coronary risk factors measured during childhood or young adult age may also be underestimated. Continued follow-up of this cohort will provide additional information on the impact of childhood and young adult coronary risk factors on the progression of coronary atherosclerosis and development of clinically significant coronary artery disease.

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