Journal of the American College of Cardiology Vol. 51, No. 2, 2008

Published by Elsevier Inc.
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.09.033

Anxiety Characteristics Independently and Prospectively Predict Myocardial Infarction in Men

The Unique Contribution of Anxiety Among Psychologic Factors

Biing-Jiun Shen, PHD,* Yael E. Avivi, MS,† John F. Todaro, PHD,‡ Avron Spiro III, PHD,§ Jean-Philippe Laurenceau, PHD,‖ Kenneth D. Ward, PHD,# Raymond Niaura, PHD¶

Los Angeles, California; Coral Gables, Florida; Providence, Rhode Island; Boston, Massachusetts; Newark, Delaware; and Memphis, Tennessee

Objectives This study investigated whether anxiety characteristics independently predicted the onset of myocardial infarction (MI) over an average of 12.4 years and whether this relationship was independent of other psychologic variables and risk factors.

Background Although several psychosocial factors have been associated with risk for MI, anxiety has not been examined extensively. Earlier studies also rarely addressed whether the association between a psychologic variable and MI was specific and independent of other psychosocial correlates.

Methods Participants were 735 older men (mean age 60 years) without a history of coronary disease or diabetes at baseline from the Normative Aging Study. Anxiety characteristics were assessed with 4 scales (psychasthenia, social introversion, phobia, and manifest anxiety) and an overall anxiety factor derived from these scales.

Results Anxiety characteristics independently and prospectively predicted MI incidence after controlling for age, education, marital status, fasting glucose, body mass index, high-density lipoprotein cholesterol, and systolic blood pressure in proportional hazards models. The adjusted relative risk (95% confidence interval [CI]) of MI associated with each standard deviation increase in anxiety variable was 1.37 (95% CI 1.12 to 1.68) for psychasthenia, 1.31 (95% CI 1.05 to 1.63) for social introversion, 1.36 (95% CI 1.10 to 1.68) for phobia, 1.42 (95% CI 1.14 to 1.76) for manifest anxiety, and 1.43 (95% CI 1.17 to 1.75) for overall anxiety. These relationships remained significant after further adjusting for health behaviors (drinking, smoking, and caloric intake), medications for hypertension, high cholesterol, and diabetes during follow-up and additional psychologic variables (depression, type A behavior, hostility, anger, and negative emotion).

Conclusions Anxiety-prone dispositions appear to be a robust and independent risk factor of MI among older men. (J Am Coll Cardiol 2008;51:113–9) © 2008 by the American College of Cardiology Foundation

A number of psychologic characteristics have been linked to the onset of coronary artery disease (CAD) independent of biomedical risk factors such as obesity, hypertension, diabetes, dyslipidemia, and insulin resistance (1). These include depression (2), anxiety (3), anger (4), type A behaviors (5), and hostility (6). Despite this wealth of research, some conceptual and methodologic issues remain unaddressed.

Several reviews have pointed out that these psychologic factors appear to share a degree of commonality. It is not clear whether they represent common or specific sources of risk for CAD (7,8), however. Most studies merely focused on one psychologic variable without testing whether its effect may be explained by other related constructs. Others combined several components, such as anxiety and depression, to form a global measure of psychologic vulnerability and examined its overall impact (9,10). Nevertheless, different psychologic constructs and emotional disturbances, though overlapping, do present distinct and differentiable features (11). Without investigating these psychologic constructs and their relative contributions simultaneously, it is difficult to discern whether they convey common or specific risk for CAD.

From the *Department of Psychology, University of Southern California, Los Angeles, California; †Department of Psychology, University of Miami, Coral Gables, Florida; ‡Brown Medical School and Miriam Hospital, Providence, Rhode Island; §Massachusetts Veterans Epidemiology Research and Information Center, Boston Veterans Administration Healthcare System, Boston, Massachusetts; ‖Department of Psychology, University of Delaware, Newark, Delaware; #University of Memphis Center for Community Health, Memphis, Tennessee; and the ¶Brown Medical School and Butler Hospital, Providence, Rhode Island. Supported by a grant from the American Heart Association and an award from the National Alliance for Research on Schizophrenia and Depression.

Manuscript received February 5, 2007; revised manuscript received August 20, 2007, accepted September 7, 2007.

JACC Vol. 51, No. 2, 2008
January 15, 2008:113–9

Abbreviations and Acronyms

BMI = body mass index
CAD = coronary artery disease
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
MI = myocardial infarction
RR = relative risk
SBP = systolic blood pressure

Anxiety and depression are among the most prevalent emotional disturbances. Although depression has been well recognized as a risk factor for CAD, few studies have scrutinized the role of anxiety. Kawachi et al. (12) reported that a short phobic anxiety measure predicted nonfatal myocardial infarction (MI) and fatal CAD over 2 years in men. Another study demonstrated that a 5-item anxiety scale predicted sudden cardiac death but not nonfatal CAD over 32 years (13). High levels of worry were associated with nonfatal MI and fatal CAD over 20 years (3). Among cardiac patients, type D personality, jointly defined by social inhibition and negative affectivity, has been found to predict poor prognosis (14). In a cross-sectional study with a representative sample of the U.S. population, generalized anxiety disorder, independent of depression, was linked to a risk index of CAD composed of obesity, smoking, and use of medication for hypertension, hypercholesterolemia, and diabetes (15). In contrast, some studies failed to demonstrate an independent association between anxiety and CAD (16,17).

Some common limitations have been noted in these studies. First, researchers either used a brief screening tool (12), examined a circumscribed aspect of anxiety (3), or provided insufficient information for the anxiety measure (16). Furthermore, earlier studies rarely considered the overlap between anxiety and other coronary-prone psychologic factors (e.g., depression, anger, or hostility), thus failing to discern whether anxiety presented a unique risk for CAD. Kubzanksy et al. (18) attempted to address this issue and found that although anger, anxiety, and general distress were associated with CAD individually, only anxiety and general distress were significant when considered simultaneously. That study did not, however, include several prominent characteristics, such as hostility and type A behavior. It remains unclear whether the observed effects were independent of these psychologic correlates.

The present study addresses the issues raised above. First, using an established and comprehensive psychologic instrument, we examined whether anxiety independently and prospectively conferred higher risk for MI while controlling for major sociodemographic and biomedical risk factors. Second, we tested whether the anxiety-MI association could be explained by other psychologic risk factors observed in earlier studies, including depression, hostility, type A behavior, anger, and negative emotion. In addition, we explored whether sociodemographic background, biomedical risk factors, health behaviors, and use of medications for cardiovascular risk factors during follow-up mediated or moderated the effect of anxiety on MI onset.

Methods

Participants. The NAS (Normative Aging Study) is a longitudinal study investigating the biomedical and psychosocial changes associated with aging among a group of initially healthy men in the Boston area. Its sampling and design have been reported in detail (19). Participants in the present study were required to: 1) have completed the Minnesota Multiphasic Personality Inventory (MMPI) in 1986; 2) have received a physical examination with blood assays near the time of MMPI administration; and 3) be without a history of CAD (angina pectoris, ischemic heart disease, and MI) and diabetes at the baseline. All participants provided written informed consent for the study.

Procedure of medical examination. After 1986, all participants received medical examinations every 3 years. During examinations, the physician updated participants' medical histories and reviewed hospital records for possible CAD events. The research team obtained participants' vital signs, anthropometric measures, and fasting blood samples for laboratory assays. Participants also completed questionnaires assessing sociodemographic background and health behaviors, including caloric intake, smoking, and alcohol consumption. In 1986, active participants received a comprehensive psychosocial assessment, including the MMPI Form AX, from which psychologic measures were derived.

Anxiety measures. Four anxiety scales from the MMPI (20) and an overall anxiety factor derived from these scales were examined. The MMPI is a comprehensive assessment of enduring personality patterns reflecting an individual's cognitive, affective, and behavioral tendencies (21). These 4 scales assess characteristics that give rise to thoughts, feelings, and behaviors indicative of anxiety tendencies. Individuals endorsing these characteristics are more likely to exhibit anxiety symptoms or develop anxiety disorders.

PSYCHASTHENIA. Psychasthenia is an MMPI basic scale with 40 true-false items that assess excessive doubts, obsessive ruminations, and irrational compulsions (22). Its test-retest reliability ranges from 0.74 to 0.93 (23). Its validity has been evidenced by its wide use in research and high associations with other anxiety scales (23).

SOCIAL INTROVERSION. Social introversion is an MMPI basic scale with 26 true-false items tapping anxiety, insecurity, and discomfort during interpersonal and social situations (20). Its test-retest reliability ranges from 0.80 to 0.96 (23). Its validity has been demonstrated by its associations with other measures of social anxiety (23) and prediction of behavioral responses to anxiety-inducing chemical agents (24).

PHOBIA. Phobia was assessed with the 27-item Phobia scale from the MMPI Wiggins content scales (25). High scores suggest excessive anxiety and fears of specific animals, situations, or objects. It has been reported as one of the most effective MMPI anxiety measures in clinical applications (26). It demonstrates high convergent validity with other

anxiety measures and utility in identifying individuals who are fearful, phobic, and worrisome (27).

MANIFEST ANXIETY. The 50-item Manifest Anxiety scale assesses a predisposition to experience tension and somatic symptoms of anxiety in stressful situations. Its test-retest reliability ranges from 0.81 to 0.89 (28) and internal consistency around 0.92 (29). Its validity is evidenced by its associations with other anxiety measures, physiologic manifestations of anxiety, and effects on test performance (29).

OVERALL ANXIETY FACTOR. To compute an index for overall anxiety, we conducted a principal components analysis and extracted a single factor that explained 70% of the total variance with factor loadings of 0.92, 0.77, 0.73, and 0.92 on psychasthenia, social introversion, phobia, and manifest anxiety, respectively. The factor scores of overall anxiety were calculated to represent a summary anxiety index in analyses.

CLINICALLY SIGNIFICANT ANXIETY. To identify individuals with excessively elevated anxiety on these measures, we defined clinical levels of anxiety, by convention, as T scores >65 (30).

Other psychosocial measures. TYPE A BEHAVIOR. The 19-item MMPI-2 Type A scale assesses time urgency, competitiveness, and hostile tendency. Individuals with high scores are hard-driving, fast-pacing, impatient, irritable, and short-tempered. This scale has been associated with CAD onset in a previous study (5).

HOSTILITY. The Cook-Medley Hostility Scale measures a person's hostile affects, cynical attitudes, and antagonistic responding style (31). Individuals with high scores are likely to interpret their environment as threatening and others as harboring harmful intent. It has been shown to predict CAD onset in past studies (6).

ANGER. Anger was measured with the 16-item MMPI-2 Anger scale, tapping excessive anger expression and inability to control anger (32). Individuals with higher scores are hot-headed, grouchy, and likely to be verbally or physically aggressive when provoked. It has been associated with CAD in a previous study (4).

DEPRESSION. Depression was assessed with the 33-item MMPI-2 Depression content scale (21). It measures various depressive symptoms, including dysphoria, lack of motivation, self-depreciation, and suicidal ideations. In a previous study that examined several depression measures, this scale was shown to have the strongest association with CAD events (33).

NEGATIVE EMOTION. Negative emotion was measured by the MMPI Welsh A scale (34). It measures various affective and cognitive symptoms of emotional disturbance, such as dysphoric mood, depressive thoughts, and social maladjustment. A previous study showed that it was associated with CAD onset over 3 years (9).

Health behaviors. Alcohol consumption and cigarette smoking were obtained by standard questionnaires. A smoker was defined as smoking >1 cigarette/day. According to earlier research (35), alcohol consumption was divided into 3 categories (<0.3, 0.3 to 2, and >2 drinks per day) to examine a possible curvilinear relationship between alcohol and MI. Daily caloric intake was derived from a food frequency survey (36).

Blood pressure and anthropometrics. Blood pressure was measured to the nearest 2 mm Hg with a standard mercury sphygmomanometer. Average readings from both arms were obtained. Height was measured to the nearest 0.1 inch, and weight was measured to the nearest 0.5 lb with the participant standing in bare feet and undershorts. Body mass index (BMI) was calculated from height and weight.

Blood chemistry assays. Fasting blood samples were assayed for glucose and lipid profiles. Values of glucose, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides were obtained by standardized procedures described in earlier studies (5,6).

Diagnosis of MI. Hospital records of all possible MIs were reviewed and confirmed by a board-certified cardiologist. Criteria for MI were consistent with those in the Framingham Heart Study (37). Diagnoses were verified by unequivocal electrocardiographic changes (pathologic Q waves) and elevated serum glutamic-oxaloacetic transaminase and lactic dehydrogenase accompanied by chest discomfort. Fatal incidents were confirmed by death certificates indicating MI as the underlying cause.

Data analysis plan. Before analysis, non-normal variables were transformed with a natural log function. Psychologic measures were transformed to z scores to facilitate interpretation. The relationships between anxiety and participant characteristics were examined with Pearson correlations. Cox proportional hazards models were used to estimate the relative risks (RRs) of MI incidence associated with anxiety variables while controlling for covariates.

STANDARD COVARIATES. All proportional hazards models were adjusted for a set of standard covariates, including age, education, marital status, fasting glucose, BMI, HDL-C, and systolic blood pressure (SBP).

PRIMARY ANALYSES. The primary analyses were conducted to estimate the RRs of MI incidence associated with anxiety variables, including psychasthenia, social introversion, phobia, manifest anxiety, and overall anxiety. For each anxiety measure, we first estimated its univariate RR and then assessed its RR adjusted for standard covariates. Furthermore, we examined whether clinical elevations (T scores >65) in these anxiety measures constituted significant risk for MI after adjusting for standard covariates.

To reduce the potential number of tests in additional analyses, we also attempted to demonstrate that overall anxiety was a representative summary index for all anxiety measures used in further analyses.

ADDITIONAL ANALYSES. More analyses were conducted to test the robustness of findings. First, in addition to standard covariates, we estimated the RR of each anxiety variable, adjusted further for drinking, smoking, and caloric intake in a subsample of 638 individuals with valid health behaviors data. Second, we investigated whether overall anxiety predicted MI beyond the contributions of other psychologic variables by controlling for standard covariates and additional psychologic characteristics (i.e., depression, type A behavior, anger, hostility, and negative emotion). Third, we investigated whether participants' sociodemographic and biomedical characteristics moderated the relationship between overall anxiety and MI incidence by testing the corresponding interaction term in the model. Fourth, we examined whether taking medication for hypertension, high cholesterol, diabetes, and/or heart disease during follow-up mediated or moderated the effect of overall anxiety on MI incidence. Finally, we conducted a chi-square test to examine whether more incidents were observed among individuals at different levels of anxiety. All analyses were conducted with SPSS 14.0 (SPSS Inc., Chicago, Illinois).

Results

Participant characteristics and MI events. The characteristics of 735 participants are shown in Table 1. Analyses involving health behaviors were based on 638 individuals because of missing data. The 97 participants with missing values did not differ from the others on any anxiety measures, sociodemographic variables, or biomedical parameters except that the former had slightly higher HDL-C (49.2 vs. 45.9 mg/dl; $p < 0.05$) and BMI (27.4 vs. 26.5 kg/m^2; $p < 0.05$). Considering the large sample size, these differences, although significant, were trivial.

Participants were predominantly Caucasian (96.9%) between 42 and 87 years of age with a mean of 60 years. Most (76%) were married and had more than a high school education (68%). Participants represented a healthy older population except for their average BMI (26.63 kg/m^2), LDL-C (157.3 mg/dl), and SBP (128.7 mm Hg) which were slightly higher than today's standards. Among them, 43% smoked >1 cigarette/day and 33% consumed >2 drinks/day. As shown in Table 1, overall anxiety was generally not associated with marital status, glucose, BMI, lipids, drinking, or smoking. Anxiety, however, was found to be somewhat lower among those with more than a high school education and mildly associated with blood pressure. In addition, manifest anxiety and psychasthenia were mildly associated with higher caloric intake.

By 2004, there were 75 new MI incidents (10.2%), including 64 nonfatal events, 8 fatal events, and 3 nonfatal MIs followed by fatal ones later in life. The average length of follow-up was 12.42 (SD 3.85) years. Because the results for nonfatal events alone did not differ from those for all events in any substantial way, we presented the findings for all MIs.

Independent and prospective relationship between anxiety and MI incidence. Table 2 summarizes the results of Cox proportional hazards regression analyses. First, in univariate analyses, all anxiety scales significantly predicted future MI incidence. The RRs (95% confidence intervals [CIs]) of MI were 1.33 (95% CI 1.10 to 1.60), 1.31 (95% CI 1.06 to 1.63), 1.38 (95% CI 1.12 to 1.70), 1.34 (95% CI 1.10 to 1.62), and 1.39 (95% CI 1.15 to 1.68) for each SD increase in psychasthenia, social introversion, phobia, manifest anxiety, and overall anxiety, respectively ($p \leq 0.017$). After adjusting for age, education, marital status, fasting glucose, BMI, HDL-C, and SBP, all anxiety variables

Table 1 Participant Characteristics and Their Bivariate Correlations With Anxiety Variables

		Correlation With Anxiety Variable				
	Mean (SD) or %	Psychasthenia	Social Introversion	Phobia	Manifest Anxiety	Overall Anxiety
Age (yrs)	60.0 (7.5)	−0.04	0.09*	0.04	−0.07*	0.00
Marital status (% married)	76%	−0.04	−0.04	−0.01	0.01	−0.03
Education (% above high school education)	68%	−0.13‡	−0.13‡	−0.07	−0.09*	−0.13‡
Fasting glucose (mg/dl)	102.4 (18.9)	−0.03	0.00	0.01	−0.06	−0.02
Body mass index (kg/m^2)	26.6 (3.4)	0.06	−0.05	0.04	0.06	0.34
High-density lipoprotein cholesterol (mg/dl)	48.8 (12.4)	0.02	−0.02	−0.04	0.00	−0.01
Low-density lipoprotein cholesterol (mg/dl)	157.3 (34.6)	0.02	0.05	0.03	0.02	0.03
Triglycerides (mg/dl)	145.2 (78.8)	0.02	0.02	0.01	0.01	0.02
Systolic blood pressure (mm Hg)	128.7 (15.9)	−0.10†	−0.02	−0.02	−0.10†	−0.08*
Diastolic blood pressure (mm Hg)	78.7 (8.7)	−0.10†	−0.06	−0.05	−0.09*	−0.09*
Daily caloric intake (kcal)	1971.4 (604.8)	0.10*	−0.06	0.02	0.08*	0.05
Smoking (≥1 cigarette per day)	43%	−0.04	−0.04	−0.01	0.01	−0.03
Drinking (drinks per day)	1.52 (2.18)	0.03	−0.03	0.00	0.01	0.00
<0.3 drinks	26.1%					
0.3 to 2 drinks	41.2%					
>2 drinks	32.7%					

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

Table 2 RRs of MI Incidence Associated With Anxiety Scales in Cox Proportional Hazards Models*

Anxiety Variable	Univariate RR (95% CI) (n = 735)	Multivariate RR (95% CI) Adjusted for Sociodemographic and Metabolic Risk Factors† (n = 735)	Multivariate RR (95% CI) Adjusted for Sociodemographic, Metabolic, and Health Behaviors‡ (n = 638)
Psychasthenia	1.33‖ (1.10–1.60)	1.37‖ (1.12–1.68)	1.37‖ (1.11–1.70)
Social introversion	1.31§ (1.06–1.63)	1.31§ (1.05–1.63)	1.33§ (1.06–1.67)
Phobia	1.38‖ (1.12–1.70)	1.36‖ (1.10–1.68)	1.33§ (1.06–1.67)
Taylor manifest anxiety	1.34‖ (1.10–1.62)	1.42# (1.16–1.73)	1.42# (1.14–1.76)
Overall anxiety	1.39# (1.15–1.68)	1.43# (1.17–1.75)	1.43# (1.15–1.77)

*Psychologic measures are standardized. The RRs represent the increase in risk of MI associated with each standard deviation increase in psychologic variables. †Adjusted for age, education, marital status, fasting glucose, BMI, HDL-C, and SBP. ‡Adjusted for age, education, marital status, fasting glucose, BMI, HDL-C, SBP, alcohol consumption, cigarette smoking, and daily caloric intake; n = 638 owing to missing values on drinking, smoking, and caloric intake. §$p < 0.05$; ‖$p < 0.01$; #$p < 0.001$.

BMI = body mass index; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; MI = myocardial infarction; RR = relative risk; SBP = systolic blood pressure.

significantly predicted MI, with RRs of 1.37 (95% CI 1.12 to 1.68), 1.31 (95% CI 1.05 to 1.63), 1.36 (95% CI 1.10 to 1.68), 1.42 (95% CI 1.16 to 1.73), and 1.43 (95% CI 1.17 to 1.75) for each SD increase in psychasthenia, social introversion, phobia, manifest anxiety, and overall anxiety, respectively ($p \leq 0.02$).

In addition to anxiety, higher BMI (RR 1.08 to 1.09; $p = 0.01$ to 0.02), lower HDL-C (RR 0.97 to 0.98; $p = 0.01$ to 0.03), and being unmarried (RR 0.46 to 0.49; $p < 0.01$) also consistently predicted MI incidence. Older age predicted, or marginally predicted, MI events (RR 1.03 to 1.04; $p = 0.03$ to 0.07). Education, glucose, and SBP were not significant.

According to conventional standard (T score >65), 8.2%, 8.3%, 5.7%, 8.8%, and 8.4% of participants endorsed clinical levels of psychasthenia, social introversion, phobia, manifest anxiety, and overall anxiety, respectively. After adjusting for standard covariates, men with clinically significant anxiety on each scale were more likely to experience an MI, with RRs ranging from 2.17 to 2.48 ($p \leq 0.03$).

Additional analyses. ADJUSTING FOR HEALTH BEHAVIORS. In a subsample of 638 men, we examined the effect of anxiety on MI onset, further controlling for drinking, smoking, and caloric intake. Results showed that these behaviors did not attenuate the relationship between anxiety and MI. The RRs ranged from 1.33 to 1.43 ($p \leq 0.02$) for various anxiety measures (Table 2).

UNIQUE CONTRIBUTION OF ANXIETY BEYOND OTHER PSYCHOLOGIC CHARACTERISTICS. Table 3 presents the adjusted RRs for overall anxiety in predicting MI after controlling for standard covariates and additional psychologic variables (type A behavior, anger, depression, negative emotion, and hostility). When additional psychologic variables were added in the model one at a time, overall anxiety remained a significant predictor, with adjusted RRs ranging from 1.32 to 1.87 ($p \leq 0.020$). None of the other psychologic variables were simultaneously significant. When all psychologic variables were entered in the model, overall anxiety (RR 1.85 [95% CI 1.15 to 2.96]; $p = 0.011$) still significantly predicted prospective MI.

INTERACTIONS BETWEEN ANXIETY AND PARTICIPANT CHARACTERISTICS. No interactions were found between anxiety and age, education, marital status, glucose, BMI, HDL-C, and SBP, indicating that the effect of anxiety on MI was not contingent on variations in these participant characteristics.

EFFECT OF MEDICATION USAGE DURING FOLLOW-UP. Individuals who started medications for hypertension (41.5%), high cholesterol (22.6%), and diabetes (4.6%) during follow-up were identified. After controlling for these medications and standard covariates, overall anxiety remained a significant predictor of MI (RR 1.55 [95% CI 1.13 to 2.12]). In addition, anxiety did not interact with medication usage; that is, the relationship between anxiety and MI did not differ between those who did and those who did not take these medications.

DOSE–RESPONSE RELATIONSHIP. We divided participants into 4 equal groups according to overall anxiety scores and compared the number of MI events in each group. There

Table 3 Prediction of MI Risk by Overall Anxiety in Multivariate Cox Regression Models Controlling for Age, Education, Marital Status, Fasting Glucose, BMI, HDL-C, SBP, and Additional Psychologic Variables (n = 735)

Additional Psychologic Variable Adjusted in Analysis and Its RR and 95% CI	RR (95% CI) of Overall Anxiety Factor in Predicting MI, Controlling for Age, Education, Marital Status, Fasting Glucose, BMI, HDL-C, SBP, and Additional Psychologic Variables
Depression (RR 0.72 [95% CI 0.50–1.03])	1.87‡ (1.33–2.61)
Type A (RR 1.23 [95% CI 0.94–1.60])	1.32* (1.05–1.66)
Anger (RR 0.98 [95% CI 0.75–1.28])	1.45† (1.14–1.84)
Hostility (RR 0.97 [95% CI 0.74–1.32])	1.44† (1.11–1.88)
Negative emotion (RR 0.79 [95% CI 0.50–1.26])	1.77* (1.11–2.82)
All of the above	1.85* (1.15–2.96)

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

Abbreviations as in Table 2.

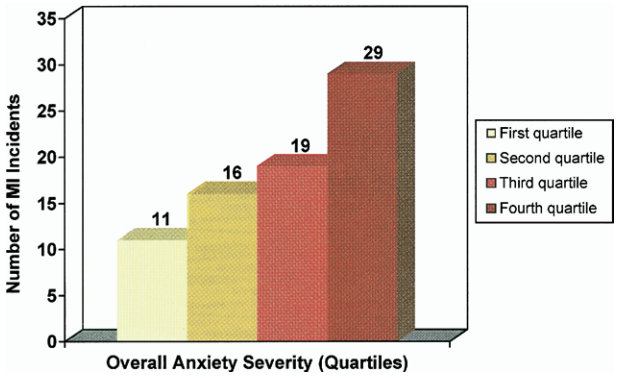

Figure 1 Number of MI Incidents at Different Anxiety Levels

Figure shows number of myocardial infarction (MI) incidents among participants in each anxiety quartile (chi-square = 9.21; degrees of freedom = 3; $p < 0.05$).

were 11, 16, 19, and 29 MIs in each anxiety group from the lowest to highest quartile (chi-square = 9.21; degrees of freedom = 3; $p < 0.05$) (Fig. 1), demonstrating that men in higher anxiety quartiles manifested more incidents.

Discussion

This study demonstrated that anxiety characteristics independently and prospectively predicted MI incidence over an average of 12.4 years among older men after adjusting for sociodemographic background, biomedical variables, health behaviors, and even other psychosocial factors. The results suggest that moderately elevated anxiety is associated with a modest risk of MI and severe anxiety represents an MI risk that may warrant clinical attention. The findings indicate that anxiety not only represents an independent, prospective, and unique risk factor for MI, but may also explain the associations between MI and other psychosocial risk factors observed in earlier studies.

Several mechanisms may account for these findings. First, evidence from animal (38), epidemiologic (39), and clinical studies (40) suggests that chronic and acute stressors may give rise to coronary events or predict clinical outcomes (41). It is plausible that highly anxious individuals are more likely to experience elevated levels of stress repeatedly and chronically, thereby exposing them to higher risk for MI. A number of pathophysiologic pathways, mostly implicating exaggerated stress reactivity, have been speculated to explain how psychosocial factors may confer higher risk for MI. These include dysregulated hypothalamic-pituitary-adrenal axis and autonomic nervous system, excessive inflammatory process, and disturbed platelet activation (7,42). Although a larger body of evidence has focused on the association between depression and markers of inflammation and coagulation (43,44), a recent study shows that anxiety is related to these markers even after controlling for depression (45). In addition, individuals with anxiety disorders show relative reductions in cardiac vagal tone and heart rate variability (46), suggesting that impaired autonomic balance in heart rate regulation may be implicated. Considering the relatively stronger effect of anxiety in predicting MI onset, it would be important to understand whether anxiety differentially promotes these pathogenic mechanisms.

Although the present study found that anxiety characteristics were the strongest predictor of MI among psychologic variables, we would not advocate abandoning assessment of depression, hostility, or other related characteristics. Psychologic factors are inter-related and may contribute to one another in a reciprocal fashion. Recognizing multiple psychosocial risk components may better inform risk assessment and management for people at higher risk for MI.

Furthermore, the anxiety measures assessed more ingrained personality tendencies that are likely to give rise to situational anxiety symptoms or chronic anxiety disorders. Interestingly, type D personality, comprising social inhibition and negative affectivity, has been associated with poor prognosis of heart disease (14). It appears that interpersonal and social difficulties constitute a major source of distress that may exacerbate progression of heart disease in either initially healthy population or people with established coronary disease.

It is worth noting that, consistent with earlier literature (47), being married was a protective factor against CAD onset. We speculated that the salutary effect of marriage was mainly mediated by its association with social support. The dichotomized marital status, however, is a relatively crude proxy for social support. More research is needed to scrutinize how marriage quality may contribute to better cardiovascular health.

Several limitations of the study should be considered, which also point to directions for future research. The sample, consisting of primarily healthy older Caucasian men, may limit the generalizability of the findings to women, ethnic minorities, or clinical populations. Furthermore, we were not able to examine promising psychophysiologic mechanisms discussed previously which might explain the observed associations. Future studies addressing these issues would promote our understanding of the role of anxiety in the development of heart disease.

Reprint requests and correspondence: Dr. Biing-Jiun Shen, Assistant Professor, Department of Psychology, University of Southern California, 3620 South McClintock Avenue, Los Angeles, California 90089-1061. E-mail: bjshen@usc.edu.

REFERENCES

1. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 1999;99:2192–217.
2. Hemingway H, Marmot M. Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. BMJ 1999;318:1460–7.

3. Kubzansky LD, Kawachi I, Spiro A 3rd, Weiss ST, Vokonas PS, Sparrow D. Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the Normative Aging Study. Circulation 1997;95:818–24.
4. Kawachi I, Sparrow D, Spiro A 3rd, Vokonas P, Weiss ST. A prospective study of anger and coronary heart disease. The Normative Aging Study. Circulation 1996;94:2090–5.
5. Kawachi I, Sparrow D, Kubzansky LD, Spiro A 3rd, Vokonas PS, Weiss ST. Prospective study of a self-report type A scale and risk of coronary heart disease: test of the MMPI-2 Type A scale. Circulation 1998;98:405–12.
6. Niaura R, Todaro JF, Stroud L, Spiro A 3rd, Ward KD, Weiss S. Hostility, the metabolic syndrome, and incident coronary heart disease. Health Psychol 2002;21:588–93.
7. Suls J, Bunde J. Anger, anxiety, and depression as risk factors for cardiovascular disease: the problems and implications of overlapping affective dispositions. Psychol Bull 2005;131:260–300.
8. Smith TW, Ruiz JM. Psychosocial influences on the development and course of coronary heart disease: current status and implications for research and practice. J Consult Clin Psychol 2002;70:548–68.
9. Todaro JF, Shen BJ, Niaura R, Spiro A 3rd, Ward KD. Effect of negative emotions on frequency of coronary heart disease (the Normative Aging Study). Am J Cardiol 2003;92:901–6.
10. Kubzansky LD, Kawachi I. Going to the heart of the matter: do negative emotions cause coronary heart disease? J Psychosom Res 2000;48:323–37.
11. Mineka S, Watson D, Clark LA. Comorbidity of anxiety and unipolar mood disorders. Annu Rev Psychol 1998;49:377–412.
12. Kawachi I, Colditz GA, Ascherio A, et al. Prospective study of phobic anxiety and risk of coronary heart disease in men. Circulation 1994; 89:1992–7.
13. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Symptoms of anxiety and risk of coronary heart disease. The Normative Aging Study. Circulation 1994;90:2225–9.
14. Denollet J. DS14: standard assessment of negative affectivity, social inhibition, and type D personality. Psychosom Med 2005;67:89–97.
15. Barger SD, Sydeman SJ. Does generalized anxiety disorder predict coronary heart disease risk factors independently of major depressive disorder? J Affect Disord 2005;88:87–91.
16. Hippisley-Cox J, Fielding K, Pringle M. Depression as a risk factor for ischaemic heart disease in men: population based case-control study. BMJ 1998;316:1714–9.
17. Allgulander C, Lavori PW. Excess mortality among 3302 patients with "pure" anxiety neurosis. Arch Gen Psychiatry 1991;48:599–602.
18. Kubzansky LD, Cole SR, Kawachi I, Vokonas P, Sparrow D. Shared and unique contributions of anger, anxiety, and depression to coronary heart disease: a prospective study in the Normative Aging Study. Ann Behav Med 2006;31:21–9.
19. Bossé R, Ekerdt DJ, Silbert JE. The Veterans Administration Normative Aging Study. New York, NY: Praeger, 1984.
20. Dahlstrom WG, Welsh GS. An MMPI Handbook: A Guide to Use in Clinical Practice and Research. Minneapolis, MN: University of Minnesota Press, 1960.
21. Hathaway SR, McKinley JC. Minnesota Multiphasic Personality Inventory-2. Manual for Administration and Scoring. Minneapolis, MN: University of Minnesota Press, 1989.
22. Dahlstrom WG, Welsh GS, Dahlstrom LE. An MMPI Handbook, Vol. II: Research Applications, Revised Edition. Minneapolis, MN: University of Minnesota Press, 1975.
23. Greene RL. The MMPI: An Interpretive Manual. New York, NY: Grune & Stratton, 1980.
24. Koszycki D, Zacharko RM, Bradwejn J. Influence of personality on behavioral response to cholecystokinin-tetrapeptide in patients with panic disorder. Psychiatry Res 1996;62:131–8.
25. Wiggins JS, Goldberg LR, Applebaum M. MMPI content scales: interpretative norms and correlations with other scales. J Consult Clin Psychol 1971;37:403–10.
26. Levitt EE, Gotts EE. The Clinical Application of the MMPI Special Scales. Hillsdale, NJ: Lawrence Erlbaum Associates, 1995.
27. Lachar D, Alexander RS. Veridicality of self-report: replicated correlates of the Wiggins MMPI content scales. J Consult Clin Psychol 1978;46:1349–56.
28. Taylor JA. A personality scale of manifest anxiety. J Abnorm Soc Psychol 1953;48:285–90.
29. Byrne DE. An Introduction to Personality: Research, Theory, and Applications. Englewood Cliffs, NJ: Prentice-Hall, 1974.
30. Graham JR. The MMPI: A Practical Guide. New York, NY: Oxford University Press, 1977.
31. Cook WW, Medley DM. Proposed hostility and pharisaic-virtue scales from the MMPI. J Appl Psychol 1954;38:414–8.
32. Graham JR. MMPI-2: Assessing Personality and Psychopathology. New York, NY: Oxford University Press, 2006.
33. Sesso HD, Kawachi I, Vokonas PS, Sparrow D. Depression and the risk of coronary heart disease in the Normative Aging Study. Am J Cardiol 1998;82:851–6.
34. Welsh GS. MMPI profiles and factor scales A and R. J Clin Psychol 1965;21:43–7.
35. Rimm EB, Giovannucci EL, Willett WC, et al. Prospective study of alcohol consumption and risk of coronary disease in men. Lancet 1991;338:464–8.
36. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
37. Shurtleff D. Some characteristics related to the incidence of cardiovascular disease and death: Framingham Study, 18-year follow-up. PHS publication no. 1693. 74. Bethesda, MD: U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, 1974.
38. Kaplan JR, Manuck SB. Status, stress, and atherosclerosis: the role of environment and individual behavior. Ann N Y Acad Sci 1999;896: 145–61.
39. Kuper H, Marmot M. Job strain, job demands, decision latitude, and risk of coronary heart disease within the Whitehall II study. J Epidemiol Community Health 2003;57:147–53.
40. Gullette EC, Blumenthal JA, Babyak M, et al. Effects of mental stress on myocardial ischemia during daily life. JAMA 1997;277:1521–6.
41. Sheps DS, McMahon RP, Becker L, et al. Mental stress-induced ischemia and all-cause mortality in patients with coronary artery disease: results from the Psychophysiological Investigations of Myocardial Ischemia study. Circulation 2002;105:1780–4.
42. Krantz DS, McCeney MK. Effects of psychological and social factors on organic disease: a critical assessment of research on coronary heart disease. Annu Rev Psychol 2002;53:341–69.
43. Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA. Clinical depression and inflammatory risk markers for coronary heart disease. Am J Cardiol 2002;90:1279–83.
44. Suarez EC, Krishnan RR, Lewis JG. The relation of severity of depressive symptoms to monocyte-associated proinflammatory cytokines and chemokines in apparently healthy men. Psychosom Med 2003;65:362–8.
45. Pitsavos C, Panagiotakos DB, Papageorgiou C, Tsetsekou E, Soldatos C, Stefanadis C. Anxiety in relation to inflammation and coagulation markers, among healthy adults: the ATTICA study. Atherosclerosis 2006;185:320–6.
46. Thayer JF, Friedman BH, Borkovec TD. Autonomic characteristics of generalized anxiety disorder and worry. Biol Psychiatry 1996;39: 255–66.
47. House JS, Landis KR, Umberson D. Social relationships and health. Science 1988;241:540–5.