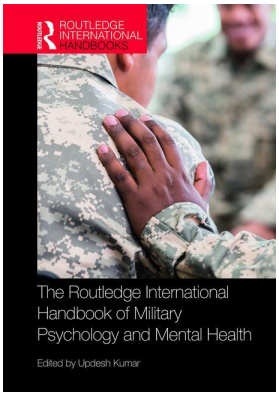


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Updesh Kumar

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# 30

# CHRONIC DISEASE RISKS AND SERVICE-RELATED POST-TRAUMATIC STRESS DISORDER IN MILITARY VETERANS

*Jeanne Mager Stellman and Steven D. Stellman*

Post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI) have come to be recognized as the hallmark signatures of the Iraq conflict (2003–2011) and of the ongoing war in Afghanistan (Institute of Medicine, 2012). By contrast, the diagnosis of post-traumatic stress disorder did not even formally enter the Diagnostic and Statistical Manual of Mental Disorders until 1980 (American Psychiatric Association, 1980), seven years after the stand-down of U.S. troops in Vietnam, despite decades—one might even say millennia—of evidence demonstrating that exposure to traumatic conditions on the battlefield leads to serious, persistent mental health problems for many war veterans.

In many ways, the relationship between the traumatic combat exposures, development of post-traumatic stress disorder and co-morbid physical health conditions is following a similar trajectory: there are dozens of peer-reviewed studies showing that co-morbidity exists, but *recognition* of such co-morbidity is missing from general public health discourse on veteran health and veteran benefit programs. Of particular importance for both treatment of those with disorders, and for gaining further understanding of the relationships, is that fact that co-morbidity of physical illness is generally absent from medical practice guidelines, especially in relevant medical specialties. As noted by Koenen et al. (2017), the American Diabetes Association does not cite stress as a risk factor, nor does the American Heart Association consider there to be an established causal relationship between disease development and stress (as of 2013 in Koenen et al.).

In this chapter we review the literature on the relationship between traumatic military exposures and post-traumatic stress disorder and on the development and the incidence of co-morbid physical health conditions, diseases and mortality. We discuss various models that have been proposed for the relationship between trauma, post-traumatic stress disorder and physical health comorbidity. We also discuss some of the methodological issues that arise when designing and executing studies to test the strength and direction of these relationships. We provide supportive longitudinal data for co-morbidity derived from our cohort study of 3,403 Vietnam veterans who were randomly selected from American Legion membership and surveyed

in 1984 and 1998. Finally, we provide suggestions for future research and for improvements in health services and benefits available to veterans.

## Reviews

A number of reviews of post-traumatic stress disorder as a precursor or predictor of a variety of physical illnesses have appeared within the past dozen years (Table 30.1). Most recently, Ryder, Azcarate and Cohen (2018) have provided an extensive review. Most reviews focus on cardiovascular diseases, varying mainly in the extent of including other co-morbidities. Some of the reviews also provide a perspective on biological mechanisms and biomarkers current at the time of publication. Bedi and Arora (2007), for example, summarize a large number of studies of stressors and heart disease, emphasizing the role of the sympathetic nervous system, such as disturbances in the sympathoadrenal and the hypothalamic-pituitary-adrenal axis, neuroendocrine responses to chronic stressors and allostatic load (see below for further discussion of biological responses). However, they provide little detail on individual studies. By contrast, Qureshi, Pyne, Magruder, Schulz and Kunik (2009) summarize, in-depth, both positive and negative findings of seven epidemiological studies that investigated associations between post-traumatic stress disorder and diseases of the heart, endocrine system (diabetes and thyroid disease), skin, digestive system (ulcers), genitourinary system and musculoskeletal system (arthritis), as well as neurological diseases (epilepsy, stroke), female reproductive system and respiratory system (asthma) (Qureshi et al., 2009). Pacella, Hruska and Delahanty (2013) carried out a formal meta-analysis of over 60 studies involving both veteran and civilian populations. Their results demonstrated significant relationships between post-traumatic stress disorder and a set of disease endpoints that include physical cardio-respiratory and gastrointestinal outcomes, as well as musculoskeletal pain, general health symptoms, medical conditions and health-related quality of life (Pacella et al., 2013). Studies of the impact of post-traumatic stress disorder on cardiovascular disease have also been presented by Levine, Levine and Levine (2014), while Cohen, Edmondson and Kronish (2015) summarize some of the same studies, but include depression along with post-traumatic stress disorder. Table 30.1 also includes narrower reviews: one on post-traumatic stress disorder and reproductive outcomes (Krulewitch, 2016) and one on post-traumatic stress disorder and diabetes (Vancampfort et al., 2016).

Given the emphasis on the potential role of external stressors in the etiology of cardiovascular diseases and the proliferation of potential explanatory mechanisms, it is not surprising that the majority of studies of post-traumatic stress disorder comorbid with physical illnesses focus on cardiovascular outcomes. Table 30.2 summarizes 11 studies published between 1994 and 2013 that present evidence for comorbid associations of cardiovascular diseases with diabetes, digestive disorders, musculoskeletal and other problems.

While epidemiological literature on physical ailments comorbid with post-traumatic stress disorder is largely dominated by cardiovascular diseases, a number of studies have addressed other endpoints as well. Post-traumatic stress disorder as a predictor of deaths due to suicide and accidental poisoning has been reported in Veteran Affairs (VA) studies (Bullman & Kang, 1994). In a nationally representative sample of veterans drawn in the mid-1980s and followed through 2000, veterans with post-traumatic stress disorder were at increased risk of death from multiple causes including total cardiovascular disease, cancer and external causes (e.g., motor vehicle accidents, accidental poisoning, suicide and homicide) (Boscarino, 2006).

Studies of reproductive outcomes among female veterans have also shown post-traumatic stress disorder effects. Female veterans of the Iraq and Afghanistan conflicts had significantly greater risks for a number of outcomes, including sexually transmitted infections, urinary

*Table 30.1* Review articles published since 2007 summarizing findings on post-traumatic stress disorder as a predictor or risk factor for cardiovascular disease and other physical health outcomes

| *Publication year* | *Reference* | *Disease or diseases covered* |
|---|---|---|
| 2007 | Bedi & Arora (2007) | Cardiovascular |
| 2009 | Qureshi et al. (2009) | Cardiovascular, diabetes, cancer, neurological, digestive, musculoskeletal |
| 2013 | Pacella et al. (2013) | Cardiovascular, digestive |
| 2014 | Levine et al. (2014) | Cardiovascular, diabetes, neurological |
| 2015 | Cohen, Edmondson & Kronish (2015) | Cardiovascular |
| 2016 | Krulewitch (2016) | Reproductive |
| 2016 | Vancampfort et al. (2016) | Diabetes |
| 2017 | Edmondson & von Kanel (2017) | Cardiovascular |
| 2017 | Koenen et al. (2017) | Cardiovascular |
| 2018 | Ryder, Azcarate, & Cohen (2018) | Cardiovascular, diabetes, musculoskeletal |

*Table 30.2* Studies of post-traumatic stress disorder and conditions comorbid with cardiovascular disease

| *Study* | *Design* | *Other endpoints* |
|---|---|---|
| Kawachi, Sparrow, Vokonas, & Weiss (1994) | Cohort | Cardiovascular and "sudden" death |
| Boscarino (1997) | Cross-sectional | Diabetes, digestive, musculoskeletal, neurological |
| Schnurr, Spiro, & Paris (2000) | Cohort | Diabetes, digestive, musculoskeletal, dermatological |
| Boscarino (2006) | Cohort | Cancer, all-cause mortality, external cause mortality |
| Boscarino (2008) | Cohort | Depression, substance use |
| O'Toole & Catts (2008) | Cohort | Digestive, dermatological, musculoskeletal, respiratory |
| Andersen, Wade, Possemato, & Ouimette (2010) | Cohort | Diabetes, neurological, digestive, musculoskeletal |
| Cohen, Marmar, Ren, Bertenthal, & Seal (2009) | Cross-sectional | Hypertension, diabetes, obesity |
| Cohen et al. (2010) | Cross-sectional | Health care utilization |
| Ahmadi et al. (2011) | Cross-sectional | Hypertension, diabetes, cardiovascular biomarkers, mortality |
| Wachen et al. (2013) | Cross-sectional | Diabetes, digestive, musculoskeletal, neurological, respiratory |

tract infections and inflammatory diseases of the pelvic organs, candida vaginitis, genital pain, endometriosis and infertility (Cohen et al., 2012). In a study of more than 16,000 deliveries covered by the Veterans Health Administration between 2000 and 2012, births to mothers with post-traumatic stress disorder were significantly more likely to experience a preterm birth (Shaw et al., 2014).

Besides concerns about diagnosed illnesses, there have been a number of studies comparing reports of multiple symptoms in veterans with post-traumatic stress disorder to those without post-traumatic stress disorder. These findings often emerge in studies that focus on a diagnosable disease outcome but that also include general questions on an array of physical symptoms. Taken individually, these associations may be difficult to categorize, but systematic study of such reports

could lead to identification of new co-morbidities or complications in veterans with post-traumatic stress disorder. In the Normative Aging Study of veterans, Schnurr and Spiro (1999) reported higher post-traumatic stress disorder scores in veterans with poorer SF-36 physical and mental health. In a study of over 2,300 Gulf War veterans, post-traumatic stress disorder symptomatology was associated with symptomatic health problems in both women and men, independent of combat exposure. Similar results were observed in a sample of 1,030 Iraq and Afghanistan veterans from Mid-Atlantic states (Schry et al., 2015; Wagner, Wolfe, Rotnitsky, Proctor, & Erickson, 2000). In the cohort of American Legionnaires, surveyed in 1984 and 1998, significantly greater number of reports of five non-specific physical symptoms (fainting spells, fatigue, aches, cold, skin problems) and poorer family functioning (marital and sexual satisfaction) in those with symptoms of post-traumatic stress disorder was observed (Koenen, Stellman, Sommer, & Stellman, 2008).

In a study of 1,022 DVA and community clinic cardiac patients, those with post-traumatic stress disorder had a greater burden of physical symptoms, diminished quality of life and greater physical limitations, irrespective of comorbid depression (Cohen, Marmar, Ren, Bertenthal, & Seal, 2009). Among National Guard and Reserve members recently returned from Iraq and Afghanistan, post-traumatic stress disorder was a strong predictor of SF-36 measures of physical and mental health aggregate scores (Asnaani, Reddy, & Shea, 2014). A cross-sectional study of more than 5,500 Vietnam-era veterans showed poorer health functioning in all domains of the Veterans RAND 36-item health survey and the WHO Disability Assessment Schedule 2.0 among those with post-traumatic stress disorder (Goldberg et al., 2014). In the National Health and Resilience in Veterans Study, post-traumatic stress disorder was found to be a predictor of sleep disorder, obstructive lung diseases (asthma, COPD), osteoporosis or osteopenia and migraine (El-Gabalawy, Blaney, Tsai, Sumner, & Pietrzak, 2018).

## *Vietnam veteran mortality studies*

The evolution of epidemiological thinking regarding the impact of PTSD on long-term health may be illustrated in mortality studies. The earliest mortality studies of Vietnam veterans focused on physical health outcomes and environmental etiologies, giving little attention to mental health conditions such as PTSD as possible predictors or modifiers of mortality risks. Identification of increased suicide risks led to awareness of possible links to mental health conditions, including PTSD, leading to incorporation of measures of PTSD, with the most recent studies providing strong evidence for higher death rates among veterans with PTSD.

Shortly after the War, states with Vietnam veteran bonus payment programs carried out epidemiological analyses by linking bonus payment files to state death records. In Massachusetts, standardized proportional mortality ratios (PMRs) and mortality odds ratios (MORs) were both significantly elevated for soft-tissue sarcoma (STS), compared to Vietnam era veterans (PMR = 880, MOR = 5.16) as well as non-veterans. STS is a cancer linked to exposure to the herbicide Agent Orange and its dioxin contaminant (Kogan & Clapp, 1985). A comparison of West Virginia veterans who had served in Vietnam to non-veterans showed Vietnam veterans with significantly high PMRs for larynx cancer (429) and STS (429) and with elevated Hodgkin disease (208, not significant). Veterans who had served in Vietnam also had significantly higher risks for total lymphoma as well as Hodgkin disease and testicular cancer, and higher STS (not significant) (Holmes, 1986). The New York State Department of Health compared MORs among veterans with Vietnam service who died in New York State to veterans of the Vietnam era with no Vietnam service (total n = 4,558). The causes with the most elevated MORs and their

95% confidence intervals were non-motor vehicular injuries of transport (MOR = 2.18, 95% CI 1.19, 3.96), other accidents and burns (MOR = 1.37, (0.95, 1.98) and homicide (MOR = 1.59, 95% CI 0.86, 2.94) (Lawrence et al., 1985). In 1988, researchers in the Department of Veterans Affairs examined proportionate mortality rates among Army and Marine veterans and observed that Marines had significantly high PMRs for lung cancer (158) and non-Hodgkin lymphoma (210) (Breslin, Kang, Lee, Burt, & Shepard, 1988).

Beginning in 1987, cohort studies of Vietnam veterans began to show unexpectedly high risks of suicide and drug-related causes, leading to subsequent consideration of behavioral and mental health factors as potential risk factors for premature death. In 1987 the Centers for Disease Control began the Veteran Experience Study (VES) with a nationwide cohort of over 18,000 Vietnam-era veterans and reported excess mortality from suicide, motor vehicle accidents and accidental poisonings during the first five years post-discharge among those who served in Vietnam, with drug-related deaths more common among those with Vietnam service throughout the follow-up period ending in 1983 (CDC, 1987).

In one of the earliest cohort studies in which PTSD was assessed in Vietnam veterans, Bullman and Kang (1994) reported that veterans with PTSD were four times more likely to die from suicide (RR = 4.0, 95% CI 2.2–7.0) and from accidental poisoning (RR = 2.9, 95% CI 1.1–2.5). In a subsequent analysis of 34,534 U.S. Army veterans followed through 1991 for an average of 21 years, the same group reported a relative risk for suicide of 1.8 (95% CI 1.1–3.0) among veterans who were wounded more than once and hospitalized for a wound. No direct measurement of PTSD, however, was available (Bullman & Kang, 1996). In a study of 1,866 men admitted to a VA PTSD residential treatment program between 1990 and 1998 and followed through 1999, the risk of death was nearly twice that of the general population with a similar age and race distribution (SMR = 1.8, 95% CI = 1.5–2.2) and even higher for "behavioral causes" such as accidents, chronic substance abuse and suicide/homicide/police intervention (SMR for suicide = 4.0, 95% CI = 1.8–7.4) (Drescher, Rosen, Burling, & Foy, 2003).

The young age of a large proportion of those who served in the military during the Vietnam Era (median birth year 1947) implies that even a very large cohort must be followed for a long time in order to detect statistically meaningful increases in chronic diseases that primarily affect older persons. By 2000, the mean cohort age of the VES cohort was only 53 years. Nevertheless, follow-up through that year revealed all-cause mortality to be 7% higher in Vietnam compared to non-Vietnam veterans (95% CI = 0.97–1.18), with significantly increased risks for death from unintentional poisoning and drug-related causes (Boehmer, Flanders, McGeehin, Boyle, & Barrett, 2004). A subsequent analysis of the same cohort by Boscarino (2006), utilized data on PTSD for 7,924 Vietnam Theater and 7,364 Vietnam-era veterans that had been assessed among VES participants in telephone interviews in the mid-1980s. Significantly elevated hazard ratios were observed for total mortality (HR = 2.2, 95% CI = 1.7–2.7), cardiovascular mortality (HR = 1.7, 95% CI = 1.0–2.7), cancer mortality (HR = 1.9, 95% CI = 1.1–3.3) and external causes (HR = 2.3, 95% CI = 1.4–3.9). The latter category included motor vehicle accidents, accidental poisonings, suicides and homicides.

PTSD was determined in 1,946 participants in the VA Normative Aging Study cohort who were followed for up to 15 years through May 2001, using either the Mississippi Scale for Combat-Related PTSD (Keane, Caddell, & Taylor, 1988) or the related Keane scale (Litz et al., 1991). Even though few individuals met established criteria for PTSD using either scale, nevertheless age-adjusted relative risks for fatal CHD associated with a one-SD increase in symptom level were 1.30 (27 deaths, 95% CI 1.01–1.7) using the Mississippi scale and 1.13 (24 deaths, 95% CI 0.97–1.43) with the Keane scale (Kubzansky, Koenen, Spiro, Vokonas, & Sparrow, 2007).

All-cause (but not cause-specific) mortality was determined in the VA Large Health Survey of over 550,000 veterans surveyed by questionnaire in 1999 and followed for nine years. Prior diagnoses of PTSD and other mental health conditions were determined via linkage to diagnostic data in VA records. The adjusted hazard ratio for total mortality comparing those with PTSD to those without the condition was 1.02 (95% CI 1.01–1.04). However, it became non-significant after adjustment for psychiatric comorbidity such as schizophrenia, bipolar disorder and major depressive disorder (HR = 0.95, 95% CI 0.83–1.00) or for an array of medical comorbidities and adverse lifestyle behaviors such as obesity and smoking (HR = 0.91, 95% CI 0.86–0.98), which the authors interpreted as suggestive of mediation by the latter factors (Chwastiak, Rosenheck, Desai, & Kazis, 2010).

A mortality analysis was carried out in a cohort of 637 veterans not previously diagnosed with coronary artery disease who had undergone coronary artery calcium (CAC) screening for "clinical indications" in VA facilities. CAC measures plaque deposits and is associated with future risk of myocardial infarction and stroke; it is generally reported as a numerical score, with scores of 101 to 400 indicating moderate risk and over 400 high risk of a coronary event. The mean CAC score for veterans with PTSD was 448 (±472 SD) compared to 332 (±336) in those without PTSD ($p < 0.001$). The prevalence of PTSD increased in a dose-dependent manner with increasing CAC score. The mean follow-up period was 42 months, during which the proportion of veterans with PTSD who died was 17.1% compared to 10.4% of those without PTSD ($p < 0.003$). Kaplan-Meier curves showed substantially worsening survival with increasing CAC score (Ahmadi et al., 2011).

Most recently, Schlenger and colleagues (2015) analyzed the mortality experience of the National Vietnam Veteran Readjustment Study based on follow-up of 1,632 Theater veterans interviewed in 1987 and followed for up to 24 years. "High probability of PTSD" was assigned using the DSM III-R criteria in effect at the time of interview. The age-adjusted hazard ratio for association of PTSD with all-cause mortality was 2.27 (95% CI 1.34–3.84); additional adjustment for other demographic characteristics reduced it to 1.87 (95% CI 1.06–3.30). (Schlenger et al., 2015).

## *Biological basis for post-traumatic stress disorder—physical health risk relationships*

The term "fight-or-flight" to describe the "normal" fear response of human beings is now a part of the everyday vocabulary. In 1914, Walter Cannon first wrote of the phenomena associated with a fear or startle response based on observations carried out in his Harvard physiology laboratory. He described the elevated levels of adrenalin (corticosteroids) liberated by fear, rage, asphyxia and pain. He observed that the stress response also led to elevated levels of blood sugars, inhibition of gastric motions and increased secretion of gastric fluids, as well as to contraction of many blood vessels involved in gastrointestinal function. He wrote of more obvious physiological responses, like bristling of hair and, in general, put together various pathways in which the body marshaled its resources for responding to (fighting or fleeing from) a threat by increasing some functions and repressing others (e.g., increased muscle activation and decreased digestion), all in response to a purely emotional input (Cannon, 1914).

Much work on the physiological response to stress has, of course, been carried out in the past century since Cannon's pioneering paper. In broad strokes, the physiological responses described by Cannon are almost certainly intimately related to the elevated risks observed for many co-morbid physical health effects. Yehuda's laboratory has been very active in this area of study, and she has published extensively in the field. Her 2002 and 2009 reviews are useful

here for a brief overview. Yehuda (2002; 2009) summarizes and updates the original Cannon formulation of the "normal fear response" biological reactions. At the heart of the stress response is the activation of the hypothalamic-pituitary-adrenal (HPA) axis. Activation of the HPA leads to elevation of both cortisol and corticotropin-releasing factor. These two components of the stress response make up a sensitive negative-feedback system where elevation of cortisol induces inhibitory responses in other parts of the endocrine system (the pituitary, the hypothalamus, the hippocampus and the amygdala). The inhibition of these systems, in turn, feeds into a negative feedback loop in which glucocorticoid receptors work to restore corticosteroid levels to the basal hormone levels at which they had been functioning. In a "normal" individual, the levels of both cortisol and corticotropin-releasing factor will return to normal basal levels after the stress has abated. People with post-traumatic stress disorders, however, often continue to exhibit low levels of cortisol and high levels of corticotropin-releasing factor, a combination that is also found in patients with major depression.

Other physiological and biochemical responses also occur. For example, the stress-response appears to also induce an arousal of the sympathetic nervous system, resulting in elevated levels of catecholamines. Blood sugar chemistry is altered, and here, too, complex feedback loops that have been related to increased risk for cardiovascular diseases are present. Immunological alterations have also been noted. A variety of chronic diseases are associated with alterations of normal functioning (homeostasis) in these basic functions.

## *Conceptually framing the issue*

The proposed pathways by which post-traumatic stress disorder can be associated with physical health are complex. Schnurr and Green (2004) have proposed a conceptual framework, shown in Figure 30.1, for "understanding relationships among trauma, posttraumatic stress disorder, and health outcomes" (Schnurr, Wachen, Green, & Kaltman, 2014). Among the many reasons underlying this complexity are:

- Individuals have personal, social and cultural factors that they bring to the traumatic situation. Such characteristics are likely to modify the nature and degree of post-traumatic stress disorder risk and of co-morbidity. Personal factors may include genetic differences that can affect both increased susceptibility to adverse effects of trauma and resilience in dealing with the trauma and its potential sequelae.
- Trauma exposure can, in and of itself, directly and separately lead to injury and other health effects, without the presence of post-traumatic stress disorder.
- Trauma can act indirectly to increase risk for co-morbidity by increasing risk for post-traumatic stress disorder which, in turn, leads to increased risk for co-morbid physical diseases. There can be a variety of pathways by this can occur, such as:
  - Biological alterations in immune function
  - Activation of various hormonal pathways associated with the stress response
  - Psychological disturbance, which, in turn, may lead to an increase in behavioral risk factors for developing disease, like smoking, drinking and poor diet
  - Continuing impediment to development of more healthful behaviors
  - Interference with normal family functioning and coping
  - Decreased likelihood of seeking and utilizing available health services, which, in turn, can lead to avoidably poorer health status and to failure to avail themselves of salutary treatment options

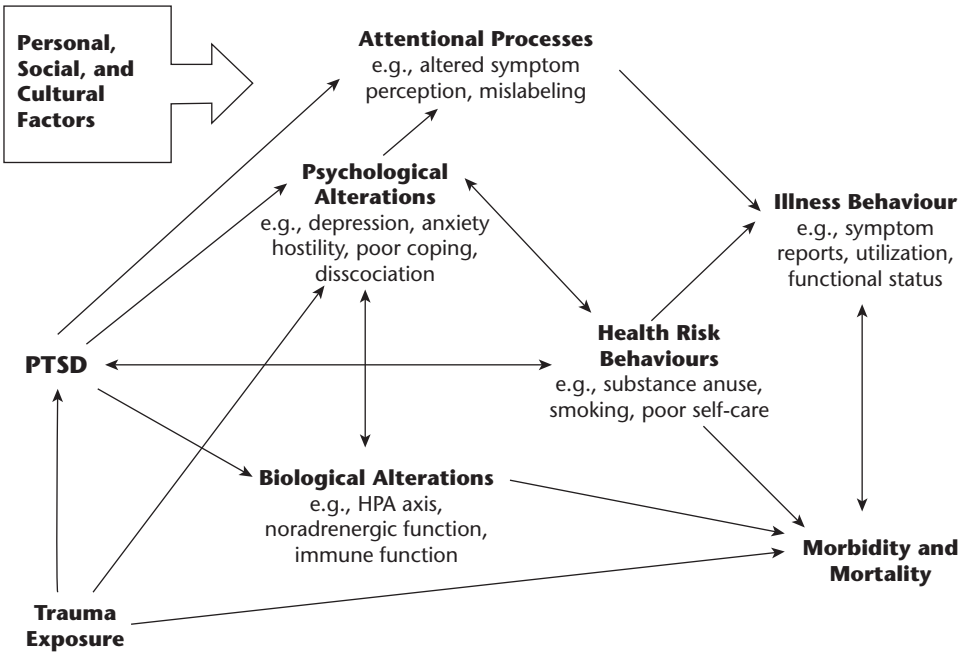


*Figure 30.1* A model relating traumatic exposure and post-traumatic stress disorder to physical health outcomes.

*Source:* From Schnurr and Green, 2004. (In the public domain.)

## *Methodological considerations in studies of post-traumatic stress disorder and physical health*

Koenen and co-workers (2017) reviewed data on the relationship between post-traumatic stress disorder and cardiometabolic disease (CMD) and presented a conceptual framework consistent with that of Schnurr and Green (2004). They also provided a comprehensive discussion of the difficulties of establishing causation, particularly since the directionality of many effects is not clear, noting, in fact, that bidirectionality can also exist. They posit their discussion on the relationship between cardiometabolic disease and post-traumatic stress disorder co-morbidity, but in fact these methodological considerations apply to virtually all chronic diseases. Adverse physical health outcomes can be modeled in at least five ways:

1. *Causation*—post-traumatic stress disorder directly causes a physical health condition through biological mechanisms associated with the stress response and its alteration of the HPA axis or stimulation of catecholamines, immune system changes and other factors.
2. *Confounding*—a traumatic risk factor explains the observed relationship between co-morbid chronic disease and post-traumatic stress disorder. They may both be independently associated with the traumatic exposure or some other factor, like socio-economic status, may be independently related to both post-traumatic health disorder and the physical health outcome in question.
3. *Reverse causation*—in which the physical health condition can increase risk for PTSD. For example, Koenen et al. (2017) note that cardiometabolic disease can increase levels of C-reactive protein, which can increase risk for post-traumatic stress disorder.

4. *Mediation*—in which post-traumatic stress disorder produces consequences that, in turn, lead to elevated risk for disease. For example, post-traumatic stress disorder is associated with risky health behaviors like smoking, which in turn lead to a variety of chronic diseases. When a condition acts as a mediator, special statistical techniques should be employed to determine whether PTSD itself makes a unique contribution to the elevated risk observed, beyond acting as a mediator.
5. *Bidirectional effects*—refers to a feedback loop model in which development of post-traumatic stress disorder increases risk for physical disease which, in turn, exacerbates reactions associated with trauma (e.g., trauma from experiencing a stroke) and hence symptoms of post-traumatic stress disorder are induced.

The sequence of events is often difficult to assess. For example, Kessler, Sonnega, Bromet, Hughes and Nelson, 1995, in their analyses of the National Comorbidity Survey, found that when co-morbid conditions arise, they are usually secondary to the onset of post-traumatic stress disorder. They note that the analytic approach to assessment of the impact of trauma-producing PTSD on subsequent physical conditions depends on how PTSD is to be treated in the model, that is, whether it is modeled as an independent causative factor, a mediator or as working through some other complex pathway. These more complex pathways will require statistical techniques beyond ordinary regression.

## *Post-traumatic stress disorder as a multidimensional disorder*

Another methodological issue to be considered is the multidimensionality of post-traumatic stress disorder. The symptoms of post-traumatic stress disorder generally fall into one of three clusters: re-experiencing the traumatic event, avoiding situations which are reminders of the event and hyperarousal. Re-experiencing of the event can manifest itself by nightmares and flashbacks. Avoidance of people, places or things reminiscent of the traumatic event can lead to social withdrawal in general and, of relevance to this discussion, to problems in interactions with the health care system. Hyperarousal is related to physiological responses that can include irritability, poor concentration and sleep disturbance. There may be an extreme startle response and hypervigilance. Recent exploration of the dimensionality of PTSD has led to proposals to define additional dimensions, in particular dysphoria (Frankfurt, Anders, James, Engdahl, & Winskowski, 2015), which would add further complexity.

The different dimensions of post-traumatic stress disorder are likely to be associated with the separate paths in the Schnurr and Green model (Schnurr & Green, 2004). Koenen et al. (2017) posit that it is likely to be useful to use dimensional components of post-traumatic stress disorder to analyze biological and behavioral effects separately.

Withdrawal from social interactions that are pathognomonic for post-traumatic stress disorder may affect utilization of health care services. For example, survivors of the World Trade Center disaster with post-traumatic stress disorder were significantly more likely to have reported unmet mental health care needs 10 to 11 years post-disaster compared to those without post-traumatic stress disorder, especially persons with severe conditions characterized by functional impairment and depression, and mental health service non-users displayed strong attitudinal barriers to seeking treatment (Ghuman, Brackbill, Stellman, Farfel, & Cone, 2014).

Much of the earlier literature on post-traumatic stress disorder in both military and civilian populations has been based on cross-sectional analysis of survey data or on baseline data from newly established cohort studies. As these cohorts have been followed over time, it has become possible to study the evolution or "trajectories" of post-traumatic stress disorder and other chronic

health outcomes, as delineated by Koenen et al. (2017). For example, in their study of Vietnam-era veteran twins followed-up for up to 20 years, Magruder and colleagues classified 4,138 study participants in five mutually exclusive categories: never had post-traumatic stress disorder (86.0%), late onset (4.7%), late recovery (2.9%), early recovery (4.1%) and chronic (2.2%). Their study, however, had a 60% response rate at 20 years, and their estimates are accordingly weighted for non-response (Magruder et al., 2016).

Such so-called "distancing" raises possible concerns regarding bias due to selective non-response by participants in cohort studies of time course of post-traumatic stress disorder and its impact on chronic disease outcomes. Thus, in addition to differential utilization of healthcare services, there is likelihood that there will be a post-traumatic stress disorder-related response bias for participation in survey and medical examination-based research.

In the American Legion–Columbia University cohort of Vietnam veterans, a disproportionate number of the most chronically ill veterans were lost to follow-up in 1998. The prevalence of severe symptomatology in the non-responders at Time 2 was 11.1% at Time 1, compared to 9.5% at Time among responders to both waves. The mean PTSD scores in 1984 were significantly higher than those who responded at both times (Koenen et al., 2008). The extent and impact of this type of bias has also been estimated by Yu, Brackbill, Stellman, Ghuman and Farfel (2015), who compared PCL-derived post-traumatic stress disorder prevalence among World Trade Center survivors participating in up to three surveys over an 11-year period. Of the 67,670 Wave 1 (baseline) participants eligible for the two later follow-ups, 69% responded at Wave 2 and 63% responded at Wave 3, but the latter group included 6,682 "drop-ins" who were Wave 2 non-respondents. The baseline prevalence of post-traumatic stress disorder (defined as a PCL score of at least 44) was significantly greater among three-wave non-participants (17.9% vs. 15.2%). Both Wave 3 dropouts and drop-ins were significantly more likely to report poor/fair health as well as lower respiratory symptomatology at earlier waves. Nevertheless, there were no significant differences in odds ratios for association between specific traumatic exposures on 9/11 and post-traumatic stress disorder at Wave 3. The authors concluded that "despite a somewhat downward bias in prevalence estimates, attrition from the WTC Health Registry follow-up studies does not lead to serious bias in associations between 9/11 disaster exposures and key health outcomes."

The time course of post-traumatic stress disorder will also vary with the individual. Variations in time course are also likely to have an effect on risk of development of co-morbid physical health outcomes. Cross-sectional studies cannot satisfactorily test such effects. Longitudinal data from the Columbia University-American Legion Vietnam Veteran Health Study carried out on a cohort study of 3,403 Vietnam veterans can shed some light on the course of post-traumatic stress disorder and comorbidity. The cohort, first surveyed in 1984 (Snow, Stellman, Stellman, & Sommer, 1988) and then again in 1998 (Koenen et al., 2008), were compared as to risks for self-reported medically diagnosed heart disease, hypertension and other chronic illnesses among veterans who served in Vietnam with those who served elsewhere and by intensity of post-traumatic stress disorder among those serving in Vietnam, adjusting for potential confounders such as cigarette smoking and obesity. Post-traumatic stress disorder was significantly associated with diagnoses of heart disease and hypertension during the 15-year observation period, as well as a wide range of measures of health, well-being and physical function.

Data from this cohort also provide insight into the effect of time-course of post-traumatic stress disorder on comorbidity. Figure 30.2 illustrates the levels of self-reported symptoms of depression as a function of presence or absence of post-traumatic stress disorder in 1984 and 1998. Respondents who never reported post-traumatic stress disorder consistently report significantly lower levels of physical signs of depression than those with post-traumatic stress disorder at either time one or time two (intermittent/recurrent PTSD) versus those with post-traumatic stress

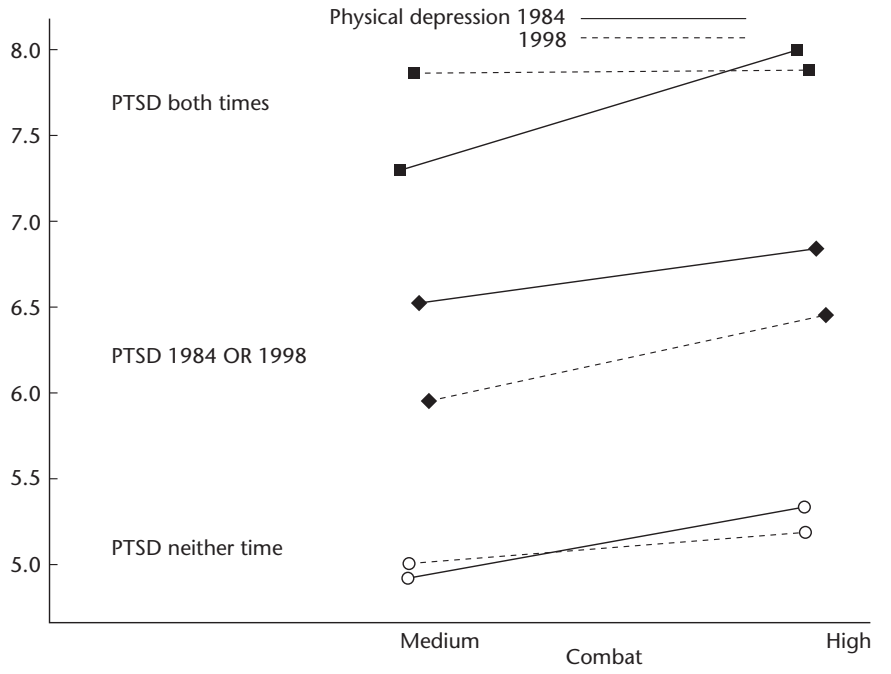


*Figure 30.2* The relationship between mean levels of physical signs of depression and level of military combat.

*Source*: Reported by respondents to both waves of the American Legion – Columbia University Vietnam Veterans Health Study (see Koenen et al., 2008 for a description of the cohort) who also reported medium and high levels of combat exposure. A similar pattern was observed for each of the health and well-being outcomes in the study.

disorder at both time periods, who scored significantly higher levels of distress than the other two groups. These data are consistent with the models described here and support the need for approaches to analyses that take both time and multidimensional nature of post-traumatic stress disorder into account. Similar patterns were observed for the other outcomes reported. In addition, substantial evidence has now been gathered demonstrating that people with levels of post-traumatic stress disorder symptoms who do not meet criteria for full-blown PTSD can still exhibit greater risk for co-morbid disease, in addition to showing elevated risk for functional impairment, suicidality and symptom severity.

Friedman, Keane and Resick (2014) have proposed that diagnoses of subsyndromal PTSD be added to the clinically accepted diagnostic criteria for the syndrome. Such a definition would assist in further studies since the revised definition of PTSD would lead to more consistent measurement in clinical and epidemiological settings than has been the case in the past. Friedman, Keane and Resick (2014) further posit that post-traumatic stress disorder may be a spectrum disorder in which "symptoms are distributed along a mild-to-severe continuum." They acknowledge that there is arbitrariness in the current definition of when PTSD is subsyndromal/partial and when it is full PTSD.

## *Directions for future research and improvements in public health practice*

Despite decades of studies demonstrating a relationship between stressful exposures, both traumatic and non-traumatic, on physical health, there has been remarkably little systematic inclusion of

diagnosis and treatment of co-morbid conditions in either in the mental health arena or in the relevant physical health specialties. In the area of occupational health and stressful working conditions, the first government publication recognizing that physical sequelae could arise from stress conditions associated with the organization of work was published in 2002 by the NORA Organization of Work Team of the U.S. National Institute for Occupational Safety and Health (NORA, 2002).

The reluctance and professional inertia in addressing this issue and in pursuing a research agenda to further elucidate it is partially attributable to the methodological difficulties described earlier. There is also, undoubtedly, a political aspect. The costs and liabilities associated with recognizing that omnipresent stress conditions could be associated with physical disease could be astronomical. In the case of post-traumatic stress disorder, it has been suggested that advocacy by veteran groups and feminist activists played an important role in the formal recognition of the disorder in the DSM-III in 1980 (Friedman, Keane, & Resick, 2014). Recognition that PTSD could also be leading to chronic physical health diseases has not yet made its way into veteran benefit programs.

An ironic twist to the lack of recognition in many professional and governmental programs policies can be found in some governmental worker compensation programs. For example, in the State of Maryland, while PTSD is compensable under certain complicated conditions, it is *only* compensable if the claimant can establish coincident physical illness purported to be associated with the PTSD (personal communication, LR Stellman, JD).

Koenen et al. (2017) note that "despite mounting evidence post-traumatic stress disorder is not acknowledged as a risk factor for either cardiovascular disease (CVD) or type-2 diabetes (T2D)" and hence "neither systematic surveillance nor treatment is provided to individuals with post-traumatic stress disorder." The same general statements can be applied to virtually every other physical health problem described here.

While post-traumatic stress disorder is a major medical care and research focus in the Veterans Administration health care system, there are currently no established mechanisms by which a veteran with a co-morbid physically condition likely either to have been caused or exacerbated by post-traumatic stress disorder can automatically have his or her co-morbid conditions "recognized" by the Veterans Administration benefits system and hence be automatically eligible for medical and disability benefits.

The Agent Orange medical and benefit programs, available to all veterans who served in Vietnam and develop a disease recognized to be associated with exposure to Agent Orange and other military herbicides, is a model for a program that could be made available to veterans who have developed post-traumatic stress disorder associated with military service *and* a recognized comorbid physical health condition. (https://www.va.gov/disability/eligibility/hazardous-materials-exposure/agent-orange/, last accessed May 30, 2019). As with Agent Orange, a registry could be established for the systematic collection of traumatic military experiences, and, going beyond the Agent Orange Registry, there could be linkage to military records so that other at-risk individuals serving in similarly traumatized units could be identified, registered and followed. This ideal-world scenario is, of course, costly but is also long overdue.

In addition to developing information on the at-risk population and keeping track of those who enter the Veterans Administration system with symptoms of both post-traumatic stress exposure and chronic physical health problems, there could also be pro-active training of medical care providers to recognize co-morbid disease. Practice guidelines could be developed to assist in this process and relevant information entered in uniform fashion into the electronic medical record, thereby facilitating follow-up studies. Clearly there is an urgent need to establish surveillance systems, to carry out further research on risks and appropriate treatment that takes into account the complex causal pathways involved in these co-morbid processes. There is also

a need to develop educational programs for medical practitioners and for veterans and their families so that treatment and medical adherence practices can be improved. Friedman, Keane and Resick (2014) outline innovative approaches to "top-down and bottom-up" mechanisms for both improving treatment and facilitating creative implementation strategies.

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