Heart disease risk factors in midlife predict subclinical coronary atherosclerosis more than 25 years later in survivors without clinical heart disease: The Rancho Bernardo Study

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Abstract

Objective—To determine which of the classic modifiable coronary heart disease (CHD) risk factors, measured in midlife, are associated with subclinical coronary atherosclerosis in older age.

Design—Prospective study

Setting—Community based

Participants—Participants were 400 community-dwelling middle-aged adults who had no history of CHD at baseline (1972–4) when CHD risk factors were measured, and who were still free of known CHD in 2000–2002.

Measurements—Coronary artery plaque burden was assessed by coronary artery calcium (CAC) score using computed tomography in 2000–2002.

Results—Ordinal logistic regression analysis was used to compare baseline risk factors with severity of CAC. Mean age was 42 years at baseline and 69 years at the time of CAC assessment; 46.5% were male. In analyses adjusted for age, sex, and all other risk factors, one standard deviation increase in body mass index [OR 1.24 (CI 95% 1.02–1.51) P = 0.03], cholesterol [OR 1.28 (CI 95% 1.03–1.58) P = 0.02], pulse pressure [OR 1.24 (CI 95% 1.03–1.50) P = 0.03], and log triglycerides [OR1.22 (CI 95% 0.99–1.50 P = 0.06] each independently predicted the presence and severity of coronary artery atherosclerosis.

Conclusions—Plaque burden in elderly survivors without clinical heart disease is influenced by modifiable risk factors measured more than 25 years earlier.

Keywords

coronary artery calcium; midlife risk factors

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Conflicts of Interest: None declared.

Introduction

Coronary artery atherosclerosis is a chronic disease that typically progresses for decades without symptoms. Autopsy studies have demonstrated early coronary artery lesions in adolescents in association with cigarette smoking and high cholesterol levels (1). In the Bogalusa Heart Study increasing numbers of heart disease risk factors in youth were associated with increasing severity of asymptomatic coronary atherosclerosis (2). In the Muscatine Study (3) heart disease risk factors measured in childhood were associated with quantitative increments of subclinical coronary atherosclerosis assessed by coronary artery calcium (CAC) years later.

Age is the strongest predictor of cardiovascular disease in adult men and women (4). Cohort studies (5;6) show that high levels of potentially modifiable heart disease risk factors measured in midlife still predict an increased risk of clinical coronary heart disease (CHD) in old age. In the Framingham Heart Study, for example, hypertension in middle age contributed consistently to future cardiovascular events (5).

Subclinical plaque burden measured using electron-beam computed tomography (CT) to quantify CAC has been shown to correlate well with coronary artery plaque burden and to predict cardiovascular events (7–9). However, the effect of midlife risk factors on CAC development later in life and the main risk factors involved have not been sufficiently evaluated (8).

The purpose of this paper was to determine which of the classic potentially modifiable CHD risk factors, measured in midlife, are associated with moderate or advanced subclinical coronary atherosclerosis two to three decades later in men and women without symptomatic heart disease.

Methods

Between 1972 and 1974, 82% of community-dwelling adult residents of Rancho Bernardo, a southern California community, enrolled in a Lipid Research Clinic Prevalence Study of heart disease risk factors. Most participants were aged 30 to 79 years, white, middle or upper-middle class, and had at least a high school education. The baseline evaluation included a brief medical history, a cigarette smoking questionnaire, and measurement of height, weight, blood pressure, fasting plasma glucose, cholesterol, and triglyceride levels. HDL cholesterol and waist girth were not measured in 1972–4.

Using a standard protocol, systolic and diastolic blood pressure were measured in seated, rested subjects. Height and weight were measured with participants wearing light clothing and no shoes. Morning blood samples were obtained. Fasting plasma cholesterol and triglycerides were measured in a Center for Disease Control-certified Lipid Research Clinic Laboratory, using an Auto Analyzer I (Technicon Instruments, Tarrytown, New York). Fasting plasma glucose was measured by a hexokinase method in a clinical laboratory. Body mass index (BMI) (kg/m2) was calculated as an estimate of obesity. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure.

Surviving members of this cohort study, renamed the Rancho Bernardo Study, have been followed periodically to the present. Between 1997 and 1999 approximately 70% of surviving local, community-dwelling, ambulatory members of the cohort attended a follow-up clinic visit when a new cardiovascular disease and medication history were obtained. Between 2000 and 2002, 422 participants who had attended the 1997–1999 clinic visits, and who had no history of myocardial infarction, angina pectoris, or coronary artery revascularization, were invited for coronary artery scan with an Imatron C-150 ultrafast electron-beam CT scanner (GE

Imatron, San Francisco, California). For this analysis we included the 400 participants with both CAC and all risk factor measurements done in 1972–1974. Heart images were obtained with 100-ms scan time using 3-mm slices starting at the level of the carina and proceeding to the level of the diaphragm, approximately 40 to 45 "slices" were obtained. Tomographic imaging was electrocardiographically triggered at 40% or 65% of the RR interval, depending on the participant's heart rate. The Agatston method (10) was used to quantify a total CAC score defined as the product of the area of calcification per coronary tomography segment and a factor rated 1 though 4 depending on the maximal calcium x-ray density in that segment. The reported inter-scan variability of the Agatston method is 15% or less (11), however, the volumetric scores have somewhat better inter-scan variability (less than 10%) (12;13).

Statistical Analysis

CAC scores were categorized according to the Rumberger criteria, which define a calcium score of 0 to 10 Hounsfield units (HU) as little/none, 11 to 100 HU as mild, 101 to 399 HU as moderate, and greater than 400 HU as severe (14). In univariate analyses, CHD risk factors were compared by CAC score category using analysis of variance for continuous variables and chi-squared analysis for categorical variables. Values for systolic and diastolic blood pressure, triglycerides, and fasting plasma glucose were skewed and therefore log-transformed for analysis.

The association of midlife classical heart disease risk factors with the CAC scores measured 26 to 30 years later was analyzed using ordinal logistic regression with little or no CAC (0–10 HU) as the reference category. Sex-specific standardized values of BMI, pulse pressure, cholesterol, and log-transformed triglycerides were included in age- and sex- adjusted ordinal logistic models. All analyses were performed using SAS (version 9.1, SAS Institute, Inc., Cary, NC).

Results

Participants were 27 to 60 years old (mean age 41.8 yrs) at baseline, and 55 to 88 years (mean age 69.4 yrs) at the CT scan visit; 46.5% were male. Thirty-five percent (n =141) had little or no CAC (CAC score 0–10 HU), 21% (n = 83) had mild CAC (score 11–100 HU), 22% (n = 86) had moderate CAC (score 101–399 HU), and nearly 23% (n = 90) had severe CAC (score ≥400 HU). The odds of increasingly severe future CAC scores were 5.43-fold (3.63–8.12) greater for men than for women, and 2.51-fold (1.90–3.32) greater for each 10-year increase in age greater than 40 years.

Age- and sex-adjusted levels of baseline risk factors by CAC scores are shown in Table 1. Those with more severe CAC were more likely to be male (P <0.001), to be older (P <0.001), and to have higher baseline BMI (P = 0.007), cholesterol (P = 0.002), and triglyceride levels (P <0.001). Systolic and diastolic blood pressure and fasting plasma glucose did not differ significantly by CAC (P = 0.14 and 0.51).

To evaluate the independent effect of each risk factor on severe CAC, age, sex, BMI, cholesterol, triglycerides, and pulse pressure were included in multivariate adjusted logistic regression models, such that all risk factors in the model are adjusted for each other. Figure 1 shows the multiply adjusted odds of increasingly severe CAC calculated for the sex-specific standard deviation of the four independent risk factors. As shown, the odds of increasingly severe future CAC scores were similar for each risk factor: 1.28 (1.03; 1.58) times higher for a standard deviation increase in cholesterol, 1.24 (1.02; 1.51) for a standard deviation increase in BMI, 1.24 (1.03; 1.50) for a standard deviation increase in pulse pressure, and 1.22 (0.99; 1.50) for a standard deviation increase in log triglycerides. None of these associations differed significantly by sex (P = 0.74, P = 0.45, P = 0.27, P = 0.37, respectively). Baseline fasting

plasma glucose and tobacco smoking were not associated with increased risk of higher CAC scores in this model and did not alter results when included in the complete model. Although increasing pulse pressure was associated with significantly higher CAC scores, in separate age and BMI-adjusted models, neither systolic nor diastolic blood pressure were independently predictive of CAC (data not shown).

Discussion

In this community-dwelling cohort of middle-aged Caucasians who were free of known CHD, age and male sex were, as expected, the strongest predictors of plaque burden 26–30 years later. Independent of age, sex, and each of the other risk factors, there remained a 22 to 28% increased odds of more severe coronary artery plaque burden with each standard deviation increase in plasma cholesterol, body mass index, pulse pressure, and log triglycerides.

Childhood or young adult CHD risk factors have been shown to predict subclinical atherosclerosis in middle age. For example, in a study of 2229 Finns, the presence of cardiovascular risk factors [smoking, low density lipoprotein (LDL), BMI and systolic blood pressure] during adolescence predicted adult carotid intima-media thickness (15). In both the Bogalusa Heart Study and the Muscatine Study, the presence of early-onset obesity was associated with carotid atherosclerosis (16) or CAC (16;17) in young adults. Clearly exposure to risk factors in childhood or youth promotes atherosclerosis in younger adults. Less attention has been paid to the role of midlife heart disease risk factors and subclinical CHD in older adults. To our knowledge, this is the first report highlighting the association between midlife heart disease risk factors and subclinical coronary calcium assessed decades later in survivors who remained free of clinical heart disease.

The CARDIA study analyzed the role of risk factors in young adults aged 18 to 30 for CAC 15 years later; in that study higher levels of total cholesterol, fasting blood glucose, and systolic blood pressure predicted future CAC (18). The magnitude of the associations with risk factors was comparable to the present longer study of older adults. Unlike Rancho Bernardo, however, the CARDIA cohort did not show an independent association between BMI and CAC. Systolic blood pressure was a strong predictor of CAC in CARDIA, while in Rancho Bernardo only pulse pressure predicted CAC. It is likely that these differences reflect the younger age or shorter duration of follow up in CARDIA. Also reflecting the age differences, only 9.6% of the CARDIA population had detectable CAC at baseline versus 64% in the Rancho Bernardo Study cohort. Unlike CARDIA, fasting blood glucose was not a predictor of CAC in the Rancho Bernardo Study. This difference is compatible with the observation that post-challenge glucose is a stronger predictor of clinical cardiovascular disease than fasting hyperglycemia in older adults (19). In the Muscatine study, diastolic blood pressure, BMI, and the ratio of total cholesterol to HDL cholesterol measured in youth predicted CAC measured in young adults (ages 20–34 years) independent of other risk factors (20).

Pulse pressure, which also represents arterial stiffness, was the only blood pressure parameter that independently predicted CAC in the Rancho Bernardo cohort. The association of pulse pressure but not systolic or diastolic blood pressure with CAC is compatible with the observation that pulse pressure is the better predictor of cardiovascular disease mainly in older adults (21).

The associations of midlife modifiable risk factors with the severity of CAC in old age reported here support the current emphasis on long-term risk as well as short-term risk for CHD. Recent calculations show that a 50-year-old man with a 7% 10-year risk for "hard" CHD events actually has an average lifetime CHD risk of nearly 70%, and his median survival is more than 11 years shorter than the calculated survival for a man of the same age with optimal risk factors

(22). Another group calculated that asymptomatic seniors aged 70 years and older with very low CAC scores (<10 HU) would have a reduced cardiovascular risk comparable to that of individuals 10 years younger (23). A recent study of CAC and all-cause mortality in 3570 elderly people (>70 years) found that CAC continues to discriminate risk mortality in old age (24).

In summary, midlife CHD risk factors predict subclinical CHD in old age, and suggest that treatment risk factors in midlife are likely to improve prognosis even in asymptomatic older adults.

Acknowledgments

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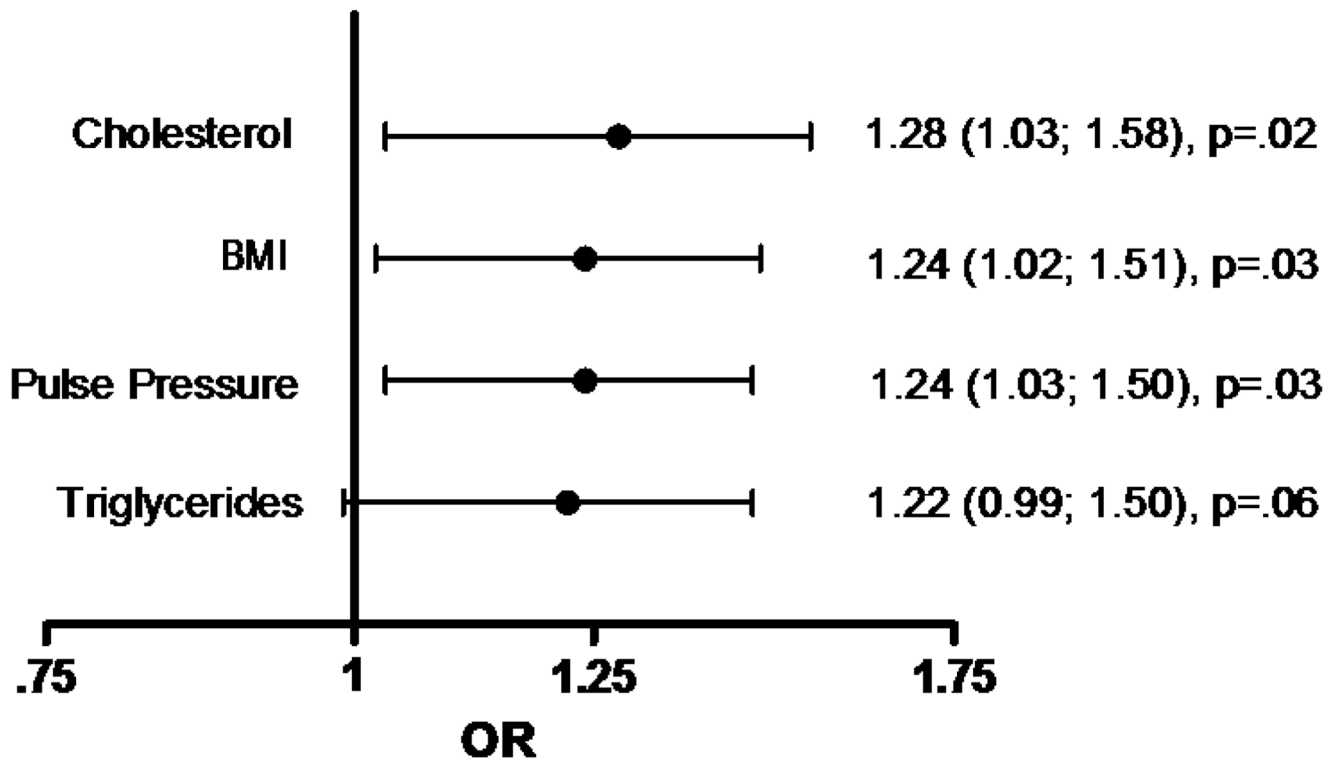
Figure 1.
Multiply adjusted (additionally adjusted for age and sex) odds ratios [OR (95% C.I.), p-value] of sex-specific standardized classical risk factors[1] and increasingly severe coronary artery calcification.

Table 1

Age- and sex-adjusted baseline characteristics.

CHD Risk Factor (measured in 1972–74)	Coronary Artery Calcium Score Categories (measured in 2000–02)				P
	0–10 HU LITTLE OR NONE (N = 141)	11–100 HU MILD (N = 83)	101–399 HU MODERATE (N = 86)	≥400 HU SEVERE (N = 90)	
Male sex (%) [1]	24.1 (16.2; 32.1)	40.9 (31.1; 50.8)	56.7 (47.0; 66.4)	76.9 (67.0; 86.8)	<0.001
Age (years) [2]	38.1 (36.9; 39.3)	41.9 (40.4; 43.4)	43.2 (41.8; 44.6)	46.0 (44.6; 47.5)	<0.001
Body mass index (kg/m^2) [2]	23.0 (22.5; 23.4)	23.7 (23.2; 24.3)	23.8 (23.2; 24.3)	24.3 (23.8; 24.9)	0.007
Systolic blood pressure (mm Hg) [3]	112.2 (109.9; 114.4)	113.3 (111.1; 116.7)	115.6 (113.3; 117.9)	116.7 (113.3; 119.1)	0.146
Diastolic blood pressure(mm Hg) [3]	73.0 (71.5; 75.2)	73.0 (70.8; 75.2)	75.2 (73.0; 77.5)	74.4 (71.5; 76.7)	0.518
Pulse pressure (mm Hg) [2]	39.6 (37.8; 41.3)	40.1 (37.9; 42.2)	40.5 (38.4; 42.6)	43.1 (40.9; 45.4)	0.115
Total cholesterol (mg/dL) [2]	182.9 (177.2; 188.5)	194.2 (187.4; 200.9)	194.4 (187.7; 201.0)	201.3 (194.3; 208.3)	0.002
Triglycerides (mg/dL) [3]	79.0 (73.0; 85.6)	86.5 (78.3; 94.6)	102.5 (92.8; 112.2)	99.5 (90.0; 109.9)	<0.001
Fasting glucose (mg/dL) [3,4]	97.5 (94.6; 99.5)	97.5 (94.6; 101.5)	101.5 (97.5; 104.6)	103.5 (99.5; 106.7)	0.077
Smoking history [1]	49.5 (40.5; 58.6)	54.2 (43.4; 65.0)	56.4 (47.1; 69.8)	58.7 (47.4; 70.1)	0.693

[1] proportions are reported; p-values represent Wald chi-square tests for differences

[2] means (95% confidence interval) reported; p-values represent F-test for differences

[3] geometric means (95% confidence interval) reported; p-values represent F-test for differences

[4] Fasting plasma glucose available for 369 individuals (N=126,77,83,83)