Association of Hostility With Coronary Artery Calcification in Young Adults
The CARDIA Study

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Context Psychosocial factors, including personality and character traits, may play a role in the development and expression of coronary artery disease.

Objective To evaluate whether hostility, a previously reported predictor of clinical coronary artery disease, is associated with coronary calcification, which is a marker of subclinical atherosclerosis.

Design Prospective cohort study.

Setting and Participants Volunteer subsample from Chicago, Ill, and Oakland, Calif, consisting of 374 white and black men and women, aged 18 to 30 years at baseline, who participated in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Cook-Medley hostility assessment data were collected at baseline from 1985 to 1986 and at year 5 examinations from 1990 to 1992. After the 10-year examinations in the 1995-1996 year, electron-beam computed tomographic scans were performed.

Main Outcome Measures Presence of any detectable coronary artery calcification (coronary calcium score >0), and coronary artery calcium scores of 20 or higher.

Results In logistic regression analysis adjusting for age, sex, race, and field center comparing those with hostility scores above and below the median of the distribution of the present sample, the odds ratio of having any coronary calcification was 2.57 (95% confidence interval, 1.31-5.22), and the odds ratio of having a calcium score of 20 or higher was 9.56 (95% confidence interval, 2.29-65.9) for calcium scores of 20 or higher. The associations with any coronary artery calcification persisted after adjusting for demographic, lifestyle, and physiological variables. Results using a cynical distrust subscale were somewhat weaker than for those using the global hostility score. Power was inadequate to perform sex- or race-specific analyses.

Conclusion These results suggest that a high hostility level may predispose young adults to coronary artery calcification.

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HOSTILITY IS A PERSONALITY and character trait with attitudinal (cynicism and mistrust of others), emotional (anger), and behavioral (overt and repressed aggression) components.[1] In epidemiological studies, hostility has been frequently measured with the Cook-Medley questionnaire, an empirical scale originally designed to characterize mistrustful attitudes.[2]

High hostility level is related to increased risk of angiographically documented coronary atherosclerosis,[3,4] essential hypertension,[5] coronary artery disease (CAD) incidence,[6-11] and all-cause mortality.[8,11] However, 3 studies have reported no relationship between hostility and CAD outcomes.[12-14] It has also been shown that hostility is a predictor of restenosis after coronary angioplasty[15] and of carotid intima media thickness among healthy postmenopausal women[16] and middle-aged men.[17]

Several mechanisms have been proposed to explain why hostility may increase cardiovascular risk, including concomitant unhealthful lifestyle behaviors.[18] For example, Everson et al[11] have shown that the association between cynical distrust and cardiovascular outcomes was explained by simultaneous adjustment for smoking, alcohol consumption, physical activity, and body mass index.

Our objective was to examine the association of hostile attitudes with coronary artery calcification, a marker of subclinical atherosclerosis,[19,20] among a subset of participants in the Coronary

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Artery Risk Development in Young Adults (CARDIA) study and to determine whether the associations of interest were independent of established CAD risk factors. The prevalence of coronary artery calcification in this CARDIA subset was determined using electron-beam computed tomographic (EBCT) scans, previously described.[21]

This is a novel investigation, for 3 reasons: first, the assessment of coronary calcification as an outcome is unique because it is free of biases associated with clinical CAD end points. These biases include physician behavior, patient awareness or denial of symptoms, and the fact that many noncases of CAD have significant but undiagnosed disease that can confound case-control comparisons. Second, our study population allowed us to examine, for the first time, the association between hostility and the natural history of atherosclerosis in its early stage, as opposed to previous investigations that focused on hostility either as a trigger of a clinical event[6,7] or a correlate of advanced atherosclerosis.[16,17] Third, our sample included men and women of both races, whereas previous studies included middle-aged and elderly populations, usually predominantly men.

METHODS

Cohort Description and Selection

CARDIA is a longitudinal investigation of CAD risk factors in a population aged 18 through 30 years at study inception. Details of study design, recruitment, and procedures have been published elsewhere.[22,23] To date, CARDIA has completed 5 examination cycles: a baseline examination during the 1985-1986 study year (n=5115) and follow-up examinations at years 2, 5, 7, and 10 that achieved high retention rates.

For the purpose of this investigation, we used coronary calcium scores obtained in a subsample of participants living in Chicago, Ill, and Oakland, Calif, between May 1996 and January 1997. Data were collected at baseline and at the year 5 examinations (1990-1992). For the EBCT study, we aimed to recruit an equal number of women and men and an equal number of black and white participants. Of 443 participants in the EBCT study, 48 were omitted in the current analysis for missing the measurement of hostility at baseline, year 5, or both. Another 21 were omitted for having 1 or more covariates of interest missing at baseline, year 5, or both, resulting in 374 qualifying subjects.

Educational attainment, smoking, and alcohol consumption were ascertained by self-report. An interviewer administered a follow-up questionnaire to all those who reported ever drinking or smoking. Alcohol consumption was assessed as the average number of drinks (beer, wine, spirits) reported per week, multiplying by the estimated concentration of ethanol, and summing the responses.[24] An interviewer-administered physical activity history was given to each participant.[25] Blood samples were drawn in the morning after an overnight fast using EDTA-containing tubes. The protocols for lipid-level determination,[26-29] blood pressure, weight, and height can be found elsewhere.[21] Body mass index was calculated as weight in kilograms divided by the square of height in meters. Insulin was measured by radioimmunoassay (Linco, St Louis, Mo). Hypertension was defined as blood pressure of 140/90 mm Hg or more or use of antihypertensive medication. Diabetes was defined as 8-hour fasting blood glucose level of 7.0 mmol/L (126 mg/dL) or more or use of antidiabetic medication.

Hostility levels were measured by the Cook-Medley 50-item scale, which uses a true-false format.[2] As an example, items included the following: "I think most people would lie to get ahead," "It is safer to trust nobody," "No one cares much what happens to you," "Most people will use somewhat unfair means to gain profit or an advantage rather than lose it," "I tend to be on my guard with people who are somewhat more friendly than I had expected," and "I have at times had to be rough with people who were rude to me." This questionnaire was self-administered at baseline and again during the year 5 examination. Based on the responses, we computed global hostility scores that ranged from 1 to 41. Cynical distrust scores were based on the 8-item subscale used by Everson et al[11] and ranged from 0 to 8. The institutional review boards of the centers involved approved the study, and all participants gave informed written consent.

EBCT Scanning and Reading Protocol

Imatron C-100 scanners (South San Francisco, Calif) were used to obtain 40 consecutive 3-mm tomographic images from the root of the aorta to the apex of the heart. Images were obtained synchronously with the heart rate, in real time, with breath held, at end diastole (80% of R-R interval), and the scan acquisition time was 100 ms (a 10th of a second). Two scans were performed on each participant at an interval of 1 to 2 minutes. The scan with the highest score was used for analysis. Women were scanned during the 2 weeks following the beginning of their menstrual cycles.

Each image was examined by a radiologic technologist who removed bony structures from the images and identified a region of interest around each potential focus of coronary calcium. A focus was defined as a region of 6 adjacent pixels or more (approximately 2 mm^2) with a computed tomographic number higher than 130 Hounsfield units. Images of lesions of this size have been found to be reproducible.[30,31] The calcium score was calculated for each scan multiplying the area of the focus in square millimeters by a coefficient based on the peak computed tomography number of the focus.[32]

Statistical Analysis

The degree of linear association between hostility and cynical distrust scores was examined using Pearson correlation coefficients. Because the calcium score was skewed to the right, the bivariate associations of the hostility and the cynical distrust scores with the calcium score were examined using Spearman rank-order correlation coefficients. Analysis of variance was applied to estimate sex- and race-specific means of hostility and cynical distrust scores

Table 1. Coronary Artery Calcification by Sex and Race Subgroups, the Coronary Artery Risk Development in Young Adults (CARDIA) Study, 10-Year Examination, 1995-1996

Subgroups	No. of Participants	Log Calcium Score +1, Mean (SD)	Calcium Score, No. (%)*		
			0	0-19	≥20
Black men	91	0.45 (1.17)	75 (82)	13 (14)	3 (3)
White men	96	0.45 (1.16)	80 (83)	9 (9)	7 (7)
Black women	110	0.29 (0.84)	96 (87)	12 (11)	2 (2)
White women	77	0.08 (0.44)	74 (96)	2 (3)	1 (1)
All participants	374†	0.33 (0.97)	325 (87)	36 (10)	13 (3)

*The row percentages do not add up to 100% due to rounding.
†CARDIA participants who had measurements of Cook-Medley hostility scores at baseline and 5-year examination and had complete data on covariates of interest.

at baseline and means of study variables according to quartiles of hostility scores at baseline. Analysis of covariance was used to estimate sex-, race-, and field center–adjusted proportions of study participants with calcium scores of more than 0 and 20 or higher, according to quartiles of hostility at baseline, respectively.

Multivariate logistic regression was used to quantify the unadjusted relative risks of calcium scores more than 0 and 20 or higher associated with 1 SD linear difference in hostility and in cynical distrust scores at baseline, respectively. Additional analyses were run dichotomizing hostility and cynical distrust scores into high vs low (determined by median cut points). The calcium score cut points (0 and 20) were chosen to examine the association of hostility with any measurable coronary artery calcification (vs none), and with the presence of a calcium score of 20 or higher (to rule out the possibility that very low calcium scores may be due to imaging artifacts).

Second, the minimally adjusted logistic models considered included baseline age, sex, race, and field center. Third, fully adjusted logistic models included the above variables plus variables found to be significantly related to hostility: education level, alcohol consumption, current smoking status, and change in systolic blood pressure between baseline and the year 5 examination, including baseline systolic blood pressure. We also included in the fully adjusted models 2 additional variables found to be positively associated with the presence of any coronary artery calcification (ie, calcium score >0): body mass index and low-density lipoprotein cholesterol. Confirmatory analysis was carried out with hostility scores measured at year 5 with similar results (data not provided).

To assess differential associations by sex and race groups, logistic models predicting calcium score of more than 0 and 20 or higher were also performed including (in addition to age and field center) terms for 2-way interactions between baseline hostility score (as a continuous variable) and sex, and between hostility score and race. The SAS version 6.11 statistical software (SAS Institute, Cary, NC) was used in all statistical analyses.

RESULTS

In comparison with the rest of CARDIA subjects, participants in this study were less likely to be white women (20.6% vs 28.2%; $P<.001$), were slightly older (25.3 vs 25.0 years; $P=.05$), and less likely to be current smokers (23.8% vs 28.9%; $P=.04$). Moreover, participants in this study had a higher total physical activity score (458 vs 419; $P=.03$) and had lower triglyceride levels (0.75 [66.4] vs 0.82 mmol/L [72.5 mg/dL]; $P<.001$). However, participants did not differ significantly from the rest of the cohort in hostility score at baseline (19.7 vs 19.1; $P=.23$).

Forty-nine (13%) subjects had a calcium score of more than 0. This percentage varied by sex and race, with men of both races having the highest scores (17%) and white women having the lowest (4%). White men had the highest percentage of participants with a calcium score of 20 or higher (7%) (TABLE 1).

The respective mean (SD) hostility and cynical distrust scores at baseline were highest in black men (23.2 [7.7]; 4.0 [1.8]), followed by black women (21.5 [7.8]; 3.4 [2.0]), white men (17.1 [7.5]; 2.1 [1.9]), and white women (16.2 [7.6]; 2.0 [1.9]). This ranking was maintained in the year 5 examination. On average, the mean (SD) hostility score declined by 1.9 points over 5 years, with the highest decrease among white men (−2.2 [6.1]) and white women (−2.1 [6.4]), and lowest decrease among black women (−1.6 [7.3]).

The sex and race distribution varied with the level of hostility. Of the 97 participants in the highest quartile, black women and men represented the highest percentage. Of the 89 participants in the lowest quartile, white men and women represented the highest percentage (TABLE 2). Age and education level were inversely related, whereas alcohol consumption was positively associated with hostility. The percentage of those who smoked at baseline increased with the level of hostility. In addition, those who smoked at baseline and who were in the lowest quartile of hostility appeared to be more likely to have quit smoking at the year 5 examination than those with higher hostility scores. Furthermore, subjects with high hostility scores displayed a smaller decline in systolic blood pressure and a slight increase in diastolic blood pressure at the year 5 examination.

The correlation between hostility scores at baseline and at 5 years was 0.67 ($P<.001$); overall hostility and cynical distrust scores were highly correlated ($r=0.82$; $P<.001$). Hostility scores at baseline (0.12 [$P=.02$]) and at 5 years (0.19 [$P<.001$]) correlated with the calcium score. The correlation of the cynical distrust score at baseline and the calcium score was 0.11 ($P=.03$).

After adjusting for sex, race, and field center, the percentage of persons with a calcium score more than 0 and 20 or higher increased in a monotonic fashion with the level of hostility at baseline (FIGURE). In unadjusted logistic regression, difference of 1 SD (8.2 units) in hostility scores at baseline was associated

with statistically significant greater odds of having any coronary artery calcification: 1.38 (95% confidence interval [CI], 1.02-1.88), and for having a calcium score of 20 or higher it was 1.96 (95% CI, 1.11-3.58) (TABLE 3). Compared with subjects with low hostility scores, those with scores above or at the median were more likely to have a calcium score of more than 0 (odds ratio [OR], 2.00 [95% CI, 1.09-3.80]) and a score of 20 or higher (OR, 6.18 [95% CI, 1.63-40.3]). These ORs were substantially unaltered (if anything, they became stronger in some cases) after minimal or full multivariate adjustments. Hostility scores measured at year 5 examination (both as a continuous and a categorical variable) showed similar risk relations (data not shown). Furthermore, each 1 unit increase in hostility between baseline and year 5, adjusting for baseline hostility scores, was also related to a statistically significant 1.09 (95% CI, 1.03-1.15) higher odds of any coronary artery calcification but was not related to having a calcium score of 20 or higher.

There was an association of borderline statistical significance between the 8 cynical distrust items as a continuous variable and having a calcium score of more than 0 (OR per SD difference, 1.41 [95% CI, 1.00-2.01]) and a significant association between the cynical distrust score, also as a continuous variable and having a calcium score of 20 or higher (OR per 1 SD difference, 1.91 [95% CI, 1.04-3.58]) after adjusting for age, race, and field center.(TABLE 3). In the minimally adjusted model, those in the upper half of cynical distrust, compared with those in the lower half, experienced an OR of 2.09 (95% CI, 1.05-4.31) of having a calcium score more than 0 and an OR of 3.86 (95% CI, 1.05-18.6) of having a calcium score of 20 or higher. Adjustment for potential mediating variables attenuated but did not completely explain the association of cynical distrust scores with the presence of any coronary calcification.

Neither the 2-way interaction between the global hostility score at baseline (as a continuous variable) and sex as predictors of calcium scores of more than 0 or 20 or higher ($P \geq .19$) nor the 2-way interaction between baseline hos-

Table 2. Associations Between Demographic, Behavioral, Physiological, and Psychological Variables and Cook-Medley Hostility Score at Baseline, the Coronary Artery Risk Development in Young Adults Study, 1985-1986*

Variables	Quartiles of Cook-Medley Hostility Score at Baseline				*P* Value†
	<14	14-19	20-25	≥26	
Baseline					
No. of participants	89	104	84	97	. . .
White men, %	34.8	30.8	25.0	12.4	<.001
White women, %	33.7	21.1	21.4	7.2	
Black men, %	11.2	24.0	19.0	41.2	
Black women, %	20.2	24.0	34.5	39.2	
Age, y	25.6 (3.4)	25.9 (3.1)	24.9 (3.7)	24.8 (3.8)	.02
Education, y	14.8 (2.1)	13.9 (2.1)	13.5 (2.4)	13.4 (2.3)	<.001
Alcohol consumption, mL/d	9.8 (15.1)	10.7 (16.4)	15.1 (25.5)	17.2 (31.9)	.01
Total physical activity score, U	506 (378)	440 (307)	448 (346)	442 (361)	.21
Body mass index, kg/m^2	24.5 (4.2)	24.4 (4.6)	24.5 (5.7)	25.7 (5.5)	.17
Systolic blood pressure, mm Hg	113 (9)	111 (11)	110 (11)	113 (12)	.43
Diastolic blood pressure, mm Hg	69 (11)	68 (9)	68 (10)	69 (9)	.53
Fasting insulin, pmol/L‡	71.5 (36.1)	67.4 (52.9)	76.4 (55.6)	79.9 (70.1)	.08
Low-density lipoprotein cholesterol, mmol/L§	2.96 (0.78)	2.93 (0.81)	2.84 (0.75)	2.89 (0.87)	.51
High-density lipoprotein cholesterol, mmol/L§	1.39 (0.30)	1.42 (0.34)	1.37 (0.28)	1.41 (0.35)	.78
Current cigarette smoker, %	7.8	20.2	27.4	39.2	<.001
Prevalent hypertension, %	2.2	0.9	2.4	4.1	.75
Change					
Quit smoking at year 5 after baseline, %	42.8	4.7	26.1	26.3	.57
Change in body mass index, kg/m^2‖	1.6 (2.3)	1.4 (2.8)	1.6 (2.6)	1.7 (2.3)	.93
Change in systolic blood pressure, mm Hg‖	–5.8 (8.2)	–3.5 (9.3)	–2.0 (8.4)	–1.7 (11.1)	<.001
Change in diastolic blood pressure, mm Hg‖	–2.1 (10.1)	1.2 (9.6)	0.5 (9.2)	2.0 (11.9)	.03
Incident hypertension, %¶	6.7	8.6	8.3	15.4	.10
Incident diabetes, %#	0.0	3.8	2.4	2.1	.45

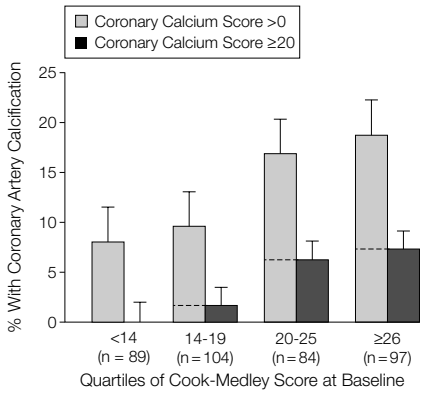
*Data are presented as mean (SD) unless otherwise indicated. Ellipses indicate not applicable.
†Derived from χ^2 test of homogeneity for sex and race groups, linear regression of hostility as a continuous independent variable on continuous dependent variables, and logistic regression of hostility as a continuous independent variable on dichotomous dependent variables.
‡To convert from pmol/L to μU/mL divide by 6.945.
§To convert from mmol/L to mg/dL divide by 0.02586.
‖Year 5 minus baseline.
¶No hypertension at baseline and hypertension at 2-, 5-, 7- and/or 10-year examinations. Defined as blood pressure 140/90 mm Hg or more or use of antihypertensive medication.
#No diabetes at baseline and diabetes at 7- and 10-year examinations or both. Defined as 8-hour fasting blood glucose level of ≥7.0 mmol/L (126 mg/dL) or use of antidiabetic medication.

tility and race were statistically significant ($P \geq .56$).

COMMENT

This population-based study in young adults demonstrates a positive graded association between hostility scores at baseline and coronary artery calcification measured using EBCT 10 years later. Persons with baseline hostility scores above the median had a 2-fold greater prevalence of any measurable coronary calcification (ie, calcium score >0), relative to those below the median. Although mean hostility levels decreased over 5 years in all sex and race groups, the 5-year change in hostility was also positively associated with coronary artery calcification. Cynical distrust, a subscale of hostility, was also associated with the presence of coronary calcium, although to a lesser degree. This finding suggests that, although the cynical distrust component may be important, other components of hostility (ie, anger or aggression) may be involved in the development of subclinical cardiovascular disease.[1]

Figure. Sex, Race, and Field Center–Adjusted Percentage Showing Coronary Artery Calcification by Quartiles of the Cook-Medley Score



Light gray bars indicate the percentage of all patients in each baseline Cook-Medley Score quartile with a coronary calcium score of greater than 0 (*P* for linear trend = .02). Patients in this group with a coronary calcium score of 20 or higher are indicated by the dark gray bars (*P* for linear trend = .008).

As reported before in the CARDIA cohort,[33,34] we found that hostility at baseline was related to a number of variables such as sex, race, age, education level, alcohol consumption, current smoking, and change in systolic blood pressure. However, controlling for these potential confounders in multivariate analysis did not explain the association between hostility scores and coronary artery calcification. Findings from the Kuopio Ischemic Heart Disease Risk study showed that adjustments for behavioral risk factors reduced substantially the association between cardiovascular mortality and cynical hostility.[11] This discrepancy may be due to a much higher prevalence of these factors among middle-aged Finnish men.

A limitation of our study was not having adequate statistical power to perform sex- and race-specific analyses. None of the interactions between hostility scores and sex or between hostility scores and race reached statistical significance. However, this lack of interaction should be viewed cautiously, and the question of whether hostility plays an equal role in atherosclerotic heart disease across sex and race groups deserves further study.

Our results are consistent with the hypothesis that hostility might contribute to the development of coronary atherosclerosis not only through poor health habits (ie, greater alcohol intake and tobacco use), but via other physiological mechanisms. For example, a number of recent investigations have found relationships between hostility and cardiovascular reactivity,[35] blood pressure morning surge,[36] increased platelet activation,[37] and reduced β-adrenergic receptor responsiveness.[38] Epinephrine is a recognized platelet activator[39,40] and hostile individuals show a marked increase of catecholamine levels during psychological stress.[41] In addition, previous studies have shown that hostile persons have a propensity toward prolonged neuroendocrine responses to either psychological stressors or chronic stress associated with frequent and prolonged bouts of anger.[42]

An alternative interpretation is that a common (confounding) factor, perhaps hormonal-like androgens,[43] may lead both to hostility and subclinical CAD. Although androgens have been linked to high levels of aggressiveness,[43] studies dealing with the relationship between circulating levels of testosterone and dehydroepiandrosterone and CAD in men are inconsistent.[44]

Table 3. Logistic Regression of Coronary Artery Calcification Status at the 10-Year Examination (1995-1996) on Cook-Medley Global Hostility Score and Cynical Distrust Score at Baseline, the Coronary Artery Risk Development in Young Adults Study, 1985-1986 (n = 374)*

	Global Cook-Medley Score		Cynical Distrust Score	
Variables	1 SD Difference (8.2 Units)	High vs Low (≥20 vs <20 Units)†	1 SD Difference (2.1 Units)	High vs Low (≥2 vs <4 Units)†
Model predicting calcium score >0				
Unadjusted	1.38 (1.02-1.88)	2.00 (1.09-3.80)	1.34 (0.99-1.81)	1.92 (1.04-3.72)
Minimally adjusted‡	1.54 (1.08-2.21)	2.57 (1.31-5.22)	1.41 (1.00-2.01)	2.09 (1.05-4.31)
Fully adjusted§	1.48 (1.00-2.22)	2.38 (1.12-5.20)	1.24 (0.85-1.80)	1.54 (0.74-3.25)
Model predicting calcium score ≥20‖				
Unadjusted	1.96 (1.11-3.58)	6.18 (1.63-40.3)	1.56 (0.91-2.77)	2.97 (0.89-13.4)
Minimally adjusted‡	2.30 (1.24-4.52)	9.56 (2.29-65.9)	1.91 (1.04-3.58)	3.86 (1.05-18.6)

*All data are presented as odds ratio (95% confidence interval).
†Medium split.
‡Includes age, sex, race, and field center.
§Includes education level, alcohol consumption, current cigarette smoking, systolic blood pressure, body mass index, low-density lipoprotein cholesterol, and 5-year change in systolic blood pressure.
‖There were too few cases with calcium scores less than 20 (n = 13) to fit fully adjusted models.

Therapy directed at reducing hostility has been shown to reduce the risk of nonfatal reinfarction by more than 50%.[45] Recent evidence suggests that formal cardiac rehabilitation and exercise training programs can reduce hostility and improve quality of life after major coronary events.[46] An important implication of our findings is that therapy directed at reducing hostility also may have value in preventing the development of subclinical atherosclerosis.

Coronary artery calcification detected by EBCT occurs early in plaque development as part of the inflammatory pathophysiologic cascade of CAD[19,47] and is regulated in part by a process similar to bone mineralization.[48] Although not all atherosclerotic segments have detectable calcification, the area of coronary artery calcification quantified on EBCT has a positive relationship with the histopathologic coronary plaque area.[48] Coronary calcification may be a stronger predictor of angiographic CAD than are standard risk factors[49] and may be a predictor of coronary events including coronary death, myocardial infarction, or revascularization.[50,51]

In summary, this prospective cohort study suggests that high hostility levels may contribute to early subclinical atherosclerotic CAD. Clinical trials are needed to test whether reduction in hostile attitudes and behaviors is an effective means of preventing atherosclerosis and thus ameliorating the burden of coronary disease.

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