Posttraumatic Stress Disorder and Physical Illness

Results from Clinical and Epidemiologic Studies

JOSEPH A. BOSCARINO

Division of Health and Science Policy, The New York Academy of Medicine, New York, New York 10029-5293, USA

Research Service, Department of Veterans Affairs, New Jersey Health Care System, East Orange, New Jersey, USA

ABSTRACT: **Research indicates that exposure to traumatic stressors and psychological trauma is widespread. The association of such exposures with posttraumatic stress disorder (PTSD) and other mental health conditions is well known. However, epidemiologic research increasingly suggests that exposure to these events is related to increased health care utilization, adverse health outcomes, the onset of specific diseases, and premature death. To date, studies have linked traumatic stress exposures and PTSD to such conditions as cardiovascular disease, diabetes, gastrointestinal disease, fibromyalgia, chronic fatigue syndrome, musculoskeletal disorders, and other diseases. Evidence linking cardiovascular disease and exposure to psychological trauma is particularly strong and has been found consistently across different populations and stressor events. In addition, clinical studies have suggested the biological pathways through which stressor-induced diseases may be pathologically expressed. In particular, recent studies have implicated the hypothalamic-pituitary-adrenal (HPA) and the sympathetic-adrenal-medullary (SAM) stress axes as key in this pathogenic process, although genetic and behavioral/psychological risk factors cannot be ruled out. Recent findings, indicating that victims of PTSD have higher circulating T-cell lymphocytes and lower cortisol levels, are intriguing and suggest that chronic sufferers of PTSD may be at risk for autoimmune diseases. To test this hypothesis, we assessed the association between chronic PTSD in a national sample of 2,490 Vietnam veterans and the prevalence of common autoimmune diseases, including rheumatoid arthritis, psoriasis, insulin-dependent diabetes, and thyroid disease. Our analyses suggest that chronic PTSD, particularly comorbid PTSD or complex PTSD, is associated with all of these conditions. In addition, veterans with comorbid PTSD were more likely to have clinically higher T-cell counts, hyperreactive immune responses on standardized delayed cutaneous hypersensitivity tests, clinically higher immunogolobulin-M levels, and clinically lower dehydroepiandrosterone levels. The latter clinical evidence confirms the presence of biological markers consistent with a broad range of inflammatory disorders, including both cardiovascular and autoimmune diseases.**

Address for correspondence: Joseph Boscarino, Division of Health and Science Policy, Room 552, The New York Academy of Medicine, 1216 Fifth Avenue, New York, NY 10029-5293. Voice: 212-419-3551; fax: 212-822-7369.
jboscarino@nyam.org

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INTRODUCTION

Research has demonstrated that exposure to severe psychological distress, as occurs during major disasters, combat operations, and other life-threatening events, can result in long-term psychological trauma and mental health disorders.[1–4] Currently, studies suggest that about 5% of men and 10% of women under 55 years old in the United States have had posttraumatic stress disorder (PTSD) resulting from traumatic exposures.[5] Although the level of exposure is commonly associated with the psychological impact of traumatic events,[1,6,7] other risk factors are also involved. For example, research suggests that increased vulnerability to PTSD occurs among those with a history of mental health disorders, child abuse, or previous trauma.[4,8,9] Furthermore, demographic, socioeconomic, and ethnic factors also appear to be risk factors.[2,10] In addition, research has identified the role of social support among those exposed to traumatic stress in terms of both protecting individuals from PTSD onset[11] and influencing effective treatment.[1,4,13] In summary, the degree of exposure, social variables, individual history, and other factors appear significant in determining the impact of traumatic events on mental health.[1,4,13] Recently, the role of heredity has also been recognized as a significant factor.[3,14] Nevertheless, whereas the psychosocial components of PTSD are now recognized, the underlying neurobiological basis of this condition has also become clear.[15–18] Recently, research has suggested that responses to traumatic stressors also appear to have a physiological foundation that could result in a host of human diseases.[16–20]

Consistent with the physiological impact of psychological trauma, studies among disaster survivors, Vietnam veterans, and others exposed to severe environmental stressors suggest higher rates of health care utilization and medical comorbidity after these exposures.[17,19,20–24] Research among Vietnam combat veterans, in particular, disclosed higher rates of postwar adjustment difficulties, mental health disorders, and medical morbidity than those found among noncombat veterans or comparable nonveterans.[2,19,25,26] In addition, research suggested that the postwar adjustment difficulties and health problems experienced by these veterans were due to combat exposures in Vietnam, not to the selection biases or measurement inadequacies that had plagued earlier studies.[3,13] Furthermore, research confirmed that Vietnam "theater" veterans as a group had higher rates of health care utilization and reported themselves to be in poorer health than did veterans without Vietnam service.[26] However, when the postwar health status of Vietnam veterans was examined by whether the veteran ever had PTSD, PTSD-positive veterans had substantially higher (i.e., 50–150% greater) postwar rates of many major chronic diseases, including circulatory, nervous system, digestive, musculoskeletal, and respiratory diseases, even controlling for the major risk factors for these conditions.[19] For example, it was shown that 25% of PTSD-positive veterans reported physician-diagnosed circulatory diseases nearly 20 years after the service (vs. 13% for PTSD-negative veterans), and 19% reported physician-diagnosed nervous system disorders (vs. 6%). Altogether,

68% of PTSD-positive Vietnam veterans reported the occurrence of a chronic disease-related medical condition after Vietnam service compared with 48% for PTSD-negative Vietnam veterans. Finally, it was also reported that PTSD-positive veterans were significantly more likely to have had abnormal electrocardiograph (ECG) results (28% vs. 14%), including a higher prevalence of myocardial (Q-wave) infarctions and atrioventricular conduction defects.[17] In addition, consistent with these cardiovascular findings, PTSD-positive veterans were found to have abnormally high white blood cell counts (>11,000/mm^3) and T-cell counts (>2,640/mm^3).[16]

Evidence linking exposure to traumatic stress and cardiovascular disease is compelling and is supported by different epidemiologic studies. In addition to the Vietnam veteran studies mentioned,[17,19] a population study involving World War II and Korean War veterans also found higher rates of physician-diagnosed cardiovascular disease among PTSD-positive veterans.[27] Another study among Dutch resistance fighters found increased rates of reported angina pectoris among these veterans with PTSD.[28] A large-scale civilian population study also found an increase in ischemic heart disease based on medical examinationss among adults exposed to childhood traumas.[29] Furthermore, in another study, adults exposed to the Chernobyl disaster had increased rates of reported heart disease 8–10 years after this event.[23] In addition, studies during the Beirut Civil War and the Croatia War found increases in arteriographically confirmed coronary heart disease, cardiovascular disease mortality, and increases in acute myocardial infarction (AMI) associated with exposure to these conflicts.[30–32] An increase in AMIs was also reported after the Hanshin-Awaki earthquake in Japan.[33] In summary, there is both clinical and epidemiologic evidence supporting the link between exposure to psychological trauma and PTSD and the onset of chronic diseases, particularly cardiovascular disease. The latter also includes numerous studies showing significant and persistent increases in basal cardiovascular activity that, over time, could potentially result in cardiovascular disease.[34]

POTENTIAL BIOLOGICAL MECHANISMS FOR DISEASE

Since coronary artery disease is generally recognized as an inflammatory disease,[17,35] it was hypothesized that PTSD-positive veterans also would have a history of autoimmune-related diseases. As suggested, there are clinical reasons to expect adverse alterations in neuroendocrine system function in chronic PTSD cases.[36] Although there have been inconsistencies across gender,[37] investigations generally indicate that individuals who have developed PTSD after exposure to severe psychological stress, particularly men exposed to combat, appear to have lower plasma cortisol concurrent with higher catecholamine levels.[15,38–41] In addition, whereas studies have documented alterations in immune functioning after acute stress exposures,[42] recent research indicates that Vietnam veterans with current PTSD had clinically elevated leukocyte and total T-cell counts.[16] A nonveteran study confirmed that although PTSD victims had reduced natural killer cell cytotoxicity, they also had significantly increased leukocyte counts.[43] Furthermore, a meta-analytic review also suggested a consistent increase in leukocyte counts after human exposures to different acute and chronic stressors.[44]

In summary, evidence indicates that exposure to severe environmental stressors and subsequent development of PTSD may be related to altered neuroendocrine and immune system functions and the onset of specific immunoendocrine-related diseases. In particular, given the reduced cortisol levels often found among PTSD victims, it has been suggested that a downregulated glucocorticoid system may result in elevations in leukocyte and other immune inflammatory activities.[45] Currently, glucocorticoids are known to influence the trafficking of circulating leukocytes and affect functions of leukocyte and immune accessory cells.[45] Recently, it became evident that the HPA stress axis, and the adrenal gland in particular, is a major site of both the synthesis and the action of numerous cytokines.[46] It has been suggested that in addition to cytokine-mediated activation of adrenal regulation, there are cytokine-independent cell-mediated immune-adrenal interactions and that this immune-endocrine crosstalk is implicated in adrenal dysfunction and disease.[46] Although complex physiologic processes seem to be involved with the stress-disease pathogenic process, one pathway often cited involves long-term alterations in the HPA stress axis together with the sympathetic-adrenomedullary (SAM) stress axis.[36,47–49]

Evidence suggests that the physiologic arousal often observed during recollection of traumatic events by PTSD victims is associated with alterations in the neuroendocrine functions related to changes in the SAM and HPA systems. In the case of PTSD, these neuroendocrine alterations are thought to reflect the consequences of an extreme state of physiopsychological conditioning that can occur after severe stress exposures. Furthermore, although this "conditioning" response is initiated in the central nervous system, it is subsequently carried out by multiple endocrine mechanisms that have wide-ranging affects on the body and nervous system. As noted, studies have reported lower cortisol levels among Vietnam veterans with PTSD as well as increased catecholamine concentrations. Although research suggests that these processes are complex,[15,19] chronicity and excessiveness of stress system activation are known to lead to pathogenesis, causing weight loss, depression, hypogonadism, immunosuppression, and other pathophysiological conditions leading to disease.[36] Furthermore, research suggests that most Vietnam veterans with PTSD developed this due to combat exposures in Vietnam.[1–3,15] Currently, estimates are that about 30% of male Vietnam veterans developed PTSD due to experiences in Vietnam, and about 15% currently have this disorder.[2] Therefore, given these rates, the long-term health consequences of severe stress exposures among Vietnam veterans, if they exist, should be detectable in large sample of these veterans.

METHOD AND RESEARCH HYPOTHESIS

Based on previous research, it was hypothesized that chronic PTSD would be associated with an increased prevalence of autoimmune diseases (ADs). In addition, those with more severe PTSD, defined as PTSD concurrent with depression, generalized anxiety, or other significant psychopathology, would more likely have these conditions. The latter assumption was based on two lines of research. The first relates to the general observation that persons with comorbid PTSD generally represent more severe cases of psychological disturbance.[2,50–52] The other relates to clinical research suggesting that in severe PTSD cases, many victims exhibit a

disassociation between traumatic events and cognitive functioning, oftentimes exhibiting extreme psychopathology and cognitive dysfunction.[53,54] Based on this body of research, a plausible biological assumption is that the greater the intrapsychic disturbances present, the greater the physiological dysfunction that occurs.[51] The more extreme form of comorbid PTSD is consistent with what also has been labeled "complex PTSD" by some investigators.[55–57] The latter designation has often been used to connote a general condition reflecting higher levels of psychopathology and psychological dysfunction.[56]

Consistent with smaller clinical studies, we recently conducted analyses involving several thousand veterans and found that Vietnam theater veterans with current PTSD, that is, long-term PTSD since this condition generally stemmed from Vietnam service, not only had lower cortisol levels, but also had combat exposure levels that were associated with plasma cortisol concentrations in an inverse "dose-response" relationship.[13,15] Subsequently, we present additional findings with regard to this veteran cohort related to autoimmune disease. Our study data have been described in detail elsewhere.[1,15–17,19] Briefly, these data are from the Vietnam Experience Study (VES), a study of health effects of Vietnam service.[25,26] The VES is based on a random sample of all 5 million US Army veterans of the Vietnam War era. Subjects were male, military rank E1-E5, and entered the military from 1965–1971. There were several phases to the study, including a mortality study (Phase I), a telephone survey (Phase II), and medical examinations (with laboratory tests) together with personal interviews (Phase III). In this report, we present data based on the 2,490 Vietnam theater veterans who participated in Phase III (collected primarily in 1986). On average, the time from combat exposure to the Phase III follow-up was about 17 years for these veterans.[19] The examinations, interviews, and laboratory tests have been described in detail elsewhere.[1,15–17,19] For this study, comorbid PTSD cases were identified using factor analysis of responses on the main MMPI psychopathology scales (including hypochondriasis, depression, hysteria, paranoia, obsessive compulsive, psychosis, hypomania, and introversion)[58] together with total PTSD symptoms reported in the last 6 months. The latter were based on the sum of 13 symptom items consistent with DSM-III PTSD Criteria B, C, and D.[59] Cases with factor scores > than the 95th percentile were classified as comorbid (complex) PTSD cases. (For this comorbid PTSD factor score, all items loaded >0.55, except introversion, which was not significant.) The kappa coefficient for our comorbid PTSD classification with the Keane PTSD scale,[60] also developed from the MMPI, was 0.62. Based on current medical research,[61] a total of 20 different ADs were identified for our study. For the current study, these conditions were classified as present, based on the veteran's reported medical history, hospitalization history, current medical treatments, medication history, and reported disabilities/work limitations, using ICD-9CM codes for the 20 identified ADs. In addition, for rheumatoid arthritis, this diagnosis was also based on reported rheumatic symptoms (e.g., morning stiffness, bilateral joint swelling, etc.) concurrent with a reported physician diagnosis of "arthritis," similar to what is commonly done in population health research.[19] Our analyses included assessment of the association between PTSD and AD using logistic regressions, both unadjusted (bivariate) and adjusted (multivariate). In the multivariate models (similar to previous studies), we adjusted for age, education, race, IQ, income, geographic region, Army volunteer status, number of times married, and history of antisocial personality, alcohol abuse, drug abuse, and history of cigarette smoking.[16,17,19]

TABLE 1. Prevalence of autoimmune diseases among Vietnam Theater Veterans by type of posttraumatic stress disorder (PTSD) (*N* = 2,490)

	Total		Current PTSD		Comorbid PTSD	
Diseases	N	%	N	%	N	%
Rheumatoid arthritis	49	2.0	3	5.6	10	8.1[b]
Psoriasis	47	1.9	3	5.6[b]	8	6.5[b]
Insulin-dependent diabetes mellitus (IDDM)	28	1.1	1	1.9	5	4.0[b]
Hypothyroidism	12	0.5	1	1.9	3	2.4[b]
Graves disease	15	0.6	1	1.9	2	1.6
Glomerulonephritis	6	0.2	1	1.9[b]	1	0.8
Inflammatory bowel disease	4	0.2	0	0.0	0	0.0
Multiple sclerosis	3	0.1	0	0.0	0	0.0
Uveitis	4	0.2	0	0.0	0	0.0
Any autoimmune disease (AD)[a]	158	6.3	9	16.7[b]	23	18.5[b]
Total *N* =	2,490		54		124	

[a]Among the 20 ADs assessed, 9 were prevalent among the veterans and are listed in TABLE 1. Any AD refers to any of the above 9 ADs in this table.
[b]$P < 0.05$, based on Chi-square test, 2-tail.

RESULTS

Results from our AD analyses are summarized in TABLES 1 and 2. Essentially, it was found that veterans with comorbid PTSD (as indicated, defined as PTSD symptoms B, C, and D, concurrent with psychopathology measured on the main MMPI scales) were more likely to have postwar autoimmune diseases. As displayed in TABLE 1, 8.1% (95% CI = 3.9–14.3%) of these men had rheumatoid arthritis, 6.5% (95% CI = 2.8–12.3%) psoriasis, 4% IDDM (95% CI = 1.3–9.2%), 2.4% hypothyroidism (95% CI = 0.5–6.9%), and 18.5% (95% CI = 12.1–26.5%) had any type of AD (compared with 1.6%, 1.6%, 1%, 0.4%, and 5.7%, respectively, for negative comorbid PTSD cases; not shown in TABLE 1). For those with current PTSD (defined as PTSD in the last 30 days), based on DSM-III diagnostic criteria, there was a higher disease rate for psoriasis (5.6%, 95% CI = 1.2-15.4%), glomerulonephritis (1.9%, 95% CI = 0.1–10%), and any type of AD (16.7%, 95% CI = 7.9–29.3%) (compared to 1.8%, 0.2%, and 6.1%, respectively, for negative comorbid PTSD cases; not shown in TABLE 1.) In multivariate analyses (controlling for the variables mentioned), significant associations, again, were found for comorbid PTSD and rheumatoid arthritis (odds ratio [OR] = 5.2, $P < 0.001$), psoriasis (OR = 4.7, $P < 0.001$), hypothyroidism (OR = 8.5, $P = 0.005$), and the presence of any type of AD (OR = 3.3, $P < 0.001$) (TABLE 2). Interestingly, in the multivariate model, only the presence of any AD was significant for current PTSD (OR = 2.6, $P = 0.016$) (not shown in TABLE 2). To validate the results, we also compared the findings to those obtained by classifying comorbid PTSD as PTSD concurrent with depression or anxiety disorder

TABLE 2. Multivariate logistic regressions predicting autoimmune diseases among theater veterans by comorbid posttraumatic stress disorder (N = 2,490)[a]

Autoimmune disease	Unadjusted OR	Unadjusted P value	Adjusted OR	Adjusted 95% C.I.	Adjusted P value
Any autoimmune disease	3.8	<0.001	3.3	2.0–5.7	<0.001
Rheumatoid arthritis	5.2	<0.001	5.2	2.3–11.9	<0.001
Psoriasis	4.1	<0.001	4.7	1.9–11.7	<0.001
Insulin-dependent diabetes mellitus (IDDM)	4.3	0.004	2.9	0.9–8.9	0.066
Hypothyroidism	6.5	0.006	8.5	1.9–37.9	0.005
Graves' disease	3.0	0.155	3.2	0.6–16.5	0.157

[a]Results adjusted for age, education, race, IQ, income, geographic region, Army volunteer status, number of times married, and history of antisocial personality, alcohol abuse, drug abuse, and cigarette smoking. P values are based on 2-tail tests.

TABLE 3. Multivariate logistic regressions predicting abnormal laboratory results among Theater Veterans by comorbid posttraumatic stress disorder (N = 2,490)[a]

Laboratory results	Unadjusted OR	Unadjusted P value	Adjusted OR	Adjusted 95% C.I.	Adjusted P value
High % lymphocytes (>48%)	3.2	0.002	2.1	0.9–5.1	0.091
High T-lymphocyte count (>2,640/mm^3)	3.5	<0.001	2.4	1.2–5.0	0.018
High reactive cell-mediated immunity response (indurations ≥2 mm on all 7 antigens)	2.2	0.004	2.0	1.1–3.5	0.019
High immunoglobulin M (>352 mg/dL)	4.8	<0.001	2.7	1.0–7.4	0.053
Low dehydroepiandrosterone (DHEA-S) (<90 μg/dL)	4.1	<0.001	3.5	1.6–7.9	0.002

[a]Results adjusted for age, education, race, IQ, income, Army volunteer status, history of antisocial personality, alcohol abuse, drug abuse as well as current alcohol use, medication use, and current cigarette smoking. P values based on 2-tail tests.

in the last 30 days, based on DSM-III criteria. These results (not shown) were very similar to our MMPI-derived comorbid PTSD measure.

To provide independent laboratory confirmation for the presence of ADs, we also examined laboratory markers potentially related to the presence of AD (TABLE 3). Consistent with our autoimmune findings, we found that veterans with comorbid PTSD had abnormally high T-lymphocyte counts (OR = 2.4, P = 0.018), highly re-

active cell-mediated immunity to delayed cutaneous hypersensitivity tests (OR = 2, $P = 0.019$),[16] and, although marginally significant, abnormally high immunoglobulin-M levels (OR = 2.7, $P = 0.053$). In addition, we also found that they had significantly lower dehydroepiandrosterone levels (OR = 3.5, $P = 0.002$). We also examined comorbid PTSD by erythrocyte sedimentation rate, but these results were not significant. Interestingly no laboratory results were significant by current PTSD. Small sample sizes prevented the comparison of the laboratory results for the second (DSM-III–derived) comorbid PTSD measure discussed.

DISCUSSION

As suggested, there is growing evidence that exposure to psychologically traumatic events is related to increased medical morbidity, including the onset of differ ent diseases and premature mortality.[20] The evidence for cardiovascular disease is particularly strong and comes from a wide range of studies spanning different populations and trauma exposures. In addition, these studies also are consistent with experimental animal studies.[17] Because cardiovascular diseases are increasingly considered inflammatory diseases and there was strong evidence for HPA involvement, we examine the prevalence of ADs about 2 decades after exposure to combat in Vietnam, controlling for potential selection biases and confounding variables. Although our data analyses were not infallible, our results seem compelling. It appears the Vietnam veterans with comorbid PTSD had a greater risk for autoimmune diseases, especially rheumatoid arthritis, psoriasis, and hypothyroidism. The adjusted results for current PTSD were only significant for the presence of any AD, but not any specific type.

The strengths and limitations of these veteran data have been discussed in detail elsewhere.[1,13,15–17,19] For the current study, since the disease outcomes of interest were partially based on self-report, the MMPI hypochondriasis scale was removed from our factor analysis and our comorbid-PTSD factor score recalculated. The logistic regression results predicting ADs, however, were about the same as before. In addition, the accuracy of self-reported medical conditions has often been validated in national studies and should not automatically be assumed to be problematic in population studies.[19] Other limitations are that our study follow-up was only 17 years on average and that the study included only men. A longer timeframe may have found a higher prevalence of diseases and our results may have been different for women.[62] It is also possible that the results found were due to other factors, such behavioral risk factors or genetics/shared vulnerabilities,[20] although we attempted to control for key variables that could produce spurious results. The major strength of the study is that it was based on a large-scale population study, not a small clinic-based sample, as has often been the case with autoimmune disease research.

Our study findings are consistent with a number of studies and clinical findings. First, whereas our overall population AD prevalence rate of 6.3% (95% CI = 5.4–7.4%) (TABLE 1) appears higher than that reported for the general population overall (3.1%),[63] it is not out of the range of possibilities for the veteran population. Second, given the lower cortisol levels often reported among PTSD victims,[37] one would expect to have a proinflammatory cytokine response, resulting in the proliferation of T lymphocytes[64–66] and a possible association with specific diseases resulting from

lower cortisol levels, such as psoriasis.[67,68] As demonstrated, comorbid-PTSD cases in our study were more likely to have had abnormally high T-lymphocyte counts. Third, these comorbid PTSD cases were more likely to have had highly reactive cell-mediated immunity responses on delayed-type cutaneous hypersensitivity tests, whereby increased erythema and induration occurred at the site of antigen invasion.[16,69,70] Fourth, our DHEA-S results were also noteworthy; the comorbid-PTSD cases were more likely to have had abnormally lower DHEA-S levels, an adrenal steroid hormone known to be involved in T-cell regulation[71] and the functioning of glucocorticoids.[72] Fifth, we also saw an association between comorbid PTSD cases and abnormally elevated levels of immunoglobulin-M, a plasma protein often associated with inflammatory responses and rheumatoid factors.[73] Sixth, given the significance of most of our findings, the issue of multiple comparisons should not be a problemin this study.

IMPLICATIONS

Although the laboratory markers for AD in our study may have lacked specificity, what seems increasingly clear is that there is a possible association between exposure to severe psychological stress and the onset of inflammatory diseases.[45,74–77] We

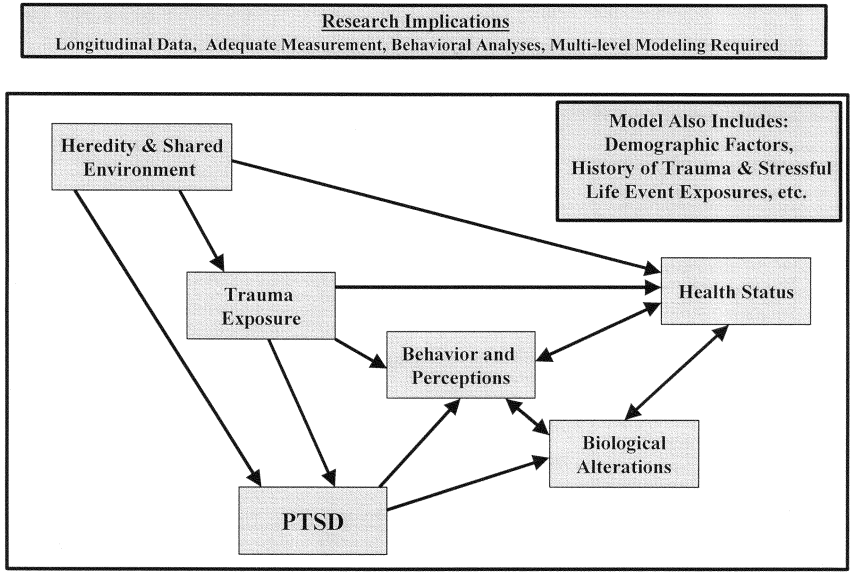

FIGURE 1. Multifactoral PTSD outcome model: different causal pathways to disease. Basic causal model showing the associations between trauma exposure, PTSD, and health outcomes. *Double-headed arrows* suggested the potential for reciprocal causation. Behavioral analyses are an important part of the model to understand the contribution of behavioral/perceptual factors in both the onset and the prevention of disease. Model also suggests that disease prevention treatment may occur on both the behavioral and the biological level.

think that our study, together with recent epidemiologic and clinical studies, suggests a link between long-term exposure to severe psychological stress and the onset of ADs. More conclusive evidence for this association will likely require more definitive research, including all or most of the data elements shown in FIGURE 1. In addition to measuring the impact of heredity, a particular challenge for this research will be to assess the impact of behavioral risk factors that could result from trauma exposures (e.g., substance abuse) and then, in turn, could result in disease. However, we suggest that such behavioral aspects of disease pathogenesis may prove to be especially promising, because acquiring the right health-enhancing behaviors could be protective of disease. For example, cognitive therapy is often recommended for treatment of PTSD and other anxiety disorders.[78] If this therapy is effective in reducing PTSD symptoms, then the burden of disease should be reduced among those properly treated. Nevertheless, as just indicated, PTSD has a biological basis that exists below the cognitive level,[79] suggesting that a purely cognitive approach may be limited. This is because the psychopathology involved with PTSD is likely related to biophysiological processes, to some degree, independent of cognitive functioning.[80] As has previously been suggested,[19] understanding both the physiological and the psychological aspects of traumatic phenomenon clearly seems warranted to effectively treat the medical sequelae of this condition. Over-focusing on either of these is likely to limit the successful prevention and treatment of a wide range of disabling conditions.

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