Psychobiologic Predictors of Disease Mortality After Psychological Trauma

Implications for Research and Clinical Surveillance

Joseph A. Boscarino, PhD, MPH

Abstract: Research has suggested that exposure to traumatic events can result in adverse health outcomes. However, the reasons for this are unclear. We examined psychobiologic factors associated with disease mortality among a community-based sample of 4462 male veterans 30 years after military service, including posttraumatic stress disorder (PTSD), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, and cortisol/dehydroepiandrosterone-sulfate (cortisol/DHEA-s) ratio. In the study, 56% ($n = 2490$) were theater veterans who served in Vietnam and 44% ($n = 1972$) era veterans who served elsewhere. During baseline in 1985, 10.2% of theater and 3.4% of era veterans had current PTSD. At follow-up in 2000, 13.6% of men with current baseline PTSD were deceased, compared with 5% without PTSD. Analyses suggested that having PTSD, a high ESR, a high WBC count, and a high cortisol/DHEA-s ratio at baseline were associated with all-cause disease mortality at follow-up. With the exception of cortisol/DHEA-s ratio, these factors also predicted cardiovascular mortality. Depression was not consistently associated with mortality, once other factors were controlled. Noteworthy was that having PTSD had an impact on mortality nearly comparable to common indicators of disease in medicine, such as an ESR >65 mm/h and a WBC count >11,000 mm^3. This study suggests that the morbidity associated with PTSD may be comparable to laboratory measures of disease pathology in common use and warrants further investigation and surveillance among at risk populations.

Key Words: Posttraumatic stress disorder, PTSD, cardiovascular disease, white blood cell count, WBC, erythrocyte sedimentation rate, ESR, cortisol, dehydroepiandrosterone sulfate, survival analysis.

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Research suggests that having a history of posttraumatic stress disorder (PTSD) or exposure to psychological trauma is associated with increased medical morbidity (Boscarino, 1997; Felitti et al., 1998; Schnurr et al., 2000; Schnurr and Green, 2004; Sibai et al., 1989). Recently, investigators from the Centers for Disease Control (CDC) ascertained the cause of death among a national sample of 18,313 US Army veterans from the end of their military service through December 31, 2000 (Boehmer et al., 2004). In the CDC study, all-cause mortality appeared higher among Vietnam-theater veterans (TVs), those who served in Vietnam, compared with Vietnam-era veterans (EVs) who served elsewhere during the 30-year follow-up (Boehmer et al., 2004). Deaths from chronic diseases did not seem to differ by theater status. However, a more recent investigation among these veterans indicated that all-cause mortality was associated with PTSD among TVs ($N = 7924$), with a hazard ratio (HR) of 2.2 ($p < 0.001$), as well as for EVs ($N = 7364$) (HR = 2.0, $p = 0.001$) (Boscarino, 2006a). For TVs, PTSD was also associated with cardiovascular-related (HR = 1.7, $p = 0.034$), cancer, (HR = 1.9, $p = 0.018$), and external mortality (i.e., deaths from accidents, suicides, homicides, drug overdoses, and injuries of undetermined intent) (HR = 2.3, $p < 0.001$) (Boscarino, 2006a).

There are several reasons to expect a link between PTSD and disease mortality. First, psychological distress could result in disease pathology through alterations in the hypothalamic-pituitary-adrenocortical (HPA) and the sympathetic-adrenal-medullary (SAM) stress axes (Boscarino, 2004). Second, this mortality link could occur through altered behaviors, such as alcohol or caloric intake related to aversive psychological states, brought on by PTSD psychopathology, such as increased anxiety levels (Boscarino, 2004). Third, this association could be because of a shared physiologic mechanism, such as inadequate adrenal functioning, which may be associated with both psychological reactions to environmental stressors and biologic vulnerability to disease (Boscarino, 2004). Fourth, these associations also could be related to self-selection, whereby those who had PTSD and disease mortality might have behavioral traits such as antisocial personalities or lower intelligence levels (Boscarino, 2006b). Consequently, these individuals might have been more likely to have been "self-selected" for traumatic exposures and, thus, more likely to have PTSD. However, this association would be spurious because it would be the character trait that was related to both increased mortality and PTSD (Boscarino, 2006b).

In the current study we expanded upon earlier research (Boscarino, 2006a). Although studies have documented alterations in immune functioning following acute stress exposures (Ader and Cohen, 1993), recent studies have specifically reported an association between inflammation and PTSD (Boscarino, 2004; Boscarino and Chang, 1999a; Ironson, et al., 1997). For example, one study reported that PTSD-positive veterans were more likely to have white blood cell (WBC) and T-cell counts above the normal range and higher mean WBC, lymphocyte, T-cell, and CD4 cell counts (Boscarino and Chang, 1999a). Those with anxiety disorders had lymphocyte and T-cell counts above the normal range and also had reactive delayed subcutaneous hypersensitivity tests, suggesting the presence of highly sensitized T-cell lymphocytes. Another study confirmed that although PTSD victims had reduced natural killer cell cytotoxicity, they also had increased WBC counts (Ironson, et al., 1997). A meta-analytic review also suggested a consistent increase in WBC counts after exposures to acute and chronic stressors (Herbert and Cohen, 1993). Although the specific reasons for the association between psychological stress and inflammation are unclear, speculation has focused on neuroendocrine alterations, particularly as these relate to circulating plasma cortisol (Boscarino, 2004; Boscarino and Chang, 1999a). Given this body of research and the evidence that markers of inflammation, such high WBC counts and high erythrocyte sedimentation rates (ESR) in clinical research were often associated with adverse health outcomes (Andresdottir et al., 2003; Grzybowski et al., 2004), it was hypothesized that the presence of these markers would increase mortality risks among a trauma-exposed population.

Furthermore, given findings related to PTSD neuroendocrinology (Boscarino, 1996; Boscarino, 2004; Mason, et al., 1988; Yehuda, et al., 1995) and the suspected role of corticoadrenal steroids in premature aging (Morgan et al., 2006; Valenti, 2004), it was also hypothesized that baseline markers of neuroendocrinologic status would be predictive of future disease mortality. To assess this, we used the cortisol/dehydroepiandrosterone-sulfate (DHEA-s) ratio (Charney, 2004), a potential marker of HPA functional decline used in current research (Ferrari, et al., 2001; Valenti, 2004). Recently it was reported that lower DHEA-s levels were associated with PTSD (Boscarino, 2004) and other studies have reported this association for other mental health disorders as well, including for mood and general anxiety disorders (Charney, 2004; Ferrari et al., 2001; Grillon et al., 2006). It is important to note that although earlier studies suggested that PTSD was associated with lower cortisol levels (Boscarino, 1996; Yehuda, et al., 1995), this finding has not been consistent (Yehuda, 2002). Furthermore, subsequent research has suggested that this association is more complex than originally conceived and likely involves other HPA axis molecular mechanisms (Yehuda, 2006). It is entirely possible, and consistent with current research, that cortisol is increased at the onset of psychological disturbances and then decreases with the onset of chronic stress and/or the aging process (Charney, 2004; Grillon et al., 2006). Consequently, based on previous research (Charney, 2004), we used the cortisol/DHEA-s ratio as a more robust measure of neuroendocrinologic status and HPA functional decline in the current study (Morgan et al., 2006; Valenti, 2004).

The objective of this study was to assess the long-term health consequences of PTSD concurrent with physiologic functions known to be associated with adverse health outcomes. Research suggests that Vietnam veterans with current PTSD generally had this condition due to past wartime exposures (Boscarino, 1995; Kulka et al., 1990). Hence, for TVs, at least, many of them had PTSD for decades in the current study. The Vietnam EVs, of course, would have acquired their PTSD from other than war zone exposures, comparable to that among men without military service (Kessler et al., 1995). Our hypothesis was that PTSD would be a significant predictor of disease mortality (Boscarino, 2006a), but that given previous research (Andresdottir et al., 2003; Charney, 2004), biologic markers, possibly related to PTSD psychobiology (Boscarino, 1996; Boscarino, 2004; Boscarino and Chang, 1999a,b), would confer additional risks. Few studies have examined these risk factors for mortality within a general population study.

DATA AND METHODS

Study Population

Our study consisted of a random sample of all men who served in the US Army during the Vietnam War. These men were identified through records from the National Personnel Records Center (St Louis, MO). From these records, 18,581 personnel met the study criteria, including entering the military between 1965 and 1971, serving 1 enlistment, and having a service rank <E6. Participants were classified as Vietnam TVs if they served in Vietnam or as Vietnam EVs if they served elsewhere. Starting in January 1985, attempts were made to complete telephone interviews. From these efforts, 87% of TVs (7924) and 84% of the EVs (7364) were interviewed by telephone (overall completion rate = 86%). Among these persons, a random sample was selected for personal interviews and examinations. Altogether, 75% of the TVs ($N = 2490$) and 63% of the EVs ($N = 1972$) participated in this study phase (total = 4462). A detailed nonresponse analysis found no significant differences between participants and nonparticipants in this study (CDC, 1989a,b). Personal interviews and examinations required several days on site and were administered at Lovelace Medical Foundation, Albuquerque, NM, between June 1985 and September 1986. Further details regarding this study have been published elsewhere (Boehmer et al., 2004; Boscarino, 2006a; CDC, 1989a,b). The CDC Human Subject Review Committee approved the study protocols (CDC, 1989a,b).

Laboratory Methods

The current study included laboratory results for WBC counts, ESR, plasma cortisol, and DHEA-s. Morning blood collection at 7 a.m., via venipuncture method, was preceded by an overnight fast (CDC, 1989d). All blood specimens were collected on the second on-site examination day. After collection, all specimens were placed in a cooler or refrigerated and maintained at 2°C to 8°C until processed. Generally all specimens were processed within 24 hours or less. For quan-

tification of WBC counts, the Coulter s880 System (Coulter Electronics, Hialeah, FL) was used. Particle counting was accomplished by the impedance method. The results for ESR were obtained using the Westergren method. Serum cortisol samples were evaluated using a double antibody radioimmunoassay system. The Aria HT cortisol system was used to analyze serum cortisol concentrations (Becton Dickinson, Orangeburg, NY). A radioimmunoassay method was also used to measure serum DHEA-s concentrations, using an antibody radioimmunoassay kit from Diagnostic System Laboratories (Webster, TX). All laboratory determinations were monitored using standard quality-control procedures and were under the supervision of board-certified clinical pathologists (CDC, 1989d). Laboratory testing was preformed at the Clinical and Research Division, Department of Laboratories, Lovelace Medical Foundation. Additional information on these laboratory procedures has been published elsewhere (CDC, 1989d). For analytical purposes, clinical reference ranges for high WBC (11,000 mm^3) and high ESR (65 mm/h) were used in our analyses, based on Lovelace Medical Foundation laboratory values. For the cortisol/DHEA-s ratio, because no reference range existed, we defined values $\geq$95th percentile ($\geq$0.185) as the high reference range, which is a standard cut point in medicine (Pagana and Pagana, 1999).

Ascertainment of Vital Status and Cause-Specific Mortality

We assessed vital status from the date of completion of the telephone interviews starting on January 1, 1985, until the end of the mortality follow-up on December 31, 2000. Vital status was ascertained using several databases: the Department of Veterans Affairs Beneficiary Identification Record Locator Subsystem Death File, Social Security Administration Death Master File, and the National Death Index-Plus file (Boehmer et al., 2004). Vital status determination was obtained by combining all 3 mortality sources. As needed, additional information, such as actual death certificates, were obtained to confirm vital status. Veterans who had a match on at least 1 of the 3 databases were determined to be deceased. All veterans whose vital status were uncertain because of a lack of data to resolve questionable matches or not identified by any of the databases were assumed to be living on December 31, 2000. Underlying cause of death was obtained from the National Death Index-Plus. Cause of death was coded according to the International Classification of Diseases (ICD) revision in place at the time of death: the Ninth Revision (ICD-9) for deaths between January 1, 1979, and December 31, 1998, and the Tenth Revision (ICD-10) for deaths between January 1, 1999, and December 31, 2000. For cases in which cause of death codes were not available, investigators obtained official copies of death certificates, which were coded by a nosologist at the National Center for Health Statistics (Boehmer et al., 2004). In the current study, outcomes of interest included mortality caused by any diseases and cardiovascular and circulatory-related conditions, more specifically. Those who died of external causes (N = 55) were excluded from the current study because our focus was on disease-related outcomes, not self-inflicted ones, which was the focus of another study (Boscarino, 2006b). In addition, we assumed that there was no strong biologic reason to suspect a link between the biomarkers we examined and external mortality.

Ascertainment of PTSD

Because the PTSD criteria used in our study were based on earlier nomenclatures (Boscarino, 2006a; Kulka et al., 1990), we used 2 measures to validate results. In our study, psychiatric evaluations were from Version III of the Diagnostic Interview Schedule (DIS), based on the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III) (APA, 1980; Robins et al., 1987). This instrument was administered at the end of the on-site examination. For our study, lifetime DIS-PTSD was defined as present if the veteran ever met the criteria for PTSD at study baseline (CDC, 1989b). The second PTSD measure used was based on a telephone survey administered by Research Triangle Institute (RTI) before the DIS (CDC, 1989a,b). For this measure, veterans were asked to report 15 PTSD-related symptoms that occurred in the past 6 months. Consistent with DSM-III, a veteran was classified as having current PTSD if he reported at least 1 criterion B symptom (re-experiencing), at least 1 criterion C symptom (avoidance), and at least 2 criterion D symptoms (hyperarousal). As previously reported, analyses of participants who completed both the RTI-PTSD and the DIS-PTSD scales confirmed that the RTI-PTSD criteria were consistent with the DIS diagnosis of PTSD (Boscarino, 2006a,b).

Study Control Variables

Our study included the following demographic variables: age, race, marital status, and place of birth. We also included variables related to character traits, such as the following: volunteer status, antisocial personality, intelligence, and history of other mental health disorders that could affect health outcomes, such as lifetime depression or alcohol abuse/dependence (CDC, 1989c). Other potential confounding variables included were baseline smoking status, pack-years of cigarette smoking, and body mass index (BMI). Age was based on the veteran's age at the time of 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 vs. nonwhite). Marital status was based on whether the veteran was married at military separation and was from the military record. Place of birth was classified as United States versus foreign and based on the military record. Army volunteer status was classified as volunteer versus draftee and based on the military record. Intelligence was taken from the military record and based on the general technical examination at induction (CDC, 1989b). This measure was used as a continuous variable. Antisocial personality disorder, lifetime depression, current depression, and lifetime alcohol abuse/dependence were based on having met the diagnostic criteria for these disorders and based on the DIS. BMI was used as a continuous variable, based on the subject's weight divided by the subject's height squared. 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. Finally, as noted below, because we combined the TVs and

EVs in the multivariate (MV) analyses, we also included a binary measure of theater status as covariate control in the analytic models. It should be noted that although the PTSD cases among the EVs were due to noncombat stressor exposures, it was not possible to characterize these exposures beyond this in the current study. Nevertheless, the data showed that 88% of TVs with lifetime PTSD had this related to combat exposure and 12% had this related to noncombat or both combat and noncombat exposures combined. Thus, the impact of noncombat PTSD, at least among the TVs, was likely limited in the current study.

Statistical Methods

First, we describe the bivariate differences found by PTSD and vital status. Next, we use Cox regressions to calculate both bivariate and MV HRs predicting all-cause disease and cardiovascular-related mortality, respectively, by PTSD and biomarker status. We conducted these assessing for PTSD and biomarker status separately and then controlling for potential bias and confounding in the final model. Because other research has suggested that depression was associated with disease mortality (Everson-Rose and Lewis, 2005; Hayward, 1995), we entered this measure into our final models and report these results. For these analyses, we analyzed the results for TVs and EVs combined, because no effect modification was confirmed statistically by veteran status for the model we examined, even though there were bivariate differences reported between these veteran groups (Boscarino, 2006a,b). In addition, for EVs, it was not possible to estimate Cox regressions for cardiovascular-related mortality, due to the lower prevalence of PTSD and cardiovascular-related mortality among this cohort. In fact, we found no PTSD cases (neither lifetime nor current PTSD) among those who experienced cardiovascular-related mortality among this group. Hence, in the current study, we present our results for the TVs and EVs combined and only briefly discuss our results for these groups separately. Because PTSD and biomarker status were only assessed in 1985 to 1986, we included only those who were alive and completed the 1985 to 1986 interviews and exams. Thus, we examined survival time from interview completion starting on January 1, 1985 through to December 31, 2000, a period of 16 years. For these analyses, we evaluated the main proportional hazards assumption (Hosmer and Lemeshow, 1999), controlled for potential confounding, and tested for effect modification for race, marital status, place of birth and, as noted, veteran status. None of these possible effect modifiers were significant. However, because previous studies related to PTSD and HPA axis activation have suggested that interactions may exist between psychological and biological disease mechanisms (Boscarino, 2004, Yehuda, 2006), we also assessed specific 2×2 interaction effects for PTSD by the biomarkers used in the current study.

Because marital status and place of birth were not significant in the MV models, these were eliminated from the models but are presented in the descriptive tables. BMI was marginally significant but retained in the models, given its clinical significance in the outcomes of interest. In addition, because WBC count was highly correlated with ESR ($r = 0.30$, $p < 0.001$) MV analyses including these 2 inflammatory markers were conducted separately. All p values presented were based on the 2-tail test. Given our combined sample size, for the bivariate descriptive statistics we only highlight percentage differences of about 10% or greater in the text, because differences of ~3% were statistically significant. All p values for these variables were presented in the bivariate tables, however. Finally, because several data sources were used in this study and the veterans were on site for several days, most data problems were limited. In addition, only positive symptoms are counted for DIS diagnoses, restricting missing information for mental health status. Consequently, missing data were rare in the current study. The one exception was for intelligence, whereby 49 missing cases were recoded to the median value. No laboratory values were missing in the current study. Statistical analyses were performed using Stata, version 9.1 and SPSS version 14.

RESULTS

As reported elsewhere, approximately 10% of TVs ($n = 255$) and 3% of EVs ($n = 68$) had current PTSD at baseline ($p < 0.001$) (Boscarino, 2006a). In the current study, 250 men were deceased at follow-up (6%), including deaths from cardiovascular-related conditions (TV = 43; EV = 22), external causes (TV = 36; EV = 19), cancer (TV = 28; EV = 24), infectious diseases (TV = 10; EV = 9), digestive conditions (TV = 13; EV = 6), and other disease-related conditions (TV = 24; EV = 16). Descriptive statistics (Table 1) indicated that current PTSD was associated with all-cause mortality, with 13.6% deceased at follow-up compared with 5% without current PTSD ($p < 0.001$). Clinically significant predictors of current PTSD in bivariate analyses included lifetime alcohol abuse/dependence, lifetime depression, nonwhite race, lower intelligence, antisocial personality disorder, and being an army volunteer. Results were similar for lifetime PTSD (available upon request). In addition to current PTSD, noteworthy variables of clinical significance for all-cause mortality in bivariate analyses included lifetime alcohol abuse/dependence, lifetime depression, nonwhite race, lower intelligence, antisocial personality disorder, high cigarette pack-years, and high ESR (Table 2).

As discussed, Cox regressions were conducted for all-cause disease mortality (Table 3) and for cardiovascular-related mortality (Table 4) for the TVs and EVs combined. For overall disease mortality, both lifetime and current PTSD were significant predictors (p values < 0.001), with HRs of 2.1 and 3.1, respectively (model 1, left panel). When the biomarkers were added (model 2), the HRs for lifetime and current PTSD remained essentially the same. In addition, for all-cause disease mortality, the coefficients for both ESR and cortisol/DHEA-s were significant (p values < 0.001), with HRs of 4.8 and 3.3 for the lifetime PTSD model and 4.5 and 3.1 for the current PTSD model, respectively. After adjusting for potential bias and confounding, although reduced, all 3 predictors in the lifetime and current PTSD models remained significant for this outcome (p values < 0.05). Next, for all-cause disease mortality, we assessed interaction effects for PTSD × ESR and PTSD × cortisol/DHEA-s ratio. Only 1 of

TABLE 1. Current PTSD at Baseline by All-Cause Mortality at Follow-Up and Study Predictor Variables ($N = 4462$)

Variable	% Total (*N*)	% No Current PTSD at Baseline	% Current PTSD at Baseline	*p**
Deceased at follow-up (all causes)	5.6 (250)	5.0 (206)	13.6 (44)	<0.001
Lifetime alcohol abuse/dependence	46.7 (2084)	45.2 (1869)	66.6 (215)	<0.001
Lifetime depression	10.5 (468)	8.8 (366)	31.6 (102)	<0.001
Age 40+ at interview	19.8 (883)	20.5 (847)	11.1 (36)	<0.001
Nonwhite race	18.1 (808)	17.0 (705)	31.9 (103)	<0.001
Married at discharge	28.6 (1275)	28.4 (1177)	30.3 (98)	0.466
Foreign born	4.2 (186)	3.9 (163)	7.1 (23)	0.006
Intelligence—lowest quintile	18.7 (836)	17.4 (720)	35.9 (116)	<0.001
Antisocial personality disorder	22.1 (988)	20.8 (861)	39.3 (127)	<0.001
Volunteered for military service	36.9 (1645)	36.2 (1497)	45.8 (148)	0.001
Pack-years of cigarette smoking: 19+ years	32.9 (1470)	32.6 (1351)	36.8 (119)	0.122
Body mass index >30	16.8 (750)	16.7 (691)	18.3 (59)	0.467
High white blood cell count	3.0 (132)	2.8 (117)	4.6 (15)	0.063
High erythrocyte sedimentation rate	6.3 (283)	6.1 (252)	9.6 (31)	0.013
High cortisol/dehydroepiandrosterone sulfate ratio	4.6 (204)	4.4 (181)	7.1 (23)	0.023
(*N*)	(4462)	(4139)	(323)	—

*2-sided χ^2 test, $df = 1$.
Table 1 percents based on percents for column variable shown. For example, of those with current PTSD in Table 1 at baseline, 13.6% were deceased at follow-up.

TABLE 2. All-Cause Mortality at Follow-Up by Study Predictor Variables ($N = 4462$)

Variable	% Total (*N*)	% Alive	% Dead	*P**
Current PTSD	7.2 (323)	6.6 (279)	17.6 (44)	<0.001
Lifetime alcohol abuse/dependence	46.7 (2084)	45.9 (1935)	59.6 (149)	<0.001
Lifetime depression	10.5 (468)	10.0 (420)	19.2 (48)	<0.001
Age 40+ at interview	19.8 (883)	19.5 (820)	25.2 (63)	0.027
Nonwhite race	18.1 (808)	17.3 (729)	31.6 (79)	<0.001
Married at discharge	28.6 (1275)	28.6 (1204)	28.4 (71)	0.950
Foreign born	4.2 (186)	4.1 (174)	4.8 (12)	0.607
Intelligence—lowest quintile	18.7 (836)	18.1 (763)	29.2 (73)	<0.001
Antisocial personality disorder	22.1 (988)	21.5 (907)	32.4 (81)	<0.001
Volunteered for military service	36.9 (1645)	36.8 (1551)	37.6 (94)	0.805
Pack-years of cigarette smoking: 19+ years	32.9 (1470)	32.2 (1357)	45.2 (113)	<0.001
Body mass index—highest quintile	16.8 (750)	16.5 (696)	21.6 (54)	0.037
High white blood cell count	3.0 (132)	2.7 (115)	6.8 (17)	<0.001
High erythrocyte sedimentation rate	6.3 (283)	5.6 (234)	19.6 (49)	<0.001
High cortisol/dehydroepiandrosterone sulfate ratio	4.6 (204)	4.1 (174)	12.0 (30)	<0.001
(*N*)	(4462)	(4212)	(250)	—

*2-sided χ^2 test, $df = 1$.
Table 2 percents based on percents for column variable shown. For example, of those deceased at follow-up in Table 2, 17.6% had current PTSD at baseline.

these was found significant at the <0.05 level—current PTSD × cortisol/DHEA-s ratio (HR = 2.6, 95% CI = 1.0–6.6, $p = 0.048$). The results for cardiovascular-related mortality were similar with 1 exception (Table 4). As seen in Table 4, the cortisol/DHEA-s ratio was neither significant in the lifetime PTSD nor the current PTSD model. No interaction was observed for either PTSD × ESR or for PTSD × cortisol/DHEA-s in these models. It should be noted that with only 1 exception (for the lifetime PTSD, all-cause model), and contrary to previous research, depression was not a significant predictor of mortality in these models.

As noted, because ESR and WBC counts were highly correlated, we ran the models that contained WBC results separately. These results were similar to those reported for ESR. For example, in the final models containing all the variables (model 3), the HRs associated with high WBC in the lifetime and current PTSD models for all-cause mortality was 2.2 ($p = 0.003$) and 2.3 ($p = 0.002$), respectively. In these same WBC models, the HR for lifetime PTSD was 1.5 ($p = 0.055$) and for current PTSD it was 2.1 ($p < 001$), respectively. In the final models, the HRs associated with high WBC in the lifetime and current PTSD models for cardiovascular-related mortality

TABLE 3. Cox Proportional Hazard Regressions for All Veterans for All-Disease Mortality at Follow-Up by PTSD, Inflammatory, and Neuroendocrine Status at Baseline ($N = 4407$)

	Any Chronic Disease Mortality – Total Deaths = 195 (Person-Years at Risk ~ 70,500 Person Years)								
	Model 1			Model 2*			Model 3**		
Psychobiologic Predictors	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Lifetime PTSD ($n = 438$)	2.1	1.5–3.0	<0.001	2.1	1.5–3.0	<0.001	1.6	1.1–2.3	0.027
High ESR ($n = 280$)	—	—	—	4.8	3.4–6.6	<0.001	3.7	2.6–5.2	<0.001
High Cortisol/DHEA-S Ratio ($n = 200$)	—	—	—	3.3	2.2–4.9	<0.001	2.8	1.8–4.3	<0.001
Current PTSD ($n = 315$)	3.1	2.1–4.4	<0.001	2.8	1.9–4.0	<0.001	2.1	1.4–3.1	<0.001
High ESR ($n = 280$)	—	—	—	4.5	3.3–6.3	<0.001	3.6	2.5–5.0	<0.001
High Cortisol/DHEA-S Ratio ($n = 200$)	—	—	—	3.1	2.0–4.7	<0.001	2.9	1.9–4.4	<0.001

*Models concurrently controlled for PTSD, ESR, and cortisol/DHEA ratio only.

**In addition to PTSD, ESR, and cortisol/DHEA ratio, models also concurrently controlled for age, race, intelligence, pack-years of smoking, BMI > 30, Army volunteer status, theater status, antisocial personality disorder, history of alcohol abuse/dependence, and history of depression.

HR indicates hazard ratio; CI, confidence interval; PTSD, posttraumatic stress disorder; ESR, erythrocyte sedimentation rate; DHEA-s, dehydroepiandrosterone sulfate; BMI, body mass index. Note: Lifetime and current PTSD models were run separately.

TABLE 4. Cox Proportional Hazard Regressions for all Veterans for Cardiovascular-Related Mortality at Follow-Up by PTSD, Inflammatory, and Neuroendocrine Status at Baseline ($N = 4277$)

	Cardiovascular-Related Mortality – Total Deaths = 65 (Person-Years at Risk ~ 68,400 Person Years)								
	Model 1			Model 2*			Model 3**		
Psychobiologic Predictors	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Lifetime PTSD ($n = 416$)	2.6	1.4–4.6	0.002	2.6	1.4–4.7	0.002	2.1	1.1–4.0	0.028
High ESR ($n = 247$)	—	—	—	4.1	2.2–7.6	<0.001	2.9	1.5–5.5	0.001
High Cortisol/DHEA-S Ratio ($n = 179$)	—	—	—	1.9	0.8–4.7	0.166	1.6	0.6–4.1	0.325
Current PTSD ($n = 290$)	3.2	1.6–6.34	0.001	3.2	1.6–6.3	0.001	2.2	1.1–4.4	0.033
High ESR ($n = 247$)	—	—	—	5.5	2.8–10.9	<0.001	2.8	1.5–5.3	0.001
High Cortisol/DHEA-S Ratio ($n = 179$)	—	—	—	2.2	0.8–6.2	0.131	1.6	0.6–4.1	0.297

*Models concurrently controlled for PTSD, ESR, and cortisol/DHEA ratio only.

**In addition to PTSD, ESR, and cortisol/DHEA ratio, models also concurrently controlled for age, race, intelligence, pack-years of smoking, BMI >30, Army volunteer status, theater status, antisocial personality disorder, history of alcohol abuse/dependence, and history of depression.

HR indicates hazard ratio; CI, confidence interval; PTSD, posttraumatic stress disorder; ESR, erythrocyte sedimentation rate; DHEA-s, dehydroepiandrosterone sulfate; BMI, body mass index. Note: Lifetime and current PTSD models were run separately.

was 3.3 ($p = 0.004$) and 3.4 ($p = 0.003$), respectively. In these same cardiovascular-related WBC models, the HR for lifetime PTSD was 2.0 ($p = 0.042$) and for current PTSD it was 2.2 ($p < 0.03$), respectively. The results for the cortisol/DHEAs ratio were essentially the same as the ESR models shown in Tables 3 and 4 (available from author upon request).

To assess Cox proportional hazards assumptions, we used Schoenfeld residuals and the "stphtest" procedure in Stata to assess fit for our models (Stata, 2006). This test is equivalent to testing that the log hazards ratio function is constant over time (Cleves et al., 2002). The results of the procedure indicated that all the final models used were adequate, with p values >0.05.

DISCUSSION

In the current study, results suggested that having lifetime or current PTSD, a high ESR, and a high cortisol/DHEA-s ratio at baseline were associated with all-cause disease mortality at follow-up. For cardiovascular-related mortality, all these variables remained significant, except the cortisol/DHEA-s ratio. WBC counts, also a measure of inflammation and related to ESR, were also significant in these models. It should be noted that when EVs were examined separately only baseline ESR (and WBC counts, respectively) was significant in predicting all-cause mortality. The reasons for the differences found between theater and EVs are unclear, but may be related to the differences in PTSD expression, perhaps reflecting variations in the duration and/or intensity of traumatic stressor exposures. However, limited trauma exposure data prevented exploration of this in more detail in this study.

Currently there is evidence that exposure to environmental stressors may alter neuroendocrine and immune functions and, therefore, directly or indirectly cause or exacerbate existing diseases (Boscarino, 2004). In particular, given the reduced cortisol levels found among PTSD victims, it has been suggested that a down-regulated glucocorticoid system may result in elevations in leukocyte and other immune inflammatory activities (Chrousos, 1995). It is currently known that glucocorticoids influence the trafficking of circulating leukocytes and affect functioning of leukocyte and

immune accessory cells (Chrousos, 1995). Recently, it has become evident that the HPA stress axis, and the adrenal gland in particular, is a major site for both the synthesis and action of numerous cytokines (Bornstein and Rutkowski, 2002). It has been suggested that, in addition to cytokine-mediated activation of adrenal regulation, there are cytokine independent immune-adrenal interactions, and that this immune-endocrine crosswalk has been implicated in disease (Bornstein and Rutkowski, 2002). Consistent with these finding, it has recently been reported that veterans with chronic PTSD were at greater risk for inflammatory and autoimmune diseases (Boscarino, 2004). However, there are questions related to specification of the psychobiologic-disease mechanisms involved in this causal pathology (Boscarino, 2004; Charney, 2004; Schnurr and Green, 2004), upon which there has been speculation (Boscarino, 1996; Yehuda, 2006).

Currently, evidence suggests that physiologic arousal experienced during recollection of traumatic events by PTSD victims is associated with a cascade of neuroendocrine processes related to HPA/SAM activity (Friedman, 2003; McEwen, 1998). Although these are initiated in the central nervous system, they are subsequently carried out by neurochemical mechanisms that have wide-ranging affects on human physiology. Although research suggests that these processes are highly complex, it is likely that excessiveness of stress axis activation may lead to a host of diseases through one or more of these mechanisms (Chrousos, 1995; McEwen, 1998). Furthermore, research suggests that there are genetic liabilities for PTSD and exposure to psychological trauma (Gurvits et al., 2006; Stein et al., 2002; True et al., 1993). However, it is also possible that genetic liabilities that make persons susceptible to PTSD (e.g., those related to adrenal functioning) may later make individuals susceptible to certain diseases, such as inflammatory conditions (Boscarino, 2004; Moncek et al., 2001).

This study has strengths and 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 (Boehmer et al., 2004). Furthermore, although our PTSD measures had concurrent and predictive validity, these were based on earlier versions of this nomenclature (CDC, 1989b). However, given the results of our validation study (Boscarino, 2006a) and the fact that the PTSD measures used showed convergent validity (Boscarino, 2006b), we conclude that our PTSD measures were generally consistent with the presence of PTSD. Other limitations were that our study included only men and those who survived to participate in the baseline survey. Another limitation was that the overall morality rate in the study was low ($<6\%$), limiting statistical power and, subsequently, the MV analyses in this study. In addition, as suggested, the results for EVs differed from those of TVs. It was not clear why this was the case. The limited prevalence of mortality outcomes, the lower prevalence of PTSD among EVs, and the lack of more detailed trauma exposure data, restricted the current study and our ability of analyzing these disparities in more detail, unfortunately. Study strengths, however, were that the research was based on a large, community-based population, mortality ascertainment was comprehensive, key measures of inflammation and neuroendocrine status were included, and potential selection biases and confounders were potentially controlled.

Nevertheless, without longitudinal risk-factor data beyond baseline, a challenge for this research is assessing time-dependent behavioral factors that could be related to psychological trauma, but also could be associated with mortality, such as sedentary lifestyle or ongoing drug abuse (Schnurr and Green, 2004). As has been suggested, understanding both the physiologic and the psychological aspects of traumatic phenomenon seem warranted to effectively treat the sequelae associated with these stressor exposures (Boscarino et al., 2006a). This clinical dualism was reflected in the current findings—both psychometric and biometric measures predicted long-term health outcomes among men exposed to psychological trauma.

CONCLUSION

Our findings suggest that persons with PTSD and clinical-level indications of inflammation and/or neuroendocrine dysregulation at baseline were at risk for future disease mortality. Each of these markers conferred mortality risks, but high ESR, a general measure of inflammatory activity, was a more consistent predictor and it was the best predictor of cardiovascular-related mortality. Previous research has associated PTSD to both immune/inflammatory and endocrine system activity (Boscarino, 1996; Boscarino, 2004; Ironson et al., 1997), but each of these in the current study contributed to mortality risk, independent of PTSD. Interaction effects between PTSD and the biomarkers examined in the current study were limited, however.

This research seems to suggest that although PTSD is a predictor of future disease mortality, there are other common biologic factors operative among trauma-exposed populations. Although only 1 interaction was detected in our study (e.g., current PTSD $\times$ cortisol/DHEA-s ratio), the degrees to which these psychobiologic factors are interrelated are still unclear and will require additional research. On the other hand, it is noteworthy that the presence of PTSD (independent of other key psychological factors, such as depression) seems to be a significant marker of future disease mortality, even in the presence of known biologic predictors for such outcomes, such as ESRs or WBC counts. However, based on the research discussed, it is possible that the biologic findings among these men were also related to past traumatic stress exposures. Given these findings, even in the absence of clear etiology, early treatment interventions for traumatic stressor exposures seem warranted (Boscarino et al., 2006). Furthermore, better clinical surveillance using both standardized PTSD instruments and biometric tests seem justified to reduce the burden of disease morbidity among at risk, trauma-exposed populations.

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