

Psychological Stress and Disease

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DESPITE WIDESPREAD PUBLIC BELIEF THAT PSYCHOLOGICAL stress leads to disease, the biomedical community remains skeptical of this conclusion. In this Commentary, we discuss the plausibility of the belief that stress contributes to a variety of disease processes and summarize the role of stress in 4 major diseases: clinical depression, cardiovascular disease (CVD), human immunodeficiency virus (HIV)/AIDS, and cancer.

What Is Psychological Stress?

Psychological stress occurs when an individual perceives that environmental demands tax or exceed his or her adaptive capacity.¹ Operationally, studies of psychological stress focus either on the occurrence of environmental events that are consensually judged as taxing one's ability to cope or on individual responses to events that are indicative of this overload, such as perceived stress and event-elicited negative affect. In this article, the definition of stress excludes psychiatric disorders that may arise as downstream consequences of stressful exposures and also excludes dispositions often linked to stress, such as hostility and type A behavior.

Pathways Linking Psychological Stress to Disease

Generally, stressful events are thought to influence the pathogenesis of physical disease by causing negative affective states (eg, feelings of anxiety and depression), which in turn exert direct effects on biological processes or behavioral patterns that influence disease risk.¹ Exposures to chronic stress are considered the most toxic because they are most likely to result in long-term or permanent changes in the emotional, physiological, and behavioral responses that influence susceptibility to and course of disease.^{1,2} This includes stressful events that persist over an extended duration (eg, caring for a spouse with dementia) or brief focal events that continue to be experienced as overwhelming long after they have ended (eg, experiencing a sexual assault).³

Behavioral changes occurring as adaptations or coping responses to stressors such as increased smoking, decreased ex-

ercise and sleep, and poorer adherence to medical regimens provide an important pathway through which stressors influence disease risk. Stressor-elicited endocrine response provides another key pathway. Two endocrine response systems are particularly reactive to psychological stress: the hypothalamic-pituitary-adrenocortical axis (HPA) and the sympathetic-adrenal-medullary (SAM) system. Cortisol, the primary effector of HPA activation in humans, regulates a broad range of physiological processes, including anti-inflammatory responses; metabolism of carbohydrates, fats, and proteins; and gluconeogenesis. Similarly, catecholamines, which are released in response to SAM activation, work in concert with the autonomic nervous system to exert regulatory effects on the cardiovascular, pulmonary, hepatic, skeletal muscle, and immune systems. Prolonged or repeated activation of the HPA and SAM systems can interfere with their control of other physiological systems, resulting in increased risk for physical and psychiatric disorders.^{1,2}

That HPA and SAM systems mediate the effects of stress on disease is supported by experimental evidence from animal as well as human studies that show a wide variety of stressful stimuli provoke activation of these systems. However, stress also may influence disease risk through its effects on other systems. For example, psychological stress has been found to impair vagal tone,⁴ which also can increase disease risk, particularly for CVD.

Effects of stress on the regulation of immune and inflammatory processes have the potential to influence depression; infectious, autoimmune, and coronary artery disease; and at least some (eg, virally mediated) cancers.⁵ Psychological stress might alter immune function through direct innervation of lymphatic tissue, through release of HPA and SAM hormones that bind to and alter the functions of immunologically active cells, or through stress-induced behavioral changes such as increased smoking.

Healthy human individuals exposed to acute laboratory stressors show an adaptive enhancement of some markers of natural immunity but a general suppression of functions of specific immunity.⁶ By comparison, exposure to real-life

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chronic stress (eg, unemployment, caregiving for the chronically ill) is associated with a biphasic immune response in that partial suppression of cellular and humoral function coincides with low-grade, nonspecific inflammation.⁶

Although stressors are often associated with illness, the majority of individuals confronted with traumatic events and chronic serious problems remain disease-free.³ There has been considerable interest in identifying individual differences in vulnerability to potential pathogenic effects of stress with emphasis on genetic as well as psychological factors.

Does Stress Cause Disease?

The fundamental question—Does stress cause disease?—can only be evaluated rigorously by experimental studies. Ethical considerations prohibit conducting experimental human studies of the effects of stress on the pathogenesis of serious disease. However, there is evidence from “natural experiments” that capitalize on real-life stressors occurring outside of a person’s control such as natural disasters, economic downsizing, or bereavement. There also have been attempts to reduce progression and recurrence of disease by psychosocial interventions. However, clinical trials in this area tend to be small, methodologically weak, and not specifically focused on determining whether stress reduction accounts for intervention-induced reduction in risk. In contrast, evidence from prospective cohort studies and natural experiments is informative. These studies typically control for potentially confounding demographic and environmental factors such as age, sex, race/ethnicity, and socioeconomic status.

Stress and Depression. Stressful life events have been linked to major depressive disorder as well as to depressive symptoms.^{7,9} During the 3 to 6 months preceding the onset of depression, 50% to 80% of depressed persons experience a major life event, compared with only 20% to 30% of nondepressed persons evaluated during the same period.⁹ Approximately 20% to 25% of persons who experience major stressful events develop depression.¹⁰

Although most investigations have focused on life events as triggers of depression onset, increased stress also predicts the clinical course of major depression, including features such as longer duration, symptom exacerbation, and relapse.^{7,8} Evidence also suggests that events that occur concurrently with treatment reduce positive response.⁸

Stress and Cardiovascular Disease. Experimental work with animals provides strong support for a stress-elicited increase in coronary artery disease, with indication that the effects of stress are mediated by protracted SAM activation.¹¹ Laboratory experiments in healthy adults and cardiac patients indicate that stress can foster pathogenic processes such as myocardial ischemia and activate inflammatory and coagulatory mechanisms.¹²

Prospective research conducted among initially healthy human populations provides considerable support for a link between psychological stress and CVD morbidity and mor-

ality.^{11,12} One meta-analysis estimated an approximate 50% increase in CVD risk associated with high levels of work stress, defined as low workplace control coupled with high demands, inadequate compensation, or organizational injustice.¹³

Long-term CVD risk is also increased among initially healthy individuals who experience traumatic events, such as the death of a child, or who are exposed to emotional, sexual, or physical abuse during early life.^{14,15} Similar patterns are found in natural experiments examining the rates of cardiovascular events following natural disasters and war.^{11,12} Recurrent CVD events and mortality among persons with preexisting CVD are similarly increased with perceived life stress, job overload, marital distress, and social isolation.¹¹

Stress and HIV/AIDS. Individuals differ with regard to rate of progression through the successive phases of HIV infection. Some remain asymptomatic for extended periods and respond well to medical treatment, whereas others progress rapidly to AIDS onset and develop numerous complications and opportunistic infections. Stress may account for some of this variability in HIV progression.

Evidence published before 2000 regarding the influence of stress on HIV progression was largely inconsistent. However, that published since 2000 has generally supported a link between stress and HIV progression.^{16(pp165-194)} Some evidence suggests that an accumulation of negative life events over several years of follow-up predicts worse AIDS-related outcomes. For example, among HIV-positive men, each additional moderately severe event increased the risk of progressing to AIDS by 50% and of developing an AIDS-related clinical condition by 2.5-fold.¹⁷ Moreover, stress has been found to influence the course of virally initiated illnesses to which persons with HIV are especially susceptible.¹⁸ These studies are supported by experimental research with animals wherein exposure to social stressors results in decreased survival.¹⁹

Better measures of stress may account for the positive findings in later studies. These studies used objective ratings of the stressfulness of events and focused on specific events with highly personal consequences, such as bereavement and stigma regarding sexual orientation. Another explanation for positive findings in later studies is that the effects of stress are due to poor adherence to highly active antiretroviral therapy. However, stress may remain a risk factor even when adherence is controlled, directly influencing HIV replication via increases in autonomic nervous system activity.²⁰

Stress and Cancer. Experimental research in animals has found that stress contributes to the initiation, growth, and metastasis of select tumors. Moreover, mechanistic experiments in humans indicate that stress affects key pathogenic processes in cancer, such as antiviral defenses, DNA repair, and cellular aging.²¹ Despite these promising findings, evidence from prospective studies linking stress and cancer incidence in humans is mixed at best.²²⁻²⁴ The lack of consistent results may be because many cancers are di-

agnosed only after they have been growing for many years, making an association between stress and disease onset difficult to demonstrate.

It is generally believed that stress is more likely to influence the progression and recurrence of cancer than initial onset of the disease. Yet the critical prospective studies in this area have been largely unresponsive. The lack of convincing data on psychological stress as a risk for cancer onset, progression, or recurrence may be at least partly attributable to the practical difficulties in designing and implementing adequate studies. For example, studies frequently collapse groups of patients across various types of cancer to maximize power. Cancer is a heterogeneous group of diseases with multiple etiologies, and the contribution of stress-related perturbations (eg, HPA and SAM activation, diminished antiviral defenses) likely varies across sites and stages. Of the more narrowly focused studies, much emphasis has been placed on breast cancer. However, stress effects are likely to be more pronounced in other cancers, especially those facilitated by impairments in antiviral immunity and sustained activation of hormonal response (eg, cervical cancer, hepatocarcinoma, and HIV-related tumors). Research in cancer progression also is limited by poor sensitivity to detect (and hence control for) premorbid states and the inability to accurately quantify severity at any disease stage.

Conclusions

Associations between psychological stress and disease have been established, particularly for depression, CVD, and HIV/AIDS. Other areas in which evidence for the role of stress is beginning to emerge include upper respiratory tract infections, asthma, herpes viral infections, autoimmune diseases, and wound healing.¹⁶

Evidence derived from prospective observational studies provides support for stress as an important factor in certain diseases but cannot establish a causal relationship. However, the results of these studies are consistent with those of natural experiments regarding the effects of real-life stressor exposure on disease risk; with those of laboratory experiments showing that stress modifies disease-relevant biological processes in humans; and with those of animal studies investigating stress as a causative factor in disease onset and progression. This consistency of research findings strongly supports the hypothesis of a causal link. The development of interventions that can reduce the behavioral and biological sequelae of psychological stress and the demonstrated efficacy of such interventions in randomized clinical trials would provide critical data on the clinical importance of this work.

Financial Disclosures: Dr Cohen reported consulting for Johnson & Johnson Consumer Companies Inc on issues of stress measurement. None of the other authors reported any financial disclosures.

Role of the Sponsor: This article is based on a paper commissioned by the Institute of Medicine Committee on Psychosocial Services to Cancer Patients and Families in Community Settings. The Institute of Medicine suggested the topic but played no role in structuring the paper; in the collection, management, and interpretation of the data; or the preparation, review, or approval of the manuscript.

Additional Contributions: We thank David Krantz, PhD (Uniformed Services University of the Health Sciences), Margaret Kemeny, PhD (School of Medicine, University of California at San Francisco), Stephen Manuck, PhD, and Karen Matthews, PhD (University of Pittsburgh), and Scott Monroe, PhD (Notre Dame University), for their comments on an earlier draft; the John D. and Catherine T. MacArthur Foundation Network on Socioeconomic Status and Health and members of the Pittsburgh Mind-Body Center (HL65111, HL65112) for their intellectual support; and Ellen Conser, MA, Ashleigh Molz, and Wesley Barnhart, BS (Carnegie Mellon University), for assistance in preparing the manuscript. None of these individuals received any extra compensation for their contributions.

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