

LACK OF CORRELATION BETWEEN PSYCHOLOGICAL FACTORS AND SUBCLINICAL CORONARY ARTERY DISEASE

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ABSTRACT

Background The relation between psychological variables and clinically evident coronary artery disease has been studied extensively, although the potential mechanisms of such a relation remain speculative. We studied the relation between multiple psychological variables and subclinical coronary artery disease to assess the possible role of such variables in atherogenesis.

Methods We conducted a prospective study of 630 consecutive consenting, active-duty U.S. Army personnel, 39 to 45 years of age, without known coronary artery disease. Each participant was assessed for depression, anxiety, somatization, hostility, and stress. Subclinical coronary artery disease was identified by electron-beam computed tomography.

Results The mean (\pm SD) age of the subjects was 42 ± 2 years; 82 percent were male, and 72 percent were white. The prevalence of coronary-artery calcification was 17.6 percent (mean calcification score, 10 ± 49). The prevalence of prior or current psychiatric disorders was 12.7 percent. There was no correlation between the coronary-calcification score and the scores measuring depression ($r = -0.07$, $P = 0.08$), anxiety ($r = -0.07$, $P = 0.10$), hostility ($r = -0.07$, $P = 0.10$), or stress ($r = -0.002$, $P = 0.96$). Somatization (the number and severity of durable physical symptoms) was inversely correlated with calcification scores ($r = -0.12$, $P = 0.003$), even after we controlled for age and sex. In multivariate logistic-regression models, a somatization score greater than 4 (out of a possible 26) was independently associated with the absence of any coronary-artery calcification (odds ratio, 0.49; 95 percent confidence interval, 0.25 to 0.96).

Conclusions Our data suggest that depression, anxiety, hostility, and stress are not related to coronary-artery calcification and that somatization is associated with the absence of calcification. (N Engl J Med 2000;343:1298-304.)

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AN association between psychological traits and coronary artery disease has been acknowledged for decades but has only recently been validated empirically.¹⁻¹⁶ Depression, anxiety, and hostility have each been demonstrated to be associated with the risk of coronary artery disease^{5-10,14,15} and of adverse outcomes after acute coronary events.¹¹⁻¹³ Several hypotheses have been proposed to explain such associations: increased platelet reactivity, decreased heart-rate variability, poor

adherence to therapies, or increased atherogenesis.¹⁷ Several studies have shown minimal or no relation between psychological variables and the degree of coronary stenosis due to plaques in symptomatic patients undergoing cardiac catheterization.¹⁸⁻²¹ One study of young adults found a weak relation between hostility and coronary-artery calcification.²²

We undertook this study to explore the relation between multiple psychological variables (depression, anxiety, somatization, hostility, and multidimensional stress) and subclinical coronary-artery calcification, as measured by electron-beam computed tomography, in a consecutive sample of an asymptomatic screening population. The a priori hypothesis was that psychological variables previously shown to be associated with clinical coronary artery disease would be associated with underlying atherosclerosis, as reflected by coronary-artery calcification.

METHODS

Subjects

The methods of the Prospective Army Coronary Calcium Study have been described previously.²³ Briefly, between October 1998 and October 1999, active-duty Army personnel from 39 through 45 years of age who were stationed in the Washington, D.C., area were recruited at the time of a periodic, Army-mandated physical examination. Persons who had a history of coronary heart disease or who reported a history of angina pectoris on the questionnaire of Rose et al.²⁴ were ineligible. Of 705 eligible subjects, 630 gave written informed consent for the study, which included examination by electron-beam computed tomography. The 75 persons who did not consent to the study were similar to the participants with respect to age, sex, education, and factors that affect the risk of cardiovascular disease (diabetes mellitus, total cholesterol level, and smoking status). The protocol was approved by the Department of Clinical Investigation of the Walter Reed Army Medical Center.

The participants provided information on their personal histories with respect to hypertension, diabetes mellitus, hypercholesterolemia, and psychiatric disorders; any family history of premature cardiovascular disease; and their smoking status. Height and weight, body-mass index (the weight in kilograms divided by the square of the height in meters), and blood pressure were measured in standard fashion. Blood was collected while the patients were fasting for the measurement of serum glucose, glycosylated hemoglobin, insulin, homocysteine, Lp(a) lipoprotein, and fibrinogen. Low-density lipoprotein (LDL) cholesterol was measured by direct assay. Standard 12-lead electrocardiograms were ob-

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tained and were evaluated by an investigator who had no knowledge of the subject's coronary-artery calcification score or other cardiovascular risk factors.

Assessment of Subclinical Atherosclerosis

To determine the presence and amount of subclinical atherosclerosis, coronary-artery calcification was measured by electron-beam computed tomography with a scanner (C-150LXP, Imatron). Each scan included 40 to 50 slices, each 3 mm thick, with image acquisition gated to 70 to 80 percent of the RR interval during electrocardiography while the subject was holding his or her breath. The scans were interpreted by an experienced radiologist using the scoring method of Agatston et al.²⁵ Scans that had at least four contiguous pixels with more than 130 Hounsfield units were considered to be positive for coronary-artery calcification, yielding a definition of "any calcification" as any score greater than 0 (scores can range into the thousands). A total score was determined from the sum of the individual scores for the four major epicardial coronary arteries. This scoring system has been demonstrated to correlate well with the histologic and angiographic burden of plaque.²⁶⁻³⁰ The radiologist who interpreted the scans was unaware of the clinical status of the participants.

Assessment of Psychological Factors

Before undergoing scanning, each participant filled out a questionnaire that included validated instruments to assess functional status, hostility, and stress and to identify depression, anxiety, and somatoform disorders according to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).³¹ Functional status was measured by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).³² Depression, anxiety, and somatization (a durable pattern of physical symptoms causing impairment for which no physical explanation can be identified) were measured with use of the validated, self-administered version of the Primary Care Evaluation of Mental Disorders (PRIME-MD).³³ Depression, anxiety, and somatoform disorders were defined as any such disorders detected on the questionnaire. Continuous scores for depression and anxiety were created on the basis of the number and severity of the symptoms that the participant reported in each domain. Somatization was quantified in terms of the number and severity of bothersome physical symptoms reported from a checklist of the 13 most common symptoms encountered in primary care (each of the 13 common symptoms was graded as follows: "bothered not at all"=0, "bothered a little"=1, or "bothered a lot"=2).³⁴ The scores for depression ranged from 0 to 27, the scores for anxiety from 0 to 14, and the scores for somatization from 0 to 26.

Hostility was measured with use of the Cook-Medley hostility scale (the 50-item tool,³⁵ as well as the refined version described by Barefoot et al.³⁶). A comprehensive stress score (range, 0 to 18) was calculated on the basis of the number and severity of responses indicating stress in nine different domains (work, finances, relationships, caregiving burden, body image, sexuality, psychological support, health, and traumatic life experiences). For each psychological variable, the validity of the continuous scores was assessed by correlating scores with mental health function as measured by the SF-36.³³

Statistical Analysis

Continuous variables were compared with use of a t-test for independent groups; categorical variables were compared with use of the chi-square test. Correlation analysis was performed with use of Spearman's rho, since the coronary-calcification scores and the psychological scores were not normally distributed. The independent relation between multiple cardiovascular and psychological factors and the dependent variable, coronary-artery calcification (defined by a score greater than 0), were assessed with multivariate logistic-regression models. A two-tailed P value of 0.05 or less was considered to indicate statistical significance.

RESULTS

The demographic characteristics, cardiovascular risk factors, coronary-calcification data, and psychological profiles of the 630 participants are shown in Tables 1 and 2.

The group was predominantly well educated. Most were white men; 18.3 percent were women, and 28.4 percent were nonwhite. According to the Framingham Risk Index,³⁷ the five-year predicted risk of coronary heart disease was relatively low (mean [\pm SD], 1.6 ± 1.2 percent).

Coronary-artery calcification was present in 20.6 percent of the men and 4.3 percent of the women. The mean calcification scores for men and women were 11 ± 53 and 3 ± 25 , respectively. Coronary-artery calcification was significantly related to higher total cholesterol, LDL cholesterol, and triglyceride levels, higher systolic blood pressure, higher body-mass index, a greater degree of somatization, and male sex.

The correlation of each psychological score (from the PRIME-MD) with mental health status was substantial, thus establishing the internal validity of the psychological measures in this sample: for depression, $r=0.69$, $P<0.001$; for anxiety, $r=0.61$, $P<0.001$; for somatization, $r=0.51$, $P<0.001$; and for stress, $r=0.60$, $P<0.001$.

TABLE 1. DEMOGRAPHIC CHARACTERISTICS, RISK FACTORS FOR CORONARY ARTERY DISEASE, AND PREVALENCE OF CORONARY-ARTERY CALCIFICATION AMONG THE 630 PARTICIPANTS.

CHARACTERISTIC	VALUE*
Male sex (%)	81.7
Age (yr)	42 ± 2
White race (%)	71.6
College education (%)	80.9
Cardiac risk factors	
Total cholesterol (mg/dl)†	202 ± 35
Low-density lipoprotein cholesterol (mg/dl)†	129 ± 33
High-density lipoprotein cholesterol (mg/dl)†	52 ± 14
Hypertension (%)	22.9
Tobacco use within previous 6 mo (%)	11.4
Diabetes mellitus (%)	1.7
Family history of coronary artery disease (%)	22.1
5-Year Framingham Risk Index (%)	1.6 ± 1.2 ‡
Coronary-artery calcification score	
Mean	10 ± 49
Median	0
Score	
>0 (% of subjects)	17.6
>10 (% of subjects)	11.4
>20 (% of subjects)	9.2

*Plus-minus values are means \pm SD.

†To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

‡The value is the probability of clinical coronary heart disease within five years.³⁷

TABLE 2. PREVALENCE OF PSYCHOLOGICAL DISORDERS, PSYCHOLOGICAL SCORES, AND CORRELATION OF PSYCHOLOGICAL SCORES WITH CORONARY-ARTERY CALCIFICATION SCORES.*

VARIABLE	PREVALENCE (%)	SCORE†	CORRELATION WITH CAC (95% CI)‡	P VALUE
Depression	7.6	2.1±3.1	-0.07 (-0.15 to 0.01)	0.08
Anxiety	5.1	1.8±2.7	-0.07 (-0.15 to 0.01)	0.10
Somatization	4.0	3.4±2.9	-0.12 (-0.20 to -0.04)	0.003
Hostility		14.1±6.0	-0.07 (-0.15 to 0.01)	0.10
Stress		3.1±2.5	-0.002 (-0.08 to 0.08)	0.96

*CAC denotes coronary-artery calcification, and CI confidence interval. CAC scores were determined with the Agatston scoring method.²⁵ Depression, anxiety, and somatoform disorders were defined as any disorders detected on the PRIME-MD³³: major depression or depression not otherwise specified; panic disorder or anxiety disorder not otherwise specified; and somatoform disorder not otherwise specified. Continuous scores for depression, anxiety, and somatization were created on the basis of the number and severity of symptoms reported in each domain. This resulted in the following ranges of possible scores for mental disorders, with higher scores indicating worse mental health: depression, 0 to 27; anxiety, 0 to 14; and somatization, 0 to 26. Hostility was measured by the Cook–Medley hostility scale (range, 0 to 50). Stress was measured by the number and severity (0, “not bothered,” 1, “bothered a little,” or 2, “bothered a lot”) of responses in nine different domains of life (work, finances, relationships, caregiving burden, body image, sexuality, psychological support, health, and traumatic life experiences) during the previous four weeks.

†Plus–minus values are means ±SD.

‡Spearman’s rho was used because coronary-artery calcification scores were not normally distributed.

Eighty participants (12.7 percent) had depression, anxiety, or a somatoform disorder; this prevalence was roughly half that in clinical populations (Table 2). Depression, anxiety, hostility, and stress were not significantly associated with coronary-artery calcification. There was no significant difference between those with and those without psychological disorders in the prevalence of coronary-artery calcification (13.8 percent vs. 18.3 percent, $P=0.33$) (Table 3). However, the somatization score was significantly and inversely correlated with the calcification score (Fig. 1).³³ This relation persisted even after we controlled for age and sex.

Logistic-regression models (with control for body-mass index, LDL cholesterol level, systolic blood pressure, the interaction of systolic blood pressure and antihypertensive treatment,³⁸ smoking status, sex, age, education, and each of the psychological variables) identified sex, LDL cholesterol level, body-mass index, and degree of somatization as independent correlates of coronary-artery calcification (Table 4). A somatization score of more than 4 out of a possible 26 was associated with an adjusted odds ratio for coronary calcification of 0.49 (95 percent confidence interval, 0.25 to 0.96).

When the same models were repeated with the in-

TABLE 3. SCORES FOR PSYCHOLOGICAL VARIABLES IN SUBJECTS WITH CORONARY-ARTERY CALCIFICATION AND THOSE WITHOUT CALCIFICATION ON ELECTRON-BEAM COMPUTED TOMOGRAPHY.*

VARIABLE	CAC PRESENT (N=1111)	CAC ABSENT (N=519)	P VALUE
	score		
Depression	1.7±2.7	2.2±3.2	0.10
Anxiety	1.5±2.4	1.9±2.8	0.17
Somatization	2.7±2.4	3.5±3.0	0.001
Hostility	13.2±5.3	14.2±6.1	0.10
Stress	3.0±2.3	3.1±2.6	0.79
Presence of any mental disorder (%)†	9.9	13.3	0.33

*Plus–minus values are means ±SD. CAC denotes coronary-artery calcification.

†Depressive, anxiety, and somatoform disorders are included.

clusion of either any psychological disorder (depression, anxiety, or somatization) or individual psychological scores, and the level of Lp(a) lipoprotein, homocysteine, fibrinogen, insulin, glycosylated hemoglobin, or high-density lipoprotein cholesterol, a persistent independent relation was found between somatization and coronary-artery calcification.

DISCUSSION

In this consecutive sample of nonreferred, asymptomatic U.S. Army personnel without known coronary disease, there was no positive association between psychological variables and coronary-artery calcification, an established marker of atherosclerosis. There was, however, an unexpected inverse association between somatization and coronary-artery calcification, even after we controlled for multiple potential confounding variables.

Previously, two studies in which the thickness of the intima and media of the carotid artery was used as a surrogate for atherosclerosis found an independent association between hostility and subclinical atherosclerosis. One study found an association between hostility and a change in intima–media thickness over a period of two years,³⁹ and the other found an independent association between hostility (but not anxiety) and intima–media thickness.⁴⁰

One prospective study of young men and women found an independent relation between hostility and coronary-artery calcification, but the study did not measure other psychological variables and had few participants with any coronary-artery calcification.²² Our study was substantially larger than those studies, assessed a more comprehensive battery of psycho-

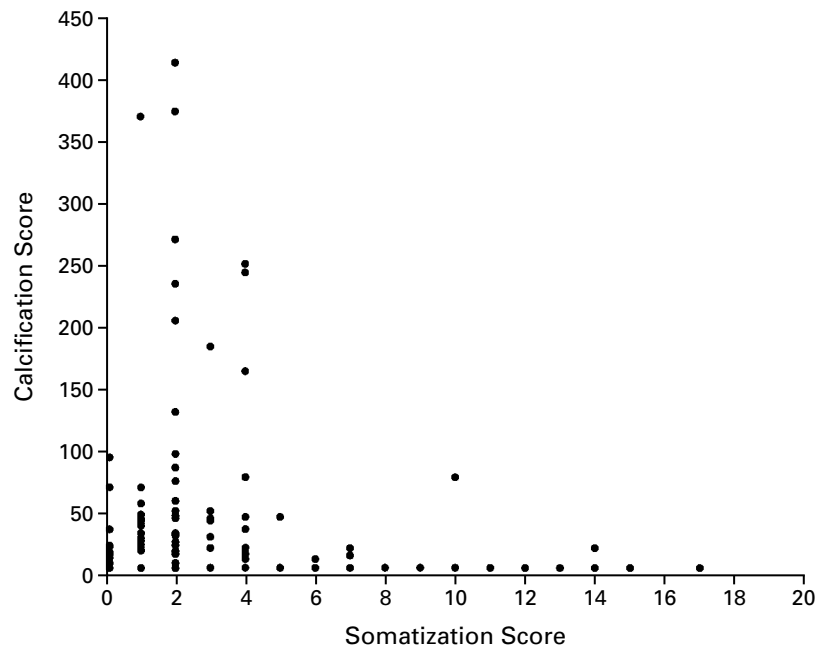


Figure 1. Inverse Correlation of Somatization Scores and Scores for Coronary-Artery Calcification in 630 Asymptomatic Subjects.

One subject with a calcification score of 790 and a somatization score of 1 is not indicated, owing to the scale of the figure.

logical variables and coronary risk factors, and had more participants with subclinical disease. These features allowed us to perform a richer multivariate assessment of the relation between psychological variables and coronary-artery calcification. In our study, hostility was not associated with subclinical coronary-artery disease. A higher degree of somatization, on the other hand, was independently associated with the absence of coronary-artery calcification, even after we controlled for other psychological variables, including depression and hostility. Our data suggest that any assessment of psychological variables and subclinical coronary artery disease must also control for somatization.

Several studies have assessed the association between psychological variables and the burden of coronary atherosclerosis in symptomatic persons undergoing angiography. The results are conflicting.¹⁸⁻²¹ However, it is difficult to draw conclusions about the mechanisms of subclinical atherogenesis from angiographic studies of largely symptomatic patients with clinically manifest disease. Angiographic studies may not be a suitable method of assessing the relation between behavioral variables and coronary artery disease, largely because of a skewed population with late-stage, severe disease (disease-spectrum bias).⁴¹ Indeed, the strength of our study lies in the use of a consecutive sample of an asymptomatic screening popula-

TABLE 4. ODDS RATIOS FOR CORONARY-ARTERY CALCIFICATION ASSOCIATED WITH SELECTED CHARACTERISTICS IN A CONSECUTIVE SCREENING SAMPLE OF 630 ASYMPTOMATIC SUBJECTS.*

CHARACTERISTIC	ADJUSTED ODDS RATIO (95% CI)
Male sex	3.57 (1.36–9.39)
LDL cholesterol (each increase of 1 mg/dl)	1.01 (1.00–1.02)
Body-mass index (each increase of 1 point)	1.07 (1.00–1.15)
Somatization score (each increase of 1 point)	0.89 (0.81–0.94)
Somatization score >4	0.49 (0.25–0.96)

*CI denotes confidence interval, and LDL low-density lipoprotein. Odds ratios were derived in a multivariate model and have been adjusted for age, education, smoking status, systolic blood pressure, use of antihypertensive medication, the interaction of systolic blood pressure and antihypertensive medication, depression, and hostility. Other models, including anxiety score, stress score, and the level of Lp(a) lipoprotein, homocysteine, fibrinogen, insulin, and glycosylated hemoglobin, did not add further explanatory power to the above model. $\chi^2=5.80$, with 8 df, $P=0.67$, by the Hosmer–Lemeshow goodness-of-fit test.

tion, which avoids the selection bias inherent in referred populations.

There has been limited research on the relation between somatization and coronary artery disease, and all of it has been in patients with clinically manifest disease.^{21,42,43} One study showed no relation between hypochondriasis and the number and extent of coronary stenoses.²¹ Two studies showed a weak association between somatization and new cases of myocardial infarction.^{42,43}

Surprisingly, we found a substantial inverse correlation between somatization and coronary-artery calcification. One can only speculate about the explanation for such a relation. Could it be that patients who have somatization are more likely to have a healthy lifestyle? This would be consistent with the health-belief model, whereby adherence to such a lifestyle is dependent on the patient's perception of his or her susceptibility to illness.⁴⁴ Also, it is known that enhanced adherence by itself, even adherence to a regimen of placebo in clinical trials, is associated with better health outcomes.⁴⁵

Somatization is a strong predictor of the absence of noncardiovascular disease among patients referred for specialty care.^{46,47} Even where coexisting medical conditions are common, patients do not indicate high numbers of symptoms on symptom checklists. In one analysis of the original PRIME-MD data set, most somatization was explained by psychological variables such as depression and anxiety, and coexisting medical conditions explained only 2 percent of the total number of physical symptoms.⁴⁸ It is important to emphasize that although our data show an association between somatization and a healthy outcome — namely, absence of coronary-artery calcification — somatization was also strongly correlated with poor mental health function, a result consistent with prior research demonstrating that somatization is a disorder.³⁴

There are several limitations to our data. It is possible that coronary-artery calcification is not a valid surrogate for atherosclerotic plaque.⁴⁹ However, despite clinical research suggesting that electron-beam computed tomography may have a lower sensitivity for atherosclerotic plaque in younger people with clinical coronary artery disease than in older ones,⁵⁰ the preponderance of evidence indicates that coronary-artery calcification predicts cardiac events and correlates with the histologic burden of atherosclerosis.^{28,29,51}

There was a relatively low prevalence of coronary-artery calcification and psychological dysfunction in our study, which could have led to an underestimation of any relation between these two variables. It is also possible that our psychometric tools were not sensitive enough to dynamic psychological states and thus missed potential associations. However, the PRIME-MD is a widely used, valid psychometric tool for the

detection of depression, anxiety, and somatoform disorders.³³ For depression, the PRIME-MD scoring system is sensitive to changes in depressive status (Kroenke K: personal communication). The Cook–Medley questionnaire³⁵ is the state-of-the-art tool for the assessment of hostility. It was derived from the Minnesota Multiphasic Personality Inventory and has been shown to be prospectively associated with adverse health outcomes.³⁶ Finally, we have shown that these tools have internal validity in our sample of participants by demonstrating strong correlations between the results of each scoring system and mental health function.

The lack of an association between psychological variables and coronary-artery calcification is unlikely to be a result of insufficient statistical power, given the negative directions and narrow confidence intervals for all the correlations. It could, however, be due to an insufficient “dose” exposure rather than to the lack of a cause-and-effect relation. That is, the measurement of psychological variables at one point in time may not accurately reflect either the cumulative psychological burden or the effect of the psychological factors on atherosclerosis over time. However, it is known that there is substantial stability of psychological variables over time.^{22,40,52} The Prospective Army Coronary Calcium Study will continue to explore this relation in a prospective fashion.²³

Our results are based on a sample with a narrow range of ages and may not be generalizable to other age groups. However, the use of such a sample may have the advantage of controlling for the powerful effect of age on atherosclerosis and coronary-artery calcification. Data from larger and more diverse populations would be needed to verify these findings.

Causal relations are difficult to infer from cross-sectional data. The problems tend to be with spurious associations, however, and so the finding of a lack of any association between several psychological variables and subclinical coronary artery disease makes it unlikely that there is actually a causal association between psychological factors and the formation of atheromatous plaque.^{53,54}

On the assumption that coronary-artery calcification is a valid surrogate marker for subclinical coronary artery disease, these data suggest that depression, anxiety, hostility, and stress are not related to atherogenesis and that somatization is a marker for the absence of atherosclerosis. Prospective data are needed to clarify the specific relation between psychological variables and the progression from subclinical to clinical coronary artery disease.

The views expressed here are those of the authors and should not be construed as those of the Department of the Army or the Department of Defense.

We are indebted to Kurt Kroenke, M.D., and Ann Shaheen O'Malley, M.D., M.P.H., for their critical review of the manuscript and their helpful comments.

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