ORIGINAL ARTICLE

Prospective Study of Posttraumatic Stress Disorder Symptoms and Coronary Heart Disease in the Normative Aging Study

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Context: Various correlates of posttraumatic stress disorder (PTSD), such as high levels of sympathetic activation and hypothalamic-pituitary-adrenal axis dysregulation, have been linked to arterial damage and coronary heart disease (CHD) risk. While psychological disturbance is frequently found among patients with cardiac disease, whether psychological problems precede or occur as a result of having a potentially fatal disease is not clear. To our knowledge, no prospective studies to date have evaluated whether PTSD is associated with increased risk of CHD.

Objective: To test the hypothesis that high levels of PTSD symptoms may increase CHD risk, using 2 different measures of PTSD.

Design: Prospective cohort study.

Setting: Community-dwelling men from the Greater Boston, Mass, area who served in the military.

Participants: Data are from the Veterans Affairs Normative Aging Study. Men who completed either the Mississippi Scale for Combat-Related PTSD in 1990 (n=1002) or the Keane PTSD scale in 1986 (n=944) were included in the study.

Main Outcome Measure: Incident CHD occurring during follow-up through May 2001.

Results: Levels of PTSD symptoms in this cohort were low to moderate. Men with preexisting CHD at baseline were excluded, and PTSD was measured with the Mississippi Scale for Combat-Related PTSD. For each SD increase in symptom level, men had age-adjusted relative risks of 1.26 (95% confidence interval, 1.05-1.51) for nonfatal myocardial infarction and fatal CHD combined and 1.21 (95% confidence interval, 1.05-1.41) for all of the CHD outcomes combined (nonfatal myocardial infarction, fatal CHD, and angina). Findings were replicated using the Keane PTSD scale and somewhat strengthened after controlling for levels of depressive symptoms.

Conclusions: To our knowledge, this is the first study to demonstrate a prospective association between PTSD symptoms and CHD even after controlling for depressive symptoms. These results suggest that a higher level of PTSD symptoms may increase the risk of incident CHD in older men.

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A LINK BETWEEN STRESS AND coronary heart disease (CHD) has long been hypothesized. Individuals who experience extraordinary trauma are at risk for developing posttraumatic stress disorder (PTSD), a disorder that reflects dysregulation of the stress response system.[1,2] Numerous studies[3-6] have found that cardiovascular disease and its risk factors are more prevalent among individuals with PTSD. However, to our knowledge, no prospective studies to date have examined PTSD in relation to CHD risk. Thus, it is as yet unknown whether PTSD and CHD share common pathways or whether PTSD itself may be a risk factor for CHD.

In a recent study[6] of outpatients with stable CHD, 29% were found to also have PTSD. Another study[5] examined electrocardiographic results among 4462 nonhospitalized male veterans, 54 of whom reported current PTSD. After controlling for numerous potential risk factors, men with PTSD were more likely to have atrioventricular conduction defects (odds ratio, 2.81; 95% confidence interval [CI], 1.03-7.66) and infarctions (odds ratio, 4.44; 95% CI, 1.20-16.43). Other work[3] found elevated concentrations of serum lipids and a higher arteriosclerosis index among veterans with combat-related PTSD compared with patients with major depressive disorder.

Investigators have also examined whether adverse experiences increase the risk of heart disease and whether this association is explained by psychological factors. Much of this work has focused on vet-

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erans. For example, several studies[7,8] have found that prisoners of war (POWs) are at higher risk for multiple health problems later in life, including CHD, when compared with non-POW veterans or with similarly aged men in the general population. However, effects of being a POW on CHD may be difficult to interpret, as POWs are subjected to physical as well as psychological harm (eg, torture and weight loss due to malnutrition). One recent study[9] did report an increased risk of CHD only among POWs with a history of PTSD. Other studies[4,10] have consistently found increased levels of physical symptoms and cardiovascular disease risk factors among men who experienced combat- and noncombat-related trauma compared with those who did not report exposure to trauma. Recent work[11,12] has suggested that PTSD rather than combat (or trauma) exposure alone may serve as a mediating factor between trauma and the risk of adverse health outcomes.

Research on civilian samples has shown similar findings. In a study[13] of effects of adverse childhood experiences (including abuse), individuals with numerous adverse childhood experiences were at greater risk of ischemic heart disease (odds ratio, 3.6; 95% CI, 2.4-5.3). This effect was explained more completely by psychological risk factors than by traditional risk factors. There is accumulating evidence that chronic stress in various forms, including caregiving strain, marital stress, and work stress, may increase the risk of CHD.[14] Taken together, research to date suggests that there may be a role for prolonged or chronic stress in the development of CHD.

Posttraumatic stress disorder has been identified as a marker of extreme distress in response to a potentially traumatic event, and it may also be indicative of a chronic stress reaction. It has long been known that exposure to severely traumatic events can lead to PTSD, but it is less clear whether PTSD has pathophysiological or atherogenic effects. Posttraumatic stress disorder is defined by the combination of exposure to a traumatic event (eg, combat) and the occurrence of 3 types of symptoms: (1) reexperiencing the traumatic event, (2) avoidance of traumatic reminders and emotional numbing, and (3) hyperarousal.[15] Diagnosis is often difficult because PTSD symptoms overlap with those of anxiety and affective disorders, both of which are generally more recognized and have been linked to CHD.[16] Self-report symptom measures may be more subject to misclassification than diagnoses derived from clinical interviews, and they often pick up general dysphoria as well as symptoms of PTSD.[17,18] However, PTSD differs in important ways from depression and anxiety. Depressive and anxiety disorders are defined by chronic or recurring symptoms occurring over an extended period, which may or may not arise in response to a discrete event. Posttraumatic stress disorder is defined by the long-term sequelae (symptom occurrence) of an acute stress exposure. The time course of PTSD can follow 1 of several patterns, where high levels of symptoms after traumatic exposure are followed by recovery, chronic symptoms persist over time, or symptoms are relapsing-remitting.[19] It is unclear what duration or chronicity of PTSD is necessary to initiate pathophysiological processes. Effects of the different patterns of PTSD will need to be determined and may depend on the toxicity of PTSD symptoms and the reversibility of their effects. In relation to CHD, effects of PTSD are likely to be most comparable to those of chronic stress and distress, particularly when PTSD follows a pattern of persisting or recurring symptoms over time.

In the present study, we provide a prospective test of the hypothesis that PTSD symptoms are related to the risk of developing CHD. Data are from the Normative Aging Study (NAS), an ongoing cohort of older community-dwelling men, most of whom are veterans. Other work[10,20] in this sample has considered the relationship between PTSD symptoms and physical symptoms as well as physician-diagnosed medical disorders. Findings from these studies are suggestive, but the studies did not directly test an association between PTSD symptoms and CHD incidence.

Given concerns that self-report measures of PTSD may overassess the depression component of PTSD and because other work[21] has identified depression as a risk factor for CHD, some investigators have suggested that any apparent PTSD-CHD association is largely due to depression. A more rigorous test of whether PTSD is related to CHD onset can be conducted by controlling for effects of depression measured separately from PTSD. Consistent effects across different PTSD symptom measures after controlling for depressive symptoms would provide compelling evidence of a role for PTSD symptoms in the development of CHD. Because 2 different measures of PTSD symptoms administered at different times[22] as well as validated measures of depression are also available in the NAS, we test the hypothesis that PTSD symptoms are prospectively associated with CHD, using each PTSD symptom scale separately and when controlling for depression. Finally, we consider the consistency of effects across PTSD symptom measures administered at different times.

METHODS

The NAS is a longitudinal study of aging established by the Veterans Administration in 1961.[23] The cohort consists of 2280 community-dwelling men (primarily white) from the Greater Boston, Mass, area aged 21 to 80 years in 1961. Most (>90%) of the men are veterans. Volunteers were screened at entry according to health criteria and were free of any known chronic medical conditions at the start of follow-up.[23] The present study includes only men who served in the military. In addition, men with preexisting CHD or diabetes were excluded.

ASSESSMENT OF PTSD

All of the participants who completed the questionnaire and were included in this study were veterans who served in the military. In 1990, the Mississippi Scale for Combat-Related PTSD was mailed to all active cohort members (n=1778), and 1444 men responded (response rate, 81.2%). Of the 1444 men who responded, 1359 (94%) were veterans who served in the military and had complete and valid questionnaire data available. A total of 357 men with preexisting CHD (angina pectoris or history of myocardial infarction [MI]) or diabetes were excluded, resulting in a baseline population of 1002 men. Comparison of nonresponders with those who completed the Mississippi Scale for Combat-Related PTSD suggested that nonresponders were somewhat younger and healthier (lower body mass index and less likely to have ever smoked or to have a history of heart disease in the family). The mean (SD) age of this study population was 63.0 (7.4) years.

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The Mississippi Scale for Combat-Related PTSD is a 35-item Likert-style self-report scale with well-established validity and reliability designed to directly assess the domain of *DSM-III* PTSD symptoms and various associated features in combat veterans.[24] Scale scores reflect symptom severity, with higher scores representing greater severity. The measure has demonstrated good discriminant and convergent validity.[25] The measure has also demonstrated high test-retest reliability, with a sensitivity of 0.93 and specificity of 0.89 when compared with diagnosis determined using *DSM-III* criteria following extensive clinical evaluation.[24] In the current sample, the internal consistency reliability was satisfactory with $\alpha = 0.77$, with higher scores indicating higher levels of symptoms. Although the scale was developed with samples of Vietnam veterans, other studies have suggested that it performs well as a measure of PTSD in older veterans and in this sample.[20,26] A clinical cut point of 89 or higher has been recommended for determining a PTSD diagnosis in male veterans.[27]

One of the first cohorts in which the revised Minnesota Multiphasic Personality Inventory (MMPI-2) scale was used, the NAS cohort, provided data from which MMPI-2 scale norms were developed.[28] In 1986, the MMPI-2 scale was mailed out to all active cohort members (n=1881), and 1550 men responded (response rate, 82.4%). Complete and valid questionnaire data were available from 1472 (95%) of those who responded. Of these men, 1210 were veterans who served in the military. A total of 266 men with preexisting CHD or diabetes were excluded, resulting in a baseline study population of 944 men. Comparison of nonresponders with those who completed the MMPI-2 scale suggested that nonresponders were somewhat younger and healthier (lower levels of body mass index, diastolic blood pressure, and cholesterol and less likely to have ever smoked). The mean (SD) age of the study population was 59.6 (7.4) years.

The MMPI-2 scale contains 46 items that compose the Keane PTSD (MMPI-2 PK) scale.[29,30] It was empirically developed for the purpose of assessing symptoms and diagnosing PTSD, using a validation sample of 60 Vietnam veterans with PTSD and 60 veterans with other psychiatric disorders, plus a cross-validation sample of 40 additional patients per group. Following prior work, T scores (mean [SD], 50 [10]) were created, with higher scores indicating more symptoms. Other research has suggested that the measure has good validity and reliability[29] as well as reasonably good sensitivity and selectivity.[31] In the current sample, the internal consistency reliability was high, with $\alpha = 0.87$. A clinical cut point of 28 for a raw score has been recommended, and we used the corresponding T score of 83 as a cut point for clinical diagnosis in this sample.[32]

The Mississippi Scale for Combat-Related PTSD and the MMPI-2 PK scale were among the first self-report measures developed to assess PTSD symptoms. The MMPI-2 PK scale was moderately correlated with the Mississippi Scale for Combat-Related PTSD ($r = 0.53$; $P < .001$). Using the recommended cut points, 9 individuals met criteria for PTSD diagnosis using the Mississippi Scale for Combat-Related PTSD and 5 individuals met criteria using the MMPI-2 PK scale. In the 2 sets of individuals, 10 individuals endorsed symptoms on both scales. Five individuals met criteria only on the Mississippi Scale for Combat-Related PTSD and 2 met criteria on both scales.

MEASUREMENT OF OTHER CARDIOVASCULAR RISK FACTORS

Every 3 to 5 years, NAS participants are assessed by physical examination, updating of medical history, and measurement of various biochemical values (including the serum cholesterol level). Cigarette smoking status (current, former, or never) is ascertained by a trained interviewer. Current smokers are defined as men who smoke 1 cigarette or more per day. Weight and height are measured with participants wearing only socks and underpants, and body mass index is calculated (as the weight in kilograms divided by the height in meters squared). Blood pressure is measured by an examining physician using a standard mercury sphygmomanometer with a 14-cm cuff. With the subject seated, systolic and fifth-phase diastolic blood pressures are measured in each arm to the nearest 2 mm Hg. The average systolic and diastolic blood pressures in both arms were used for analysis. Information on family history of heart disease and educational attainment is obtained via self-report.

Two measures of depression administered in the same time frame as each of the PTSD measures are also available. In 1990, depressive symptoms were assessed using the Center for Epidemiological Studies Depression Scale.[33] The Center for Epidemiological Studies Depression Scale has demonstrated good reliability and validity and was correlated with the Mississippi Scale for Combat-Related PTSD in this sample ($r = 0.59$; $P < .001$). The depression subscale from the Symptom Checklist 90 scale is also considered to have good reliability and validity.[34] This measure was correlated with the MMPI-2 PK scale ($r = 0.62$; $P < .001$). Measures of all potential confounders were obtained either from a mailed questionnaire or from the examination closest to the time of each PTSD assessment.

ASSESSMENT OF MORBIDITY AND MORTALITY

This study included all of the confirmed CHD end points (angina pectoris, MI, and fatal CHD) that occurred between May 2001 and the return of either the 1986 or the 1990 survey, with a mean (SD) of 13.2 (3.5) or 9.8 (2.9) years of follow-up, respectively. Individuals were censored either at the time of developing a coronary event (or death) or at the time of their most recent follow-up visit.

Medical history was obtained from each participant at his regular follow-up visit every 3 to 5 years. Hospital records were obtained for every report of a possible CHD event and reviewed by a board-certified cardiologist (P.S.V.) who was blind to the patients' PTSD symptom scores. Diagnostic categories of CHD included angina pectoris, nonfatal MI, and total CHD (nonfatal MI plus fatal CHD). Criteria for MI and angina pectoris were those used in the Framingham Study.[35] Myocardial infarction was diagnosed only when documented by unequivocal electrocardiographic changes (ie, pathological Q waves), by a diagnostic elevation of serum enzyme (serum glutamic-oxaloacetic transaminase and lactic dehydrogenase) levels together with chest discomfort consistent with MI, or by autopsy. Diagnosis of angina pectoris was made by a board-certified cardiologist (P.S.V.) based on medical history and physical examination using Framingham Study criteria.[35] Angina was diagnosed when a subject reported recurrent chest discomfort that lasted up to 15 minutes, was distinctly related to exertion or excitement, and was relieved by rest or nitroglycerin.[35] If an individual developed more than 1 event (eg, angina, then nonfatal MI), he was censored at the time of the earlier event.

Death from CHD was confirmed when a death certificate (coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification*[36]) indicated an underlying cause of death coded to rubric 410-414. Medical records for each CHD death were reviewed by a board-certified cardiologist (P.S.V.) to ensure accurate coding.

DATA ANALYSIS

We ran Cox proportional hazards models using SAS software[37] version 6.12 (SAS Institute, Cary, NC) to estimate the

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Table 1. Distribution of Coronary Risk Factors in the Sample

Risk Factor	1986 MMPI-2 PK Scale	1990 Mississippi Scale for Combat-Related PTSD
Participants, No.	944	1002
Age, mean (SD), y	59.6 (7.4)	63.0 (7.4)
Current smokers, No. (%)	207 (21.9)	158 (15.8)
Former smokers, No. (%)	447 (44.9)	535 (53.4)
Systolic blood pressure, mean (SD), mm Hg	127.6 (15.3)	127.8 (16.4)
Diastolic blood pressure, mean (SD), mm Hg	78.2 (8.5)	78.3 (8.9)
Serum cholesterol level, mean (SD), mg/dL	246.7 (46.4)	233.4 (42.9)
Body mass index, mean (SD)*	26.5 (3.1)	26.6 (3.2)
Family history of CHD, No. (%)	209 (22.1)	230 (22.9)
Participants who consume ≥2 drinks of alcohol, No. (%)	246 (26.1)	235 (23.5)
Participants who attained education beyond high school, No. (%)	563 (59.6)	650 (64.5)

Abbreviations: CHD, coronary heart disease; MMPI-2 PK, revised Minnesota Multiphasic Personality Inventory, Keane Posttraumatic Stress Disorder; PTSD, posttraumatic stress disorder.

SI conversion factor: To convert cholesterol to micromoles per liter, multiply by 0.2586.

*Body mass index is calculated as the weight in kilograms divided by the height in meters squared.

relative risks (RRs) of CHD according to the level of PTSD, controlling for the following factors: age (years); body mass index; smoking status (never, former, or current); systolic and diastolic blood pressures (millimeters of mercury); serum cholesterol level (milligrams per deciliter); family history of CHD (yes or no); whether participants consumed 2 or more drinks of alcohol per day (yes or no); and whether participants had completed education beyond high school (yes or no). We compare the probability of developing CHD across individuals with higher vs lower scores on PTSD symptom measures. Parameter estimates derived from these analyses represent the effect of a 1-SD change in PTSD symptoms on CHD risk. Age- and multivariate-adjusted analyses are presented to illustrate the role of potential confounders.

Few individuals meet the criteria for PTSD on either scale. As a result, we expect to have greater power when examining PTSD symptoms using a continuous measure as opposed to a dichotomous measure. However, to examine whether individuals with higher scores were at greater risk, we dichotomized PTSD scores according to whether individuals scored in the highest 10th percentile, and we examined effects on CHD.

RESULTS

Table 1 describes the sample for each analysis. The mean (SD) Mississippi Scale for Combat-Related PTSD score among 1002 men was 57 (9) (range, 36-140). Scores were skewed toward lower levels of symptoms, with 75% of individuals scoring 63 or lower and only 1% scoring higher than the clinical cut point for PTSD. We examined the association of coronary risk factors with PTSD symptom scores. Correlation analyses found that the Mississippi Scale for Combat-Related PTSD scores were unrelated to systolic blood pressure, body mass index, or cholesterol level. Older age ($r=0.12$; $P<.001$) and lower diastolic blood pressure ($r=-0.06$; $P=.04$) were modestly correlated with the Mississippi Scale for Combat-Related PTSD score. The t test analyses suggested no difference in PTSD scores between those who had more than 1 alcoholic drink per day and those who did not. However, men with heart disease in the family had higher Mississippi Scale for Combat-Related PTSD scores relative to those without a family history of heart disease (mean [SD], 59 [11] vs 57 [9], respectively; $t_{322}=-3.03$; $P=.003$), as did those with less than a high school education relative to those with more than a high school education (mean [SD], 59 [11] vs 56 [9], respectively; $t_{639}=4.24$; $P<.001$). Analysis of variance indicated that men who were current smokers had somewhat higher Mississippi Scale for Combat-Related PTSD scores (mean [SD], 59 [11]) compared with men who were former or never smokers (mean [SD], 57 [9] and 57 [10], respectively), and these differences were significant ($F_{2,979}=3.94$; $P=.02$). Findings were similar with the MMPI-2 PK scale. Mean (SD) scores were 49 (7.8) (range, 38-92), and like the Mississippi Scale for Combat-Related PTSD scores, they were skewed toward lower levels of symptoms. The pattern of associations between coronary risk factors and PTSD scores assessed with the MMPI-2 PK scale was similar to findings using the Mississippi Scale for Combat-Related PTSD. However, there was no association between the MMPI-2 PK scale scores and either diastolic blood pressure or family history of heart disease. We adjusted for all of the potential confounders described here in the proportional hazards analyses.

In analyses with the Mississippi Scale for Combat-Related PTSD, of the 1002 men in the study sample, 116 developed CHD over the follow-up period. There were 36 cases of incident nonfatal MI, 27 cases of fatal CHD, and 53 cases of angina pectoris. Men with a higher score were at somewhat elevated risk for incident CHD. For each SD increase in the score, the RR of total CHD was 1.26 (95% CI, 1.05-1.51; $P=.01$), and this relationship was marginally significant after controlling for standard coronary risk factors (**Table 2**). There was a positive but nonsignificant association between PTSD score and elevated risk of angina (age-adjusted RR=1.16; 95% CI, 0.93-1.46; $P=.19$). When all of the end points were combined (nonfatal MI, fatal CHD, and angina pectoris), each SD increase in the Mississippi Scale for Combat-Related PTSD score was associated with an approximately 18% increased risk of combined angina and total CHD after controlling for known coronary risk factors. Controlling for depressive symptoms generally resulted in maintaining or strengthening the effect of PTSD symptoms on most CHD outcomes (Table 2), and there was little evidence of an independent association of depressive symptoms with CHD outcomes in these models (with the exception of angina). When depressive symptoms were included, the association between the Mississippi Scale for Combat-Related PTSD score and angina was significantly attenuated ($P=.80$).

Analyses with the MMPI-2 PK scale were strikingly consistent with those conducted using the Mississippi Scale for Combat-Related PTSD measure, even though the MMPI-2 PK scale score was obtained 5 years earlier.

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Table 2. Age-Adjusted and Multivariate Relative Risks of a 1-SD Increase in the Mississippi Scale for Combat-Related PTSD Score

Outcome	Age-Adjusted Analysis	Adjusted Multivariate Analysis*	Analysis Adjusted for Age and CES-D Score	Adjusted Multivariate Analysis With CES-D Score*
Angina pectoris				
Cases, No.	53	52	53	52
RR (95% CI)	1.16 (0.93-1.46)	1.15 (0.90-1.48)	1.04 (0.77-1.41)	1.01 (0.74-1.37)
Nonfatal MI				
Cases, No.	36	35	36	35
RR (95% CI)	1.23 (0.94-1.59)	1.18 (0.92-1.50)	1.39 (0.98-1.98)†	1.30 (0.92-1.84)
Fatal CHD				
Cases, No.	27	25	26	24
RR (95% CI)	1.30 (1.01-1.67)‡	1.21 (0.92-1.61)	1.29 (0.89-1.88)	1.11 (0.75-1.64)
Total CHD§				
Cases, No.	63	60	62	59
RR (95% CI)	1.26 (1.05-1.51)‡	1.19 (0.98-1.43)†	1.34 (1.04-1.74)‡	1.21 (0.93-1.57)
Total CHD with angina§				
Cases, No.	116	112	115	111
RR (95% CI)	1.21 (1.05-1.41)‖	1.18 (1.01-1.37)‡	1.20 (0.98-1.46)†	1.12 (0.92-1.36)

Abbreviations: CES-D, Center for Epidemiological Studies Depression Scale; CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; RR, relative risk.

*A small number of cases (1-5 depending on outcome) were dropped in multivariate analyses because of missing information on covariates. Unless otherwise stated, all of the multivariate analyses are adjusted for age, smoking status (never, former, or current), systolic and diastolic blood pressures (millimeters of mercury), serum total cholesterol level (milligrams per deciliter), body mass index (calculated as weight in kilograms divided by height in meters squared), family history of CHD (yes or no), educational attainment, and alcohol intake (≥2 drinks per day).

†$P<.10$.

‡$P<.05$.

§Nonfatal MI and fatal CHD.

‖$P<.01$.

Table 3. Age-Adjusted and Multivariate Relative Risks of a 1-SD Increase in the Keane Posttraumatic Stress Disorder Scale Score

Outcome	Age-Adjusted Analysis	Adjusted Multivariate Analysis*	Analysis Adjusted for Age and SCL-90 Scale Score	Adjusted Multivariate Analysis With SCL-90 Scale Score*
Angina pectoris				
Cases, No.	63	61	62	60
RR (95% CI)	1.23 (1.01-1.50)†	1.20 (0.97-1.49)‡	0.90 (0.66-1.22)	0.93 (0.67-1.29)
Nonfatal MI				
Cases, No.	52	51	51	51
RR (95% CI)	1.20 (0.95-1.51)	1.22 (0.97-1.55)‡	1.30 (0.94-1.79)	1.26 (0.90-1.75)
Fatal CHD				
Cases, No.	24	23	24	23
RR (95% CI)	1.13 (0.78-1.64)	1.19 (0.81-1.73)	1.58 (0.98-2.54)‡	1.78 (1.08-2.93)†
Total CHD§				
Cases, No.	76	74	75	74
RR (95% CI)	1.18 (0.97-1.43)‡	1.21 (0.99-1.48)‡	1.36 (1.04-1.77)†	1.35 (1.03-1.78)†
Total CHD with angina§				
Cases, No.	139	135	137	134
RR (95% CI)	1.19 (1.04-1.37)†	1.19 (1.03-1.38)†	1.11 (0.90-1.37)	1.14 (0.92-1.41)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; RR, relative risk; SCL-90, Symptom Checklist 90.

*A small number of cases (1-4 depending on outcome) were dropped in multivariate analyses because of missing information on covariates. Unless otherwise stated, all of the multivariate analyses are adjusted for age, smoking status (never, former, or current), systolic and diastolic blood pressures (millimeters of mercury), serum total cholesterol level (milligrams per deciliter), body mass index (calculated as weight in kilograms divided by height in meters squared), family history of CHD (yes or no), educational attainment, and alcohol intake (≥2 drinks per day).

†$P<.05$

‡$P<.10$.

§Nonfatal MI and fatal CHD.

For analyses with the MMPI-2 PK scale, of the 944 men, 139 developed CHD over the follow-up period. There were 52 cases of incident nonfatal MI, 24 cases of fatal CHD, and 63 cases of angina pectoris. Men with a higher score were at a somewhat increased risk for incident CHD. For each SD increase in score, men had an age-adjusted RR of total CHD of 1.18 (95% CI, 0.97-1.43; $P=.10$), and this relationship was significantly strengthened after controlling for known coronary risk factors (**Table 3**). There was a positive association between the MMPI-2 PK scale score and an elevated risk of angina (age-adjusted RR=1.23; 95% CI, 1.01-1.50; $P=.04$). When all of the end

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points were combined, each SD increase in the level of the MMPI-2 PK scale score was associated with an approximately 20% increased risk of combined angina and total CHD after controlling for known coronary risk factors. Controlling for depressive symptoms resulted in maintaining or strengthening the effect of MMPI-2 PK scale PTSD symptoms on most CHD outcomes, with the exception of angina.

We examined whether either measure of PTSD symptoms was associated with mortality. Neither PTSD measure was significantly associated with all-cause mortality or with mortality after excluding deaths due to CHD. These findings were unchanged when controlling for depressive symptoms. Finally, we examined the risk of CHD for individuals scoring in the highest 10th percentile relative to those with lower scores on either scale. The findings are highly consistent with those derived from the continuous PTSD measures. However, with the use of this dichotomous variable, the levels of significance are marginal.

COMMENT

Investigators have frequently speculated that stress may increase the risk for CHD and other cardiovascular problems. To our knowledge, the present study provides the first prospective test of the hypothesis that the level of PTSD symptoms is associated with an increased risk of incident CHD. Effects were most clearly apparent in relation to the hard outcomes of nonfatal MI and fatal CHD. Somewhat surprisingly, effects were less strong for angina, particularly after controlling for depressive symptoms. This pattern of effects suggests that individuals with higher levels of PTSD symptoms are not simply prone to reporting higher levels of chest pain or other physical symptoms but may well be at higher risk for developing CHD. It is also striking that the results are maintained after controlling for depressive symptoms and similar when 2 different measures of PTSD symptoms are used. Such findings strengthen the validity of the results.

Despite their consistency, effects of PTSD symptoms on the risk of CHD appear to be somewhat modest. This may reflect the size of the true effect. However, we note that power is somewhat limited with only a modest number of cases (eg, quite small numbers for fatal CHD) and low levels of PTSD symptoms in this cohort. For example, mean symptom levels were more than 2 SDs below the clinical cutoff score on the Mississippi Scale for Combat-Related PTSD; even among those in the highest 10th percentile, many have scores that are well below the PTSD criteria cut points. Findings in this study may suggest a dose-response relationship between PTSD symptoms and CHD, as for each SD increase in symptoms, there was a significant increase in the risk of developing CHD. If effects of symptoms are cumulative, with more symptoms conferring increased risk, then these results may be viewed as conservative. We might expect individuals with clinically relevant levels of PTSD symptoms to be at an even greater risk for developing CHD.

This work is consistent with a model of prolonged stress reaction that suggests impaired adaptation and increased wear and tear on the body, which may ultimately lead to atherosclerosis and cardiovascular system damage.[38] Although the biological mechanisms by which PTSD may influence CHD have yet to be determined, a number of pathways are possible. Posttraumatic stress disorder has been associated with numerous health-related behaviors that are themselves considered risk factors for CHD. For example, studies[39-46] have found PTSD to be associated with a greater likelihood of smoking and alcohol consumption. In fact, our data suggest that men with higher levels of PTSD symptoms were more likely to smoke, report a family history of CHD, and have lower levels of education. A family history of CHD may suggest a genetic predisposition, learned behaviors that are deleterious for cardiovascular health, or both. However, we controlled for these behaviors and predispositions, and findings were largely maintained. Furthermore, we note that the levels of PTSD symptoms among those individuals who smoke, have a family history of CHD, or have lower levels of education are less than a third of an SD above PTSD scores of individuals without these risk factors, making it unlikely that these factors could fully account for the observed relationships between PTSD symptoms and CHD risk. However, data on other relevant health-related variables (eg, exercise frequency) were not available for most participants, and further work is needed to more fully explore whether such behaviors can help to explain a relationship between PTSD and CHD.

Other work has considered the neuroendocrinology of PTSD and suggested that it is characterized in many adults by enhanced negative feedback sensitivity of glucocorticoid receptors in the stress response system and lower-than-normal urinary and plasma cortisol levels. Exaggerated catecholamine responses to trauma-related stimuli have also been found in adult patients with PTSD.[1] Catecholamine release may lead to injury of the intimal endothelium of the coronary arteries by hemodynamic and/or biochemical processes and may also encourage the release of fatty acids above levels needed for metabolic requirements. These processes may eventually cause or exacerbate endothelial damage and promote the development of atherosclerosis, especially near bifurcations in major arteries.[47,48] Animal research has also demonstrated that stress and emotional arousal may aggravate atherosclerosis by mechanisms associated with flow-related arterial injury.[49]

Studies of psychosocial risk factors for CHD often raise methodological concerns.[50,51] Strengths of the present study include the use of an objectively determined and verified outcome and information on a range of potential confounders. Given other research that has suggested that psychosocial factors may have their strongest effects on CHD in younger populations,[52] it is possible that the effects of PTSD symptoms were modest partly because of the older age of the sample. The findings of the present study do pertain largely to older white men who served in the military; thus, they cannot be generalized to women, nonwhite populations, or civilians. However, the findings are consistent with other work[14] that has found a link between CHD and other forms of mood dysregulation and prolonged stress in both men and women. Another limitation of our findings relates to our

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assessment of PTSD symptoms, which relies on self-report scales rather than on clinician-administered diagnostic interviews and may therefore capture general dysphoria in addition to PTSD symptoms. Moreover, the chronicity and duration of PTSD symptoms were not assessed; addition of this information may increase the magnitude of the observed effects. We also did not specifically evaluate exposure to trauma, which could have occurred either in the military or as a civilian. However, the prospective nature of the data collection, with the assessment of PTSD occurring well before the ascertainment of the coronary outcomes, strengthens our findings and decreases the possibility of recall or information bias.

Although an association between PTSD and CHD has often been speculated, much of the evidence to date has been indirect, linking PTSD with coronary risk factors or with neuroendocrine processes known to be related to cardiovascular dysregulation. Findings from the present study are prospective, consistent across 2 different measures of PTSD symptoms, and based on objectively assessed CHD morbidity and mortality. These data suggest that prolonged stress and significant levels of PTSD symptoms may increase the risk for CHD in older male veterans. These results are provocative and suggest that exposure to trauma and prolonged stress not only may increase the risk for serious mental health problems but are also cardiotoxic.

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