A Prospective Study of PTSD and Early-Age Heart Disease Mortality Among Vietnam Veterans: Implications for Surveillance and Prevention

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Objective: To examine prospectively early-age heart disease (HD) among a national random sample of 4328 male Vietnam veterans, who did not have HD at baseline in 1985. Studies have suggested that posttraumatic stress disorder (PTSD) may result in cardiovascular disease. However, many past studies had important methodological limitations to their designs. **Method:** Using Cox regressions, we assessed PTSD, age, race, intelligence, family history, obesity, smoking, alcohol abuse, antisocial personality, and depression in predicting HD mortality at follow-up in December 31, 2000. The men were <65 years old at follow-up. **Results:** Using two PTSD measures, a Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition (DSM-III) measure (D-PTSD) and one developed by Keane (K-PTSD), we found that among Vietnam theater and era veterans combined (era veterans had no Vietnam service), having PTSD was associated with HD mortality for D-PTSD (hazard ratio (HR) = 2.25, $p = .045$) and approached significance for K-PTSD (HR = 2.16, $p = .066$). However, having higher PTSD symptoms on either scale was associated with mortality, with a 5-point increase associated with ~20% increase in mortality risk (all $p < .05$). Controlling for lifetime depression only slightly altered the results. The effects for theater veterans alone were stronger (D-PTSD: HR = 2.58, $p = .025$; K-PTSD: HR = 2.73, $p = .022$). Among theater veterans, controlling for lifetime depression or combat exposure made little difference. **Conclusion:** PTSD was prospectively associated with HD mortality among veterans free of HD at baseline. This study suggests that early-age HD may be an outcome after military service among PTSD-positive veterans. **Key words:** posttraumatic stress disorder, cardiovascular disease, survival analysis, depression, veterans.

TV = theater veteran; **EV** = era veteran; **POW** = prisoner of war; **PTSD** = posttraumatic stress disorder; **DIS** = Diagnostic Interview Schedule; **DSM-III** = Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition; **HD** = heart disease; **ECG** = electrocardiogram; **BP** = blood pressure; **HPA** = hypothalamic-pituitary-adrenocortical; **SAM** = sympathetic-adrenal-medullary; **NDI** = National Death Index; **HR** = hazard ratio; **CI** = Confidence Interval.

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a disabling mental health disorder affecting those exposed to traumatic events and is associated with reexperiencing, avoidance, and hyperarousal symptoms related to such events (1). Research has suggested that having PTSD was associated with increased medical morbidity (2–4). Recently, in a national study, Boscarino reported that all-cause mortality was associated with PTSD among Vietnam theater veterans (i.e., those with Vietnam service) (hazard ratio (HR) of 2.2, $p < .001$) as well as Vietnam era veterans (i.e., those with service elsewhere) (HR = 2.0, $p = .001$) 30 years after military service (4). For theater veterans, PTSD was also associated with cardiovascular-related disease (HR = 1.7, $p = .034$), cancer (HR = 1.9, $p = .018$), and external mortality (HR = 2.3, $p < .001$) (4). Although this study was noteworthy, it did not prospectively assess new-onset disease among these veterans (4). Currently, there are no long-term national prospective studies that have examined early-age heart disease (HD) mortality, defined here as ischemic- or atherosclerotic-related HD (including myocardial infarction and congestive heart failure) among those <65 years old among a trauma-exposed population. This is important because this type of HD is plausibly related biologically to past traumatic stressor exposures.

It has been suggested that the prevalence of PTSD among Armed Forces personnel returning from current theaters of war in Iraq and Afghanistan may be comparable to those experienced by Vietnam veterans (5,6). In addition, recently, concerns have been expressed related to access to mental health care for these service personnel (5). Understanding the burden of illness associated with military service is important for service planning, disease prevention, and public health (7). In addition, this research may provide insights related to the hazards for those working in other high-risk service occupations (8). The goal of the current study was to prospectively examine the association between PTSD and early-age HD mortality in a national study potentially unconfounded by factors that have limited previous research.

Consistent with the impact of traumatic exposures, studies among those exposed to such stressors have suggested that higher rates of comorbidity and psychological problems were not uncommon (1–7,9–14). Noteworthy was that then the postwar health status of Vietnam veterans was retrospectively examined by whether these veterans had PTSD, those with PTSD had 50% to 150% higher rates for many chronic diseases, including circulatory, nervous system, digestive, musculoskeletal, and respiratory diseases (2). Past research has suggested that psychosocial factors were likely implicated in atherosclerosis and coronary HD (15–18). More recent research has generally reinforced these earlier results (4,9,19,20). Research has suggested that exposure to environmental stressors induce neuroendocrine changes that may contribute to atherogenesis (21,22). For example, it has been suggested that HD may develop in response to recurrent sympathoadrenal arousal associated with catecholamine releases, which promotes arterial injury via hemodynamic (e.g., turbulence and sheer stress)

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and metabolic (e.g., platelet aggregation and lipolysis) changes and eventually causes coronary atherosclerosis due to plaque rupture and thrombus formation (17). It has been noted that sympathoadrenal activity seemed to injure arterial endothelium and initiated atherogenesis, even in the absence of hypercholesterolemia and that administration of β-adrenergic blocking agents seemed to prevent such injury (16,17). More recently, it has been reported that low-grade systemic proinflammation seemed to be present in PTSD cases and that this likely contributed to the atherosclerotic/ischemic disease process (23,24).

To date, evidence linking traumatic stressor exposures and HD has been supported by different studies. For example, it was reported that PTSD-positive Vietnam veterans were more likely to have had physician-diagnosed circulatory diseases and abnormal electrocardiograph (ECG) results nearly 20 years after military service (2,21). In addition, it was also reported that Vietnam theater veterans with PTSD were more likely to die from cardiovascular-related diseases 30 years after military service (4). Other studies involving World War II and Korean War veterans also found higher rates of physician-diagnosed cardiovascular disease among PTSD-positive veterans (25). A study of former prisoners of war (POWs) reported that those with PTSD were at increased risk for cardiovascular diseases compared with PTSD-negative POWs and non-POWs (26). A retrospective study of the traumatic war experiences of US Civil War veterans, based on archival data, reported that greater exposure to war trauma was related to an increase of postservice cardiovascular ailments (27). Furthermore, a recent prospective cohort study of men recruited as part of a local VA study of older veterans reported a prospective association between coronary HD and PTSD symptoms (28). Investigations conducted among other populations have reported similar results (29–31).

Research has suggested that Vietnam veterans with PTSD generally had this condition due to past wartime exposures (13,14). Hence, for theater veterans, at least, many have had PTSD for decades in the current study. The era veterans (EVs) would have acquired PTSD from other than war-zone exposures (1,32). Our hypothesis was that, prospectively, PTSD would be a significant predictor of early-age atherosclerotic/ischemic HD mortality (4). Few studies have examined this risk factor for HD prospectively within a random, community-based population. For example, increases in sudden cardiac deaths have been reported after earthquakes (33,34), but these associations likely represent exacerbation of underlying atherosclerotic/ischemic disease, not direct causation, per se. In the current study, because the population was assessed for HD in 1985 to 1986 and the follow-up ended on December 31, 2000, it was thought that examination of the onset of subsequent atherosclerotic/ischemic HD among veterans by eliminating those with HD at baseline would aid causal inferences. During the baseline, veterans received a physical examination that included ECGs, blood pressure (BP) measurements, and gathered medical history and current medication data. Based on this information, we excluded cases with ischemic- and atherosclerotic-related HD, including myocardial infarction, angina pectoris, and congestive heart failure at baseline. In addition, we also controlled for key confounders, lifetime depression, and combat exposure in the current study to assess the prospective contribution of PTSD in early-age HD independent of the latter factors, something rarely done in past investigations.

METHODS

Study Population

This research was based on a random sample of men who served in the US Army during the Vietnam War. These men were identified through the National Personnel Records Center (St Louis, Missouri). The random sample was generated by a computer program that selected veterans from computer tapes containing essentially all Army personnel from this period. Altogether, 18,581 men were selected who met the study criteria, including: entering the military between 1965 to 1971; serving one enlistment; and having a service rank of E5 or lower (i.e., sergeant or lower). Participants were classified as theater veterans (TVs), if they served in Vietnam, or as era veterans (EVs), if they served elsewhere. In January 1985, attempts were made to complete telephone interviews with these men. From these efforts, 87% of TVs (n = 7924) and 84% of the EVs (7364) were interviewed (overall completion rate = 86%). Among these men, a random sample was selected for interviews/examinations. Altogether, 75% of the TVs (n = 2490) and 63% of the EVs (n = 1972) participated in this phase. Noteworthy was that detailed nonresponse analysis, based on military records and telephone interview data, found no appreciable differences between participants and nonparticipants in terms of key demographic or health status measures in this study (35,36). Personal interviews and examinations required several days on site at Lovelace Medical Foundation (LMF), Albuquerque, New Mexico, between June 1985 and September 1986. Detailed reports regarding this study have been published elsewhere (4,35,36). The Centers for Disease Control's Human Subject Review Committee approved the study protocols (35,36).

Ascertainment of Cardiovascular-Specific Mortality

For the current study, vital status was assessed from the date of completion of the telephone interviews starting in January 1985 until the end of the mortality follow-up in December 31, 2000. Vital status was ascertained using three databases: the Department of Veterans Affairs Beneficiary Identification Record Locator Death File, Social Security Administration Death Master File, and the National Death Index-Plus (NDI Plus) file (37). Status determination was obtained by combining all mortality sources (4). Veterans with uncertain vital status were assumed to be living on December 31, 2000. Underlying cause of death was obtained from the NDI Plus. Cause of death was coded according to the International Classification of Diseases (ICD) revision in place at the time of death (4,37). For cases in which cause-of-death codes were not available, investigators obtained copies of official death certificates, which were coded by a nosologist at the National Center for Health Statistics (37). In the current study, the outcome of interest included mortality due to HD, which included myocardial infarction (ICD-9 = 410), chronic ischemic HD (ICD-9 = 414), atherosclerotic HD (ICD-9 = 440), heart failure (ICD-9 = 428, hypertensive HD (ICD-9 = 402), and related disease outcomes. Thus, our focus was on those conditions at least plausibly related biologically to PTSD via the hypothalamic-pituitary-adrenocortical (HPA)-inflammation mechanisms discussed. Thus, mortality mainly due to other forms of cardiovascular-related disease, such as congenital, rheumatoid, cerebral-vascular, and other disease-related HDs, were not counted as outcomes in this study.

Medical History, Physical Examinations, and Elimination of Baseline HD Cases

During the examination phase, physician assistants administered a standard medical history (36,38). Men reporting a history of physician-diagnosed angina, myocardial infarction, or heart failure were eliminated from the current study. Four BP measures were also taken (twice in each arm), using a BP cuff and a sphygmomanometer. The averages for the systolic and

diastolic BPs, respectively, were used in the current study. If a veteran had stage 3 hypertension, defined as an average systolic of >179 mm Hg or an average diastolic BP of >109 mm Hg, the subject was eliminated from the current study. Resting ECGs were obtained during the physical examination (36). Technicians administered 12-lead ECGs using a microcomputer augmented cardiograph II ECG machine (Marquette Electronics, Milwaukee, Wisconsin). Initial ECGs were analyzed by a Marquette computer program and then confirmed by Board-certified cardiologists. We summarized these findings using the *Minnesota Code Manual of Electrocardiographic Findings* (21,39,40). In the current study, we used evidence of Q-wave infarctions to indicate the presence of HD, indicating the subject had ECG evidence of anterior, lateral, inferior, posterior extension, anteroseptal, anterolateral, or possibly acute infarctions based on these readings (39). Veterans with these ECG findings were eliminated from the current study. During the medical history, current prescription medication use was also ascertained. If the subject reported taking anticoagulant, thrombolytic, antiarrhythmic, antianginal, vascular disorder, or coronary vasodilator medicines, they were also eliminated. Based on these combined measures, 134 veterans were eliminated due to preexisting HD, resulting in a total study population of 4328 men. The mean age of these veterans at follow-up was 54 years (range = 47–64 years). Given the age of these veterans and that our outcome was HD mortality and not disease onset/symptoms, per se, the goal was to eliminate clear, nonborderline HD cases in the current study.

PTSD Measures

Because the PTSD criteria used in the study were based on earlier nomenclatures (4,13,41), we used two different PTSD measures. The first PTSD measure was related to Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition (DSM-III) criteria (D-PTSD) and was administered by telephone just before the physical examination (35,36). For this, veterans were asked to report 15 PTSD-related symptoms that occurred in the past 6 months (recorded as: never = 0, sometimes = 1, often = 2, very often = 3). Consistent with DSM criteria, a veteran was classified as having current PTSD if he reported at least one criterion B symptom (reexperiencing), at least one criterion C symptom (avoidance), and at least two criterion D symptoms (hyperarousal). Analyses of participants who completed both the D-PTSD and the Diagnostic Interview Schedule (DIS) PTSD scale confirmed that a diagnosis on the D-PTSD scale was consistent with the diagnosis of PTSD (4,7). The baseline prevalence for D-PTSD in the current study was 7% (95% Confidence Interval (CI) = 6% to 8%). The D-PTSD scale also provided a PTSD symptom severity measure, based on summation of the 15 PTSD symptoms (mean ± standard deviation (SD) = 9.6 ± 8.1; range = 0–45). To assist in interpretation of multivariate results, we also collapsed the raw symptom scores on this scale into 5-point increments (D-PTSD-5). The second PTSD measure was the Keane PTSD (K-PTSD) scale, also administered during the examination (38,42). The K-PTSD scale was based on 49 items from the Minnesota Multiphasic Personality Inventory (recorded as "yes/no"), which was previously developed among samples of Vietnam veterans and reported to be a valid and reliable measure of PTSD (38,42). For the K-PTSD scale, we used a cut-off score of 28 to define a PTSD case (42). The baseline prevalence for K-PTSD at this cut-off was 6% in the current study (95% CI = 5% to 7%). The K-PTSD scale also provided a symptom severity measure of PTSD, based on a count of positive scale items (10.4 ± 8.9; range = 0–47). Again, to assist in the interpretation of multivariate results, we also collapsed the raw scores on this scale into 5-point increments (K-PTSD-5). Thus, for our two PTSD scales (D-PTSD and K-PTSD), we had three measures each—a case measure, a raw symptom measure, and a collapsed 5-point incremental scale measure.

Baseline Control Variables

Our study included age, race, and veteran status as demographic variables. Also included were variables related to character traits, such as intelligence, as well as history of other mental health disorders that could affect health outcomes. Other potential confounding variables assessed included pack-years of smoking and body mass index (BMI). Age was based on the veteran's age at the interview and used as a continuous variable. Race was based on reported race (White 82%; Black 11%; Hispanic 5%; other 2%) and coded as an indicator variable (White versus non-White), given the small numbers for Hispanics and other races and previous findings (4,9). Intelligence was taken from the military record and based on the General Technical examination at Army induction and used as a continuous variable (36). This measure has been reported to be a reliable and valid indicator of general adult intelligence (36,38). Antisocial personality disorder, lifetime depression, and lifetime alcohol abuse/dependence were based on having met the diagnostic criteria for these disorders at baseline and based on the DIS (43,44). BMI was used to classify obesity as present, based on the subject's weight (in kilograms) divided by the subject's height (in meters) squared, with a score of 30 used to define obesity. Pack-years of cigarette smoking were based on the average number of reported cigarette packs smoked per day and the number of years smoked and used as a continuous variable. Because we combined the TVs and EVs in some multivariate analyses, we also included a binary measure to control for theater status in these models. It should be noted that, although the PTSD cases among EVs were due to noncombat stressor exposures, it was not possible to further characterize these exposures in the current study. Altogether, 88% of TVs with lifetime PTSD had this due to combat exposure and 12% related to noncombat or both combined, but the limits of the data instruments prevented further characterization of these data (10). Reported family history of HD was also used as a binary control variable in the current study. Finally, based on self-report, TVs were classified as having high combat exposure if they scored in the upper quartile on the combat exposure index, a reported valid and reliable measure of combat exposure among these veterans (45).

Statistical Methods

For the statistical analyses, first, we described the bivariate differences by PTSD and HD status. Next, we used Cox regressions to calculate multivariate HRs predicting early-age HD mortality by PTSD status. We conducted these assessing for D-PTSD and K-PTSD status separately and then controlling for potential bias and confounding in the final models. Because research has suggested that depression was associated with HD (19,46,47), we entered this measure into our final models and reported these results. We analyzed the results for TVs and EVs combined, because no effect modification was confirmed by veteran status for the models examined, even though there were differences reported between these groups (4,7). For the EVs, it was not possible to estimate Cox regressions, due to the lower prevalence of HD mortality. Hence, in the current study, we present results for the TVs and EVs combined and then for the TVs separately. Because PTSD and risk factors were assessed in 1985 to 1986, we included only those who were alive and completed the 1985 to 1986 interviews and physical examinations. Thus, survival time was examined from interview completion starting January 1, 1985 through December 31, 2000, a period of approximately 16 years. In addition, study risk factors were only measured at baseline; hence, they are treated as invariant in the current study. In the analyses, we examined HD mortality by PTSD status defined both categorically as a case and by PTSD symptom level. For these analyses, we evaluated the main proportional hazards assumption (48), controlled for potential confounding, and tested for effect modification by veteran status. To avoid overadjustment due to the degrees of freedom available and the number of events that occurred during the study (48), we eliminated predictor variables from multivariate models if their p values were >.10 in minimum regression models predicting mortality with PTSD included as well, with two exceptions. First, theater status was retained in the combined veteran models to account for residual differences between these veteran groups. Second, intelligence was retained in all models because this predictor had $p < .05$ for TVs and ≤0.17 for EVs. In all, four predictors were removed from multivariate analyses due to lack of significance: race, family HD history, alcohol abuse history, and antisocial personality disorder.

All p values presented were based on two-tail tests. Finally, it is noted that because several data sources were used in this study and the veterans were on site for several days, most missing data were limited. The one exception was for intelligence, whereby 48 cases (~1%) were missing and coded at the median level. Statistical analyses were performed using Stata, version 9.2 (49).

RESULTS

As reported elsewhere (4), approximately 10% of TVs ($n = 255$) and 3% of EVs ($n = 68$) had PTSD at baseline ($p < .001$), based on the D-PTSD scale. Descriptive findings for the current study indicated that PTSD, as classified by the D-PTSD scale, was associated with HD mortality, younger age, non-White status, TVs, lower intelligence, lifetime alcohol abuse/dependence, lifetime depression, and history of antisocial personality (all $p < .05$) (Table 1). In addition, HD mortality at follow-up was associated with not only D-PTSD, but also with K-PTSD, pack-years of cigarette smoking, and obesity at baseline (all $p < .05$) and approached significance ($p = .052$) for lower intelligence (Table 2).

Cox regressions were first conducted for HD mortality for the TVs and EVs combined (Table 3). The results for these veterans for the six PTSD measures, adjusted for theater status only, and each as a separate model, were all significant (all $p < .05$) (Table 3, second panel). The combined veteran-adjusted models without depression indicated that five of the six PTSD measures were significant, and that a sixth, K-PTSD diagnosis, approached statistical significance ($p = .066$). Noteworthy is that having a diagnosis of PTSD at baseline, such as having a positive D-PTSD case definition, doubled the risk of death from early-onset HD at follow-up (HR = 2.25, $p = .045$). A 5-point increase in PTSD symptoms on either the D-PTSD or the K-PTSD scale resulted in approximately a 20% increase in the risk of death from HD

TABLE 1. PTSD at Baseline by Early-Age HD Mortality at Follow-Up and Study Predictor Variables[a]

Variable	% Total (*n*)	% No Current D-PTSD at Baseline	% Current D-PTSD[b] at Baseline	*p**
HD mortality	1.2 (52)	1.1 (44)	2.6 (8)	.021
Age >40 years at interview	19.7 (853)	20.4 (818)	11.3 (35)	<.001
Non-White race	17.9 (773)	16.8 (675)	31.5 (98)	<.001
Theater veteran	55.7 (2409)	53.8 (2163)	79.1 (246)	<.001
Intelligence-lowest quintile	18.4 (789)	17.2 (691)	34.4 (107)	<.001
Lifetime alcohol abuse/dependence	46.3 (2006)	44.8 (1799)	66.6 (207)	<.001
Lifetime depression	10.5 (456)	8.9 (358)	31.5 (98)	<.001
History of antisocial personality disorder	22.1 (958)	20.8 (835)	39.5 (123)	<.001
Family history of HD	6.7 (290)	6.7 (269)	6.8 (21)	.970
Pack-years of cigarette smoking >19 years	32.8 (1421)	32.5 (1307)	36.7 (114)	.136
BMI >30	16.3 (705)	16.2 (650)	17.7 (55)	.489
n	4328	4017	311	—

PTSD = posttraumatic stress disorder; HD = heart disease; BMI = body mass index.
* Two-sided χ^2 test, $df = 1$.
[a] HD mortality included myocardial infarction, chronic ischemic HD, atherosclerotic HD, heart failure, and hypertensive HD.
[b] Current PTSD was based on the D-PTSD scale classification. Note: Table 1 percents based on percents for column variable shown. For example, of those with current PTSD in Table 1 at baseline, 2.6% had HD mortality at follow-up.

Table 2. Prospective HD Mortality at Follow-Up by Study Predictor Variables[a]

Variable	% Total (*n*)	% No HD Mortality	% HD Mortality[a]	*p**
D-PTSD[b]	7.2 (311)	7.1 (303)	15.4 (8)	.021
K-PTSD[b]	6.1 (264)	6.0 (257)	13.5 (7)	.026
Age >40 years at interview	19.7 (853)	19.6 (839)	26.9 (14)	.188
Non-White race	17.9 (773)	17.8 (761)	23.1 (12)	.323
Theater veteran	55.7 (2409)	55.6 (2376)	63.5 (33)	.255
Intelligence-lowest quintile	18.4 (798)	18.3 (783)	28.8 (15)	.052
Lifetime alcohol abuse/dependence	46.3 (2006)	46.4 (1982)	46.2 (24)	.977
Lifetime depression	10.5 (456)	10.5 (447)	17.3 (9)	.110
History of antisocial personality disorder	22.1 (958)	22.2 (947)	21.2 (11)	.863
Family history of HD	6.7 (290)	6.7 (285)	9.6 (5)	.398
Pack-years of cigarette smoking >19 years	32.8 (1421)	32.7 (1397)	46.2 (24)	.040
BMI >30	16.3 (705)	16.1 (690)	28.8 (15)	.014
n	4328	4276	52	—

HD = heart disease; PTSD = posttraumatic stress disorder; BMI = body mass index; HR = hazard ratio.
* Two-sided χ^2 test, $df = 1$.
[a] HD mortality included myocardial infarction, chronic ischemic HD, atherosclerotic HD, heart failure, and hypertensive HD.
[b] For the PTSD measures used, the bivariate Cox regression results for HD mortality by PTSD-positive status were: D-PTSD = hazard ratio (HR) of 2.23, $p = .031$; K-PTSD = HR of 2.39, $p = .033$.
Note: Table 2 percents based on percents for column variable shown. For example, of those with HD at follow-up in Table 2, 15.4% had D-PTSD at baseline.

TABLE 3. Cox Proportional Hazard Regressions for Early-Age Heart Disease Mortality at Follow-Up: All Veterans Combined by Baseline PTSD Status (n = 4328)[a]

Baseline PTSD Measures	All Veterans Combined: Early-Age HD Mortality – Total Deaths = 52 (65,174 Person Years at Risk)								
	Theater Status Adjusted Models[b]			Adjusted Models[c]			Adjusted Models With Depression[d]		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
D-PTSD case definition	2.32	1.08–5.00	.031	2.25	1.02–4.95	.045	2.06	0.92–4.62	.081
D-PTSD symptom level	1.04	1.01–1.07	.004	1.04	1.01–1.08	.009	1.04	1.01–1.07	.024
D-PTSD symptoms—5-point groups (D-PTSD-5)	1.23	1.06–1.42	.006	1.22	1.04–1.42	.013	1.20	1.01–1.41	.034
K-PTSD case definition	2.39	1.07–5.33	.033	2.16	0.95–4.89	.066	1.87	0.77–4.55	.168
K-PTSD symptom level	1.04	1.01–1.06	.007	1.03	1.00–1.06	.022	1.03	1.00–1.06	.064
K-PTSD symptoms—5-point groups (K-PTSD-5)	1.20	1.06–1.37	.005	1.18	1.03–1.36	.016	1.17	1.00–1.35	.046

HR = hazard ratio; CI = Confidence Interval; PTSD = posttraumatic stress disorder; BMI = body mass index; HD = heart disease.
[a] HD mortality included myocardial infarction, chronic ischemic HD, atherosclerotic HD, heart failure, and hypertensive HD.
[b] Models adjusted for theater status only.
[c] Models concurrently adjusted for theater status, baseline age, intelligence, pack-years of smoking, and BMI >30.
[d] Models concurrently adjusted for theater status, baseline age, intelligence, pack-years of smoking, BMI >30, and history of depression.
Variables assessed but deleted from models due to nonsignificance included: race, family history of HD, history of alcohol abuse/dependence, and history of antisocial personality disorder.

(D-PTSD-5 = 1.22, p = .013; K-PTSD-5 = 1.18, p = .016). Adding lifetime depression to the combined veteran models (Table 3, far right panel) reduced the PTSD diagnostic categories to nonsignificance, but generally not the PTSD symptom categories (D-PTSD-5: HR = 1.20, p = .034; K-PTSD-5: HR = 1.17, p = .046). Noteworthy, however, was that lifetime depression was not significant in any of the six fully adjusted models assessed and shown in Table 3.

There were insufficient HD cases to assess outcomes among the EVs alone, but it was possible to assess HD outcomes among the TVs, including assessment of the impact of lifetime depression and previous combat exposure (Table 4). As with previous Cox regressions, each of the six PTSD classifications shown represents a separate regression model. The bivariate results for the TVs separately were all significant for the six PTSD measures assessed (all $p < .01$) (Table 4, panel 2). Furthermore, among the TVs, all PTSD measures were significant in the overall adjusted models as well, with HRs larger than for the veteran groups combined (Table 4, panel 3). When lifetime depression was added to these models (Table 4, panel 4), there were slight reductions in HRs for the PTSD measures, with all of these remaining significant, except K-PTSD (p = .066). The TV final model assessed included a measure of high combat exposure (Table 4, far right panel). Again, there was only a slight reduction in the HRs for the six PTSD measures after combat exposure was included, with all PTSD measures remaining significant, except for D-PTSD-5, which now had p = .053 (Table 4). It is noteworthy that neither lifetime depression nor high combat exposure was significant in any of the TV-adjusted models that were assessed.

To further assess our multivariate models, we did not exclude cases based on high BP status, but instead entered high BP in the models (classified as an ordinal variable: normal, above normal, moderate, high, or very high BP) as a covariate. This was done to determine if there was bias associated with the BP cut-off used to eliminate cases. These results were nonsignificant for BP and had little effect in the models. Next, from medical history information collected during the physical examination, we further assessed history of diabetes as a covariate in our regression results. Although this variable was significant in all models and the results for PTSD were reduced, both symptoms scales used remained significant in these models. Most importantly, for the high exposure group, the TVs, all PTSD measures remained significant even in the models containing depression and diabetes, with only one PTSD measure with $p > .05$, D-PTSD symptoms, which now had p = .069.

To assess Cox proportional hazards assumptions, we used Schoenfeld residuals and the "stphtest" procedure in Stata to assess fit for our models (49). This test is equivalent to testing that the log HR function is constant over time (50). The overall results of the procedure indicated that the final models used were generally adequate.

DISCUSSION

As noted, reports related to personnel returning from current theaters of war in Iraq and Afghanistan have indicated that the prevalence of PTSD may be comparable with those experienced during the Vietnam War (5,6). Understanding the burden of illness associated with this service will be important for service planning and prevention among this at-risk population (7). There are no long-term, national prospective studies that have examined incident cases of early-age HD among the veteran population. Studies conducted to date have either included local area samples (28) or have not examined onset of HD prospectively (4,29). One recent study reporting results similar to the current one and which was prospective was

TABLE 4. Cox Proportional Hazard Regressions for Early-Age Heart Disease Mortality at Follow-Up: Theater Veterans Separately by baseline PTSD Status (n = 2409)[a]

Baseline PTSD Measures	Theater Veterans Only: Early-Age HD Mortality – Total Deaths = 33 (38,904 Person Years at Risk)											
	Unadjusted Models			Adjusted Models[b]			Adjusted Models With Depression[c]			Adjusted Models With High Combat Exposure[d]		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
D-PTSD case definition	2.94	1.33–6.52	.008	2.58	1.13–5.91	.025	2.39	1.03–5.55	.044	2.32	1.00–5.37	.049
D-PTSD symptom level	1.05	1.02–1.09	.003	1.05	1.01–1.08	.016	1.04	1.00–1.08	.038	1.04	1.00–1.08	.043
D-PTSD symptoms — 5-point groups (D-PTSD-5)	1.28	1.08–1.51	.004	1.24	1.03–1.49	.020	1.22	1.00–1.47	.046	1.20	1.00–1.45	.053
K-PTSD case definition	3.33	1.44–7.67	.005	2.73	1.16–6.46	.022	2.44	0.94–6.32	.066	2.51	1.05–5.96	.037
K-PTSD symptom level	1.05	1.02–1.08	.002	1.04	1.01–1.08	.010	1.04	1.00–1.08	.031	1.04	1.01–1.07	.020
K-PTSD symptoms — 5-point groups (K-PTSD-5)	1.27	1.10–1.48	.002	1.24	1.05–1.45	.009	1.22	1.02–1.45	.026	1.21	1.04–1.42	.017

HR = hazard ratio; CI = Confidence Interval; PTSD = posttraumatic stress disorder; BMI = body mass index; HD = heart disease.

[a] HD mortality included myocardial infarction, chronic ischemic HD, atherosclerotic HD, heart failure, and hypertensive HD.

[b] Models concurrently adjusted for baseline age, intelligence, pack-years of smoking, and BMI >30.

[c] Models concurrently adjusted for baseline age, intelligence, pack-years of smoking, BMI >30, and history of depression.

[d] Models concurrently adjusted for baseline age, intelligence, pack-years of smoking, BMI >30, and high combat exposure.

Variables assessed but deleted due to nonsignificance included: race, family history of HD, history of alcohol abuse/dependence, and history of antisocial personality disorder.

limited by both the fact that subjects were recruited only from the Boston area, and it included men between 21 and 80 years of age at the study baseline in 1961 (28). The current study adds to these findings and suggests that having PTSD was prospectively associated with early-age HD mortality among same-aged men free of major HD at baseline, even after controlling for HD risk factors, among a national, representative sample of service veterans from the Vietnam War period. Our study suggests that early-age HD may be an adverse outcome among PTSD-positive veterans after military service and warrants further investigation.

There were several specific reasons to expect a link between PTSD and HD in the current study (3). Research has suggested that PTSD could result in inflammatory injuries through overactivation of the HPA and sympathetic-adrenal-medullary (SAM) stress axes, subsequently followed by hypocortisolism related to molecular downregulation of this system (9,51,52). Although the pathophysiology of hypocortisolism seems complex (53), it has been hypothesized that this condition could increase inflammation activity (9). Concordant with this observation, recent research suggested the presence of low-grade systemic proinflammation in PTSD cases (23,24). In addition, it was possible that this disease link could be due to shared physiologic mechanisms, such as inadequate adrenal functioning, which could be associated with both psychological reactions to environmental stressors and biologic vulnerability to disease (10). Furthermore, this link could have occurred through altered health behaviors, such as alcohol use, caloric intake, or cigarette smoking related to self-regulation of aversive psychological states, brought on by PTSD psychopathology (3,11). Another possibility was that these associations could be related to self-selection, whereby those who developed PTSD and HD might have certain character traits that were related to both HD and exposure trauma, rendering this association spurious (7). Finally, it was possible that the causal sequence was reversed—that is, it was the occurrence of HD that caused the PTSD (54). The research design implemented in the present study, however, attempted to mitigate these confounding factors.

There is growing evidence that exposure to environmental stressors may alter neuroendocrine and immune system functions and might eventually cause diseases (9). In particular, given the reduced cortisol levels found among some victims with PTSD, it has been suggested that a downregulated glucocorticoid system may result in elevations in leukocyte and other immune inflammatory activities (55). It is known that glucocorticoids influence the trafficking of leukocytes and affect functioning of leukocyte and immune accessory cells (10,56). Consistent with these findings, it has been reported that veterans with chronic PTSD were at greater risk for inflammatory and autoimmune diseases (9), although there is uncertainty related to detailed specification of the disease mechanisms involved in these pathways (3,9,11,57,58).

Currently, research suggests that physiologic arousal experienced during recollection of traumatic events by victims with PTSD was likely associated with neuroendocrine processes tied to HPA/SAM activity (59). Although these are

initiated in the central nervous system, they are subsequently carried out by neurochemical mechanisms that have wide-ranging affects on mammalian physiology (2,9,10,58,59). Although research has suggested that these processes were complex, it is plausible that excessiveness of stress axis activation may directly lead to disease through the biological pathways discussed (9,56,59). This link, as suggested, could also have occurred indirectly through adverse health behaviors, such as alcohol abuse or cigarette smoking, actions often related to self-regulation of aversive arousal triggered by psychopathologic states (e.g., increased anxiety symptoms), which themselves have likely emanated from neuroendocrine secretions associated with HPA/SAM activation (9,59). Furthermore, research has suggested that there were genetic liabilities for PTSD as well as for exposure to psychological trauma (60–62). However, it cannot be ruled out that genetic liabilities that have made persons susceptible to PTSD may have also made them susceptible to certain diseases as well (9,63). Regardless of the causal mechanisms involved, however, it was highly noteworthy that HD mortality was related to the severity of PTSD. For example, in the findings reported in this study, a 5-point increase on either the D-PTSD or the K-PTSD scale (<1 SD on these scales) resulted in a 20% increase in future HD mortality. The fact that this study was prospective adds to the validity and potential psychotherapeutic significance of these findings.

This study had several limitations. Use of multiple sources of vital status allowed for a comprehensive mortality assessment. However, cause of death, as reported on death certificates, is known to overreport circulatory and ill-defined conditions (4,37). Furthermore, although our PTSD measures were reported to have concurrent and predictive validity (4,10,63), these scales were based on earlier versions of this nomenclature (13,38). However, given the results of a validation study (4) and the fact that the PTSD measures used showed convergent validity (7,63), we conclude that our PTSD measures were consistent with the presence of PTSD. Another limitation was that the new-onset HD rate, as defined for the study, was relatively low—only 52 persons died during the study follow-up period, limiting the multivariate analyses and study results. In addition, only major HD cases (not potential borderline cases) were eliminated at baseline, possibly confounding our results. To assess this, we enter BP in the models to determine if there was a potential bias associated with the BP cut-off point used; the results for BP were nonsignificant and had little effect in the models. In addition, controlling for a history of diabetes did not appreciably change the study findings.

Study strengths included the following: 1) this research was based on a large, random, community-based national population; 2) mortality ascertainment was comprehensive; 3) preexisting HD cases were eliminated; and 4) key selection biases and confounders were controlled or assessed. In addition, because we controlled for variables on the causal pathway between PTSD and HD (e.g., baseline smoking and obesity), more likely than not, our estimates were conservative.

Clearly, a limit of this research was not being able to assess time-dependent factors related to psychological trauma, but also likely associated with HD, such as an increasing sedentary lifestyle, changing psychosocial status, or ongoing drug/alcohol abuse (3). At this time, more comprehensive longitudinal studies are now just being conducted (64), so more definitive findings are not yet available. Nevertheless, the current findings suggested that persons with PTSD were at risk for early-age HD. It is noteworthy that PTSD, independent of other key psychological factors such as depression or combat exposure, seemed to be a significant marker of early-age HD mortality. Recently, it was reported that this PTSD association held, even in the presence of known biologic predictors for HD outcomes, such as abnormal erythrocyte sedimentation rates and abnormal white blood cell counts (10). Although it is well known that depression and PTSD were often comorbid (1,32), the robustness of PTSD as a marker for future mortality, independent of depression, was highly noteworthy (10), especially given previous reports related to the significance of depression in predicting adverse health outcomes (18,19,46,47). It is currently unclear if depression would have been significant in these previous studies if PTSD were also controlled. Further research is needed to assess this factor in future studies, especially among high-risk trauma-exposed populations.

Given these and other findings, early treatment interventions for traumatic stressor exposures seem warranted. After the World Trade Center attacks in New York City, early worksite interventions seemed to have been highly effective among the civilian workforce population (65). There is no reason to assume that this would not be the case for returning military personnel. It is worrisome, however, that on return service personnel have often not availed themselves of existing treatment services (5). This problem was not unique to military populations (66). Nevertheless, better clinical surveillance using both standardized PTSD screening scales and other tests seem justified for reducing the long-term burden of morbidity among trauma-exposed populations (63). Given that current conflicts will likely last for years (67), the occupational impact of war-zone service will be concentrated among select groups of personnel and will likely impact the federal budget and Veterans Administration disability compensation for decades (68). This study suggests, that in addition to the short-term psychological consequences previously reported among returning war-fighters (5,6), for some we can also expect longer-term stress injuries to manifest as clinical disease decades after exposure (69). Furthermore, although the toxic nature of these stressor exposures may differ from traditional occupational exposures, such as occupational exposure to toxic chemicals or heavy metals, they may be no less deadly.

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