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A Prospective Study of Posttraumatic Stress Disorder Symptoms and Coronary Heart Disease in Women

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Objective: Posttraumatic stress disorder (PTSD) reflects a prolonged stress reaction and dysregulation of the stress response system and is hypothesized to increase risk of developing coronary heart disease (CHD). No study has tested this hypothesis in women even though PTSD is more prevalent among women than men. This study aims to examine whether higher levels of PTSD symptoms are associated with increased risk of incident CHD among women. ***Design:*** A prospective study using data from women participating in the Baltimore cohort of the Epidemiologic Catchment Area study (n = 1059). Past year trauma and associated PTSD symptoms were assessed using the NIMH Diagnostic Interview Schedule. ***Main Outcome Measures:*** Incident CHD occurring during the 14-year follow-up through 1996. ***Results:*** Women with five or more symptoms were at over three times the risk of incident CHD compared with those with no symptoms (age-adjusted OR = 3.21, 95% CI: 1.29–7.98). Findings were maintained after controlling for standard coronary risk factors as well as depression or trait anxiety. ***Conclusion:*** PTSD symptoms may have damaging effects on physical health for civilian community-dwelling women, with high levels of PTSD symptoms associated with increased risk of CHD-related morbidity and mortality.

Keywords: coronary disease, posttraumatic stress disorder, depression, stress, women

Posttraumatic stress disorder (PTSD) reflects a prolonged stress reaction and dysregulation of the stress response system (Vanitallie, 2002). Evidence that dysregulated stress responses are associated with atherosclerosis and other cardiovascular system damage has suggested that PTSD may increase risk of developing coronary heart disease (CHD) (Rozanski, Blumenthal, Davidson, Saab, & Kubzansky, 2005). In a recent prospective study among older men who served in the military, risk of incident CHD was greater among men with higher versus lower levels of PTSD symptoms (Kubzansky, Koenen, Spiro, Vokonas, & Sparrow, 2007). Although PTSD is highly prevalent among war veterans (Hoge, Castro, Messer, McGurk, Cotting, & Koffman, 2004), it is also common in the general population and in fact is more prevalent among women (Kessler, Berglund, Demler, Jin, Merikangas, & Walters, 2005). Women's risk of developing PTSD is twice that of men; one in nine women will develop PTSD at some point in their lives (Kessler et al., 2005). Given that CHD is the leading cause of death among older women (Rosamond et al., 2007), the relation of PTSD and CHD incidence in women deserves closer attention. Though health-damaging effects of PTSD are hypothesized to be similar for men and women, no prospective studies have examined PTSD in relation to CHD risk among women or in a nonmilitary population.

PTSD is defined by the combination of exposure to a traumatic event and the occurrence of three types of symptoms: reexperiencing the traumatic event, avoidance of traumatic reminders and emotional numbing, and hyper-arousal. Though much of the work on PTSD and cardiovascular risk has been conducted among male combat veterans, there is little evidence to suggest that potential health-damaging effects of PTSD are constrained to this population. In the limited existing work that considers both men and women civilians with PTSD, a higher prevalence of cardiovascular disease and related risk factors has been documented (Spindler & Pedersen, 2005). Moreover, consistent with other work suggesting that PTSD rather than trauma exposure alone may mediate between trauma and risk of adverse health outcomes (Kang, Bullman, & Taylor, 2006), Dong and colleagues found that civilian men and women with numerous adverse childhood experiences were at greater risk of ischemic heart disease [Odds Ratio (OR) = 3.6, 95% Confidence Interval (CI)} = 2.4–5.3], an effect that was explained more completely by psychological distress than by traditional risk factors (Dong et al., 2004).

The present study provides a prospective test of the hypothesis that PTSD symptoms are associated with increased risk of developing CHD among community dwelling women. Data are from the Baltimore cohort of the Epidemiologic Catchment Area (ECA) study, a survey of psychiatric disorders in the general population. Work in this and other samples has considered the relationship between depression or anxiety and CHD (Kubzansky & Kawachi, 2000; Pratt, Ford, Crum, Armenian, Gallo, & Eaton, 1996). To address concerns that an observed association between PTSD and CHD may be because of other forms of distress, this study also considers whether PTSD is

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related to CHD onset after taking account of depression or anxiety (measured separately from PTSD).

Method

The Epidemiologic Catchment Area (ECA) program was a national study aimed at measuring the incidence and prevalence of psychiatric disorders in the general population (Regier et al., 1984). Five sites participated in this study between 1980 and 1983 and the final sample included over 20,000 respondents. Participants gave informed consent before the interview. The protocol was approved by the Committee on Human Research of the Johns Hopkins School of Hygiene and Public Health.

The first wave of the Baltimore ECA was conducted in 1980 through 1981 and included a probability sample of 3,481 (62.0% female) household residents of east Baltimore, a population of 175,211 adults. The completion rate for the first wave survey was 82%. The second wave of the Baltimore ECA study ($n = 2768$ participants, 62.9% female), conducted in 1982, included an assessment of PTSD and therefore serves as the baseline for the current study. The Baltimore ECA Follow-up study involved a third wave of interviews, conducted in 1993 through 1996, and included 1,920 participants (63.1% female) who completed the first wave interview. Approximately 73% of those alive were successfully interviewed during this follow-up. Details on the study design and methods of the Baltimore ECA follow-up have been described, including work suggesting that PTSD is unlikely to be related to sample attrition (Badawi, Eaton, Myllyluoma, Weimer, & Gallo, 1999).

Women who completed the second wave Baltimore ECA interview in 1982 and who participated in the subsequent follow-up are included in the present study. Of the 1,741 women who completed the second wave assessment, 354 women (20.3%) were excluded from the baseline sample because they did not complete the PTSD interview ($n = 1$) had evidence of heart disease in their first or second wave interviews ($n = 314$), or were missing information on health status at baseline ($n = 39$) Of the eligible women 285 were missing either a Wave 3 interview or available death records, and 43 were missing data on heart disease at follow-up, resulting an analytic sample of 1,059 women. No significant differences were evident between women included in versus excluded from the analytic sample with regard to race/ethnicity. However, women excluded from the analyses were significantly more likely to be older, have less than high school education, and have income less than $14,999.

Assessment of PTSD

Past-year PTSD was assessed at the second wave assessment during face-to-face interviews conducted by lay interviewers using the NIMH Diagnostic Interview Schedule (DIS) according to the Diagnostic and Statistical Manual Third Edition (DSM-3) (Robins, Helzer, Croughan, & Ratcliff, 1981). The PTSD interview began with a gate question to determine whether participants had experienced a traumatic event *in the past year*. Participants who experienced more than one distressing event were asked to focus on the most distressing event. PTSD symptoms were then queried in relation to that event. Using DSM-3 criteria, only 28 (2.6%) women in the analytic sample met diagnostic criteria for past-year PTSD. Because of the small number of women who met criteria and related power concerns, PTSD symptom counts were used as a continuous measure for statistical analyses. In addition, to assess the possibility of a threshold effect on CHD risk, symptom levels were categorized into low (0), moderate (1–4) and high (5 or more) based on the distribution of scores in the sample and based on the recognition that diagnosis of PTSD according to the *DSM–IV* requires five or more symptoms.

Measurement of Other Cardiovascular Risk Factors

Basic demographic information, including age, race/ethnicity, educational attainment, and income, along with information on history of hypertension or diabetes, smoking status, and alcohol use was collected as part of the second wave (1,982) interviews. Educational attainment was taken from the Wave 1 interview. Family history of heart disease and body mass index (BMI) were assessed at the Wave 3 interview but 234 participants (22%) were missing information on family history and 263 participants (25%) were missing information on BMI. Current major depression (yes/no) was assessed at Wave 2 via the DIS according to DSM-3 criteria (Pratt et al., 1996). Trait anxiety was also assessed at Wave 2 with a single item question "Do you now consider yourself a nervous person?" (yes/no).

Assessment of Morbidity and Mortality

Cardiovascular outcomes were assessed via detailed questions during the third wave interviews (1993–94) as follows. Participants were asked whether they ever had heart trouble. Those who responded affirmatively were then asked to specify the type of heart trouble. The interviewer queried five specific conditions: rheumatic fever, rheumatic heart disease, angina pectoris, a heart attack, and congestive heart failure. Consistent with other work in this area (Dong et al., 2004; Kubzansky & Koenen, 2007), those who reported having a heart attack or angina pectoris were considered positive for the outcome. Participants were also tracked via the National Death Index and death certificates were obtained for decedents. Death from CHD was designated when a death certificate (coded according to the 9th revision of the International Classification of Diseases) indicated an underlying cause of death coded to rubric 410–414. All other 1993 through 1996 respondents were considered negative for the outcome. Because of the small number of cases for each CHD outcome ($n < 30$), the incident CHD measure combined cases across angina pectoris, nonfatal MI, fatal MI, and other cardiac death.

Data Analysis

Logistic regression models using the Statistical Analysis System (SAS Institute, 1990) were used to estimate the relative risks of CHD according to level of PTSD, controlling for age (years); race/ethnicity (White/non-White), smoking status (never, former, current); history of high blood pressure (yes/no); history of diabetes (yes/no); whether participants drank two or more drinks of alcohol per day (yes/no), whether participants had completed education beyond high school (yes/no), income (<$14,999, $15,000–$24,000, > $25,000). Because many participants lacked information on family history of heart disease and body mass index (kg/m^2), to maximize our power to detect effects these

variables were not included in the primary analyses. Primary analyses consider the association between PTSD symptom level and likelihood of developing CHD. To assess the possibility of threshold effects, analyses subsequently compare the probability of developing CHD across individuals with more versus fewer PTSD symptoms. Odds ratios derived from these analyses represent the effect of PTSD symptom level (low as reference) on CHD risk. Age- and multivariable-adjusted analyses are presented to illustrate the role of potential confounders. Effects of PTSD on noncardiac mortality are also considered. Follow-up analyses examine whether findings change when current depression, trait anxiety, family history, or BMI is included in the models.

Results

The analytic sample consists of 1,059 women, with mean age of 44.4 years at the start of follow-up (range = 19–93). Of these women, 59.9% are White, 48.9% have high school education or more, and 20.8% have income > $25,000. PTSD symptomatology was skewed toward low levels, with 89.1% of the sample reporting 0 symptoms, 7.0% reporting 1 to 4 symptoms, and 4.0% reporting five or more symptoms. Table 1 demonstrates the association of coronary risk factors measured at baseline with PTSD symptom scores. PTSD symptoms were higher among individuals with less income and among those also reporting depression or trait anxiety. Symptom levels did not differ according to any other covariates.

Of the 1,059 women in the study sample, 86 developed CHD over the follow-up period. There were 30 cases of incident nonfatal MI, 27 cases of fatal MI, 15 cases of other cardiac death, and 14 cases of angina pectoris. Women with more symptoms had greater risk of incident CHD and relative risks for age- and multivariable-adjusted models were virtually identical. For each additional symptom, women were at 17% increased risk of developing incident CHD (age-adjusted OR = 1.17, 95% CI: 1.06–1.29, $p < .01$). However, examination of categorical symptom levels suggested a possible threshold effect (see Table 2). Women with five or more symptoms were at approximately three times the risk of developing heart disease compared with those with no symptoms (age-adjusted OR = 3.21, 95% CI: 1.29–7.98, $p < .05$). Findings were maintained after controlling for standard coronary risk factors. Women with 1 to 4 symptoms did not appear to be at significantly elevated risk (age-adjusted OR = 1.22, 95% CI: 0.46–3.24, $p = .69$).

To ensure that findings could not be attributed to reporting bias (i.e., women with greater distress also report more pain, resulting in more diagnosed angina), the association of PTSD symptoms with fatal and nonfatal MI only was examined. When considering PTSD symptoms as a continuous measure, each additional symptom was associated with 15% increased risk of incident MI (age-adjusted OR = 1.15, 95% CI: 1.03–1.29, $p < .05$). Women with five or more symptoms were at significantly elevated risk for incident MI relative to women with no symptoms (age-adjusted OR = 3.25, 95% CI: 1.16–9.11, $p < .05$), and effects were similar after adjusting for standard coronary risk factors (see Table 2). Sensitivity analyses suggested findings were somewhat attenuated but were maintained when lowering the cut-off for high symptom levels. Trait anxiety and current depression were independently associated with incident CHD in this sample, but controlling for either of these factors did not significantly change any of the associations between PTSD symptoms and incident CHD reported above. For example, when current depression was included in the models the association between PTSD symptoms and total cardiac outcomes was attenuated but still significant (high vs. low PTSD symptom levels multivariable-adjusted OR = 2.91, 95% CI: 1.1–7.59, $p < .05$), and effects of depression remained as well. PTSD symptoms were not significantly associated with all-cause mortality or with mortality after excluding deaths because of CHD (see Table 2).

Table 1
Distribution of Coronary Risk Factors in Women in the Baltimore Epidemiologic Catchment Area Study

	PTSD symptoms		
Risk factor	0	1–4	5+
Number in sample	934 (89.1%)	74 (7.0%)	42 (4.0%)
Age at baseline (years) ($p = .0800$)	45.8	40.3	44.2
Race/ethnicity			
White	558 (59.2%)	51 (68.9%)	25 (59.5%)
Non-White	385 (40.8%)	23 (31.2%)	17 (40.5%)
Current smokers (%)	402 (42.7%)	31 (41.9%)	24 (57.1%)
Former smokers (%)	232 (24.7%)	15 (20.3%)	9 (21.4%)
History of high blood pressure	316 (33.7%)	20 (27.0%)	15 (35.7%)
History of diabetes	70 (7.5%)	3 (4.1%)	1 (2.4%)
Consume two or more drinks of alcohol per day[a]	158 (16.8%)	17 (23.0%)	8 (19.1%)
Educational attainment high school or more	484 (51.3%)	46 (62.2%)	21 (50.0%)
Income ($p < .0001$)			
<$14,999	467 (55.8%)	31 (47.0%)	24 (61.5%)
$15,000–24,000	202 (24.1%)	16 (24.2%)	6 (15.4%)
$25,000	168 (20.1%)	19 (28.8%)	9 (23.1%)
Current depression ($p < .001$)	12 (1.3%)	1 (1.4%)	5 (11.9%)
Trait anxiety ($p < .0001$)	189 (20.1%)	29 (39.2%)	22 (52.4%)

[a] Reported values are *N* (%).

Table 2
Age-Adjusted and Multivariable Odds Ratio (OR) of CHD According to Level of PTSD Symptoms (Confidence Intervals are in Parentheses) in Women in the Baltimore Epidemiologic Catchment Area Study

	Level of PTSD symptoms		
	0	1–4	5+
Total cardiac outcomes[†]			
Cases[‡]	74	5	7
Age-adjusted OR	1.00	1.22 (0.46–3.24)	3.21[*] (1.29–7.98)
Multivariable-adjusted OR[§]	1.00	0.73 (0.21–2.53)	3.46[**] (1.35–8.90)
Total MI			
Cases[‡]	48	4	5
Age-adjusted OR	1.00	1.50 (0.51–4.42)	3.25[*] (1.16–9.11)
Multivariable-adjusted OR[§]	1.00	1.24 (0.35–4.34)	3.36[*] (1.15–9.76)
Noncardiac mortality			
Cases[‡]	190	9	7
Age-adjusted OR	1.00	0.77 (0.35–1.72)	1.00 (0.39–2.56)
Multivariable-adjusted OR[§]	1.00	0.99 (0.41–2.41)	0.85 (0.31–2.34)

[*] $p < .05$; [**] $p < .01$.
[†] Angina, nonfatal MI, fatal CHD, and other cardiac death combined.
[‡] A small number of cases ($n = 7–8$ for CHD outcomes) were dropped in multivariable analyses because of missing information on covariates.
[§] Adjusted for age, race/ethnicity (White/non-White), smoking status (never, former, current), history of high blood pressure (yes/no), history of diabetes (yes/no), alcohol intake (at least two drinks per day), educational attainment (high school or more), and income.

Another potential concern is whether individuals with PTSD may be more likely to have either family history of heart disease or higher BMI and therefore at greater risk for developing the outcome. Analyses in the limited samples for which this information was available indicated that findings reported above were unchanged although confidence intervals were wider. For example, women with five or more symptoms had significantly elevated risk for incident MI relative to women with no symptoms when family history was included in the models (multivariable-adjusted OR = 5.89, 95% CI: 1.79–19.40, $p < .01$), and when BMI was included (multivariable-adjusted OR = 6.94, 95% CI: 2.07–23.33, $p < .01$). The possibility of reverse causality was considered. Date of event was unavailable for a significant fraction of those with incident MI, but was more often available for cardiac death. However, only two deaths were recorded in the first 2 years, suggesting that reverse causality is unlikely to account for the observed PTSD-CHD associations.

Discussion

Findings from this study suggest that damaging effects of PTSD symptoms are not limited to military men, but are also evident among civilian women. Community-dwelling women with high levels of PTSD symptoms had over three times the risk of incident CHD relative to women who reported no PTSD symptoms. This effect was maintained after controlling for known coronary risk factors, as well as current depression or trait anxiety, and excluding angina pectoris. Findings are particularly striking given the limited number of CHD events in this sample. It is important to note that past-year PTSD only was assessed. Despite this potentially limited duration of PTSD symptom exposure an increased risk of incident CHD was evident. Because PTSD in this study was assessed only among women who reported exposure to a traumatic event *in the past year*, women with PTSD resulting from exposure to a traumatic event *before* the past year would not have been captured in this PTSD assessment; however, such misclassification would likely bias our risk estimates toward the null.

Findings from the present study differ in some important ways from the recently reported findings on PTSD and incident CHD in men. In the prior study, the sample was comprised of men for whom trauma exposure was likely combat-related. In contrast, the present study sample was comprised of civilian, community-dwelling women who were likely exposed to different types of trauma. For example, PTSD in community-dwelling women has been linked with sexual and physical assault, serious accidents or injuries, and natural disasters (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). The ECA sample was also younger compared with the men in the previous study, which likely explains the smaller number of CHD events available for study and the wider confidence intervals around the risk estimates.

Other work has proposed that prolonged stress reactions and high distress lead to impaired adaptation and increased wear and tear on the body which may ultimately initiate disease processes (McEwen, 2003). The time course of PTSD can follow one of several patterns, where high symptoms levels after traumatic exposure are followed by recovery, chronic symptoms persist over time, or relapsing—remitting symptoms (Koenen, Stellman, Stellman, & Sommer, 2003). If PTSD indeed has pathophysiologic or atherogenic effects, they are most likely to be evident when PTSD follows a pattern of persisting or recurring symptoms over time. Specific mechanisms by which PTSD might influence CHD are as yet unknown, but two primary pathways have been proposed. PTSD may directly alter biological processes in ways that lead to atherosclerosis and cardiovascular system damage. PTSD may also motivate health-related behaviors that

influence risk of developing CHD. In fact, these are not mutually exclusive processes.

PTSD has been associated with greater likelihood of smoking and excess alcohol consumption, behaviors that increase risk of CHD (Breslau, Davis, & Schultz, 2003). Consistent with prior findings, in this ECA sample individuals with more PTSD symptoms were also more likely to smoke or consume more than two alcohol drinks per day. Somewhat surprisingly, after controlling for these behaviors and other coronary risk factors, the PTSD-CHD association was stronger. Data on other relevant health-related variables (e.g., exercise frequency, diet) were not available for most participants, and further work is needed to more fully explore whether these behaviors might help to explain the relationship between PTSD and CHD.

Biological alterations that may be attributed to PTSD have been considered. For example, some work has focused on the hyperarousal associated with PTSD and hypothesized that excess cardiovascular reactivity, altered vagal tone, and neuroendocrine dysregulation associated with PTSD may lead to increased CHD risk. Both sympathetic and parasympathetic dysfunctions have been implicated in the pathophysiology of PTSD, with resting states characterized by low vagal tone and excess sympathetic activity (Cohen, Benjamin, Geva, Matar, Kaplan, & Kotler, 2000). Reduced vagal tone has been identified as a risk factor for sudden cardiac death even among individuals free of diagnosed CHD (Molgaard, Sorensen, & Bjerregaard, 1991). Individuals with PTSD also exhibit enhanced negative feedback sensitivity of glucocorticoid receptors in the stress response system, lower than normal urinary and plasma cortisol levels, as well as exaggerated catecholamine responses to trauma-related stimuli (Vanitallie, 2002). PTSD has further been linked with chronically elevated systemic proinflammatory activity and hypercoagulability (von Kanel, Hepp, Buddeberg, et al., 2006; von Kanel, Hepp, Kraemer, et al., 2006). Together these processes may cause or exacerbate endothelial damage and promote the development of atherosclerosis (Schneiderman, 1987).

Findings from this study have several limitations. It is possible there was a differential rate of CHD events among the 285 women who were lost to follow-up at Wave 3, and if they were included in our sample, findings would change. Only a small number of CHD events occurred in this sample limiting the analyses and their interpretation. Relatedly, whether PTSD is associated with CHD among community dwelling men is also of interest; however, levels of PTSD symptoms among men in this sample were quite low making it difficult to examine this question. Neither exposure to trauma nor the nature of the trauma was specifically evaluated, and we lacked or had incomplete information on several traditional risk factors, including cholesterol, BMI, and family history of heart disease. Moreover, assessment of diabetes may have been somewhat underreported as criteria have changed since the Wave 2 assessment. Evaluation of lifetime occurrence of PTSD was not available, but may be expected to increase the magnitude of the observed effects. The CHD measure is based on self-report and may be subject to misclassification, and does not include all possible cardiac outcomes (e.g., congestive heart failure, arrhythmias). Other work has considered the level of agreement between self-reported MI and medical records, and reported agreement rates ranging from 53% to 81%, but also noted that misclassification is most commonly with other cardiovascular diagnoses (O'Donnell et al., 1999). Moreover, although there is evidence that distressed individuals with PTSD are more likely to report more illness-related symptoms, as well as be high utilizers in the health care system (de Waal, Arnold, Spinhoven, Eekhof, & van Hemert, 2005; Gerber et al., 1992; Kisely, Goldberg, & Simon, 1997; Kroenke, Jackson, & Chamberlin, 1997; Watson & Pennebaker, 1989), there is little evidence that suggests distressed individuals are more likely to report a *diagnosed* illness in the absence of ever receiving such a diagnosis. The prospective nature of the data collection with PTSD assessment based on clinical criteria and occurring well before ascertainment of coronary outcomes, and the consistency of our findings with other work using objectively measured outcomes strengthens confidence in our findings and decreases the possibility of recall or information bias.

This is the first prospective study of PTSD and CHD in civilian women. The strength of the association after controlling for known risk factors and depression or trait anxiety, and its consistency with recently reported findings among men suggests that the relationship is valid and may operate in diverse groups. PTSD has been identified as a marker of extreme distress in response to a potentially traumatic event. These data suggest that the prolonged stress that can occur in response to trauma exposure not only increases risk for serious mental health problems, but may also increase risk of CHD. The duration or chronicity of PTSD that is necessary to initiate pathophysiological processes is unclear. Moreover, it is as yet unknown how reversible these pathophysiologic processes are and whether effective treatment for PTSD will also reduce coronary risk. However, from a public health perspective, it may be prudent to view individuals with PTSD as an at-risk population, and implement preventive and intervention strategies accordingly.

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