
Psychosocial Influences on Immunity and Infectious Disease in Humans

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I. INTRODUCTION

There is substantial evidence for the plausibility of psychosocial influences on infectious disease in humans. We now have (1) psychologically and biologically plausible explanations of psychosocial influences on the pathogenesis of infectious agents; (2) substantial evidence that stressors can alter both cellular and humoral immune function; (3) evidence for a role of stress in determining susceptibility for a small number of infectious agents; and (4) evidence for the role of stress in activating latent viral (herpes) infections. However, we still know little about the characteristics of psychosocial factors that increase or decrease risk of disease onset and progression and of the nature of immune changes that are responsible for psychosocial-induced changes in disease risk. There are still no direct demonstrations that proposed mechanisms link psychosocial factors to disease and hence little real

understanding of the extent to which evidence deriving from one infectious disease model generalizes to another.

II. CURRENT STATE OF KNOWLEDGE

When exposed to an infectious agent, only a portion of people develop clinical disease, and severity and duration of symptomatology vary widely among those who do become ill. There are also substantial unexplained differences between people in the course of reactivation of latent viral infections. Reasons for variability in response are not well understood and the possibility that psychological factors play a role has received increased attention (Bierman, 1983; Cohen & Williamson, 1991; Stein, 1981).

A. Plausible Explanations of Psychosocial Influences on the Pathogenesis of Infectious Disease

Given exposure to a pathogenic agent, susceptibility to infection is presumed to be primarily mediated by immune function. There is substantial evidence that stress and other psychosocial factors influence immunity (Herbert & Cohen, 1993b; Jemmott & Locke, 1984; O'Leary, 1990), as well as basic research delineating the pathways through which this influence may occur. Stress may influence immunity through direct innervation of the central nervous (CNS) and immune systems or through neuroendocrine-immune pathways. Direct neural pathways linking the CNS to the immune system have been identified (Felten et al., 1985; Felten & Olschowka, 1987). In the case of hormonal pathways, catecholamines secreted by the adrenal-medulla in response to stressors, and stressor-triggered pituitary mediated hormones such as cortisol and prolactin have been associated with modulation of immune function (see Hall & Goldstein, 1981; Laudenslager, 1988; Rabin et al., 1989). Moreover, receptors for ACTH, TSH, growth hormone, prolactin, and catecholamines have been found on lymphocytes (see reviews by Rabin et al., 1989). The existence of these receptors suggests that these hormones play a role in modulating lymphocyte function.

Behavioral changes that occur as adaptations or coping responses to stressors may also influence immunity. For example, persons exposed to stressors often engage in poor *health practices*, for example, smoking, poor diets, and poor sleeping habits (Cohen & Williamson, 1988; Conway et al., 1981) which may have immunosuppressive effects (Cohen et al., 1993; Kiecolt-Glaser & Glaser, 1988b). Aggressive or affiliative behaviors triggered by prolonged social stressors may also influence immunity, for example, it may be these behaviors (not the stressors themselves) that trigger sympathetic or endocrine responses that modulate the immune system (Cohen et al., 1986; Manuck et al., 1978; Obrist, 1981).

Stress can also influence susceptibility to infection by influencing whether and for how long persons are exposed to pathogenic agents. For example, stressed persons often engage in social coping, i.e., drawing on resources from their social networks (Cohen & Wills, 1985). Increased interaction with others results in greater probability of exposure to infectious agents and consequent infection. However, social interaction under stress is influenced by both the nature of the stressor and individual differences in social skills and affiliative tendencies. Hence, under some conditions stress may lead to social withdrawal and decreased risk of exposure. Other stress elicited behaviors, for example, unsafe sexual practices or poor hygienic practices, could also increase exposure to infectious agents.

Stressors may also play a role in reactivating latent pathogens (agents already in the body but not currently multiplying). Diseases with latent viral states include oral and genital herpes and possibly AIDS. Reactivation could occur through hormonal or neural stimulation of pathogen replication, or through suppression of cellular immune processes that might otherwise hold the pathogen in check (e.g., Glaser & Gotlieb-Stematsky, 1982; Kiecolt-Glaser & Glaser, 1987).

B. Evidence for Stressor Alteration of Immune Function

Both human and infrahuman studies indicate that various stressors modulate both cellular and humoral measures of immune function (see Ader et al., 1991; Herbert and Cohen, 1993b). This includes human research on immunomodulating effects of chronic stressors such as separation and divorce (Kiecolt-Glaser et al., 1987; Kiecolt-Glaser et al., 1988), caregiving for Alzheimer patients (Kiecolt-Glaser et al., 1987), and bereavement (e.g., Bartrop et al., 1977; Schleifer et al., 1983).

Similar evidence derives from studies of social stressors on immunity in nonhuman primates. For example, the separation of offspring from their mothers results in suppression of both mitogen stimulated lymphocyte proliferation and antibody production in response to an antigenic challenge in young animals (Laudenslager et al., 1982, 1986; Coe et al., 1988). Chronic social stress has also been found to suppress cellular immunity among adult cynomolgus monkeys. Animals randomly assigned to 2 years of exposure to an unstable social environment demonstrated a suppression of mitogen stimulated lymphocyte proliferation in comparison to animals assigned to a stable social environment. However, there were individual differences in immune response to stress. Animals who responded to the social stressor with high levels of affiliative behaviors did not show immunosuppression (Cohen et al., 1993).

Although the effects of stressors on immune response are often described as immunosuppressive, the implications of stressor-induced immune changes for disease susceptibility are not clear (Calabrese et al., 1987; Her-

bert & Cohen, 1993b; Jemmott & Locke, 1984). First, in studies of stressor effects on immunity, the immune responses of stressed persons fall within *normal* ranges (Laudenslager, 1987; Rabin et al., 1989). Second, there are few data on immune status in *healthy* persons as a predictor of disease susceptibility. Finally, the immune system is complex. One or even several measures of immune function may not provide an adequate representation of host resistance.

The first two comments, however, apply primarily to the risk for infection among healthy individuals. Stress and other psychosocial factors may have their greatest effect on those whose immune systems are already compromised, individuals whose health is already impaired, and patients with immunosuppressive disease (Kiecolt-Glaser & Glaser, 1987). Thus, it can be argued that even relatively small psychosocial-elicited changes in immunity may contribute to triggering viral activation or disease progression in persons who are HIV positive or have ARC or AIDS.

There are also individual differences in stress-elicited immune changes and disease susceptibility (Rabkin & Struening, 1976). Variation in response may be attributable to individual differences in the meaning of a stressor, in ability to cope with a stressor, in physiologic reactivity to stressors either at the level of sympathetic or hormonal mediation, or in the sensitivity of the immune system itself. Although there are few studies directly addressing the possible role of biologic, sociologic, and psychologic characteristics as moderators of the relation between stress and immunity (e.g., Cohen, Kaplan, Cunnick, Manuck, & Rabin, 1993; Manuck, Cohen, Rabin, Muldoon, & Bachen, 1991), evidence from other areas of health suggests that further understanding of the importance of individual differences in response to stressors is paramount in understanding the role of stress in disease susceptibility and progression (see reviews by Cohen & Wills, 1985; Cohen & Edwards, 1989; Gentry & Kobasa, 1984).

C. Stressors and Susceptibility to Infectious Disease

Of the many published papers addressing the role of psychological factors in infectious disease in humans, relatively few meet contemporary scientific criteria. The following discussion is limited to studies that employ standardized measurement, include control groups, and use procedures allowing statistical inference. We also limit ourselves to studies in which clinical illness is diagnosed by a physician using a standard protocol, or illness is verified through biological means, e.g., viral shedding or increases in pathogen-specific antibody. We focus on studies of verified illness because those using self-reports of symptoms or illnesses may reflect psychosocial influences on illness cognition (perception and reporting) rather than underlying pathology (Cohen & Williamson, 1991).

Although there are relatively few human studies on the role of psychosocial factors in verified infectious disease that meet the criteria set above, the evidence in support of a relation is provocative (see reviews by Cohen & Williamson, 1991; Laudenslager, 1987). There is evidence from epidemiologic studies which suggests that social stressors increase risk for verified upper respiratory infections. Two prospective epidemiologic studies find that family conflict and disorder predicted serologically verified infectious illness (Meyer & Haggerty, 1962; Graham, Douglas, & Ryan, 1986). Converging evidence comes from viral challenge studies, where volunteers who fill out stressful life event or psychological distress scales are subsequently challenged with a cold or influenza virus and then monitored for the development of infection and illness. Although the early viral challenge work was often methodologically flawed, it provided mixed support for a relation between stress and susceptibility to upper respiratory infections (Broadbent et al., 1984 and Totman et al., 1980 found effects; Greene et al., 1978 and Locke & Heisel, 1977 did not). Later, we will describe our own viral challenge work using a large sample and more sophisticated methodologies (Cohen, Tyrrell, & Smith, 1991, 1993). This work provides more convincing evidence in support of a link between stress and infectious disease.

Although we have focused on the role of stressors in disease susceptibility, individual differences in *affiliative* skills also predict susceptibility to primary infections. For example, introverts are more susceptible to upper respiratory infection following a viral challenge (Broadbent et al., 1984; Totman et al., 1980) and have more severe periodontal infections (Manhold, 1953). Similarly, persons with relatively few social skills or little social support have more verified episodes of oral and genital herpes (Katcher et al., 1973; Friedmann et al., 1977; Manne & Sandler, 1984; McLarnon & Kaloupek, 1988).

1. Infrahuman Studies on Stress and Susceptibility to Infection

Studies of rodents randomly assigned to a stressor (almost always an acute physical stressor) or control condition and exposed to an infectious agent do not provide any clear conclusions. They do, however, suggest the complexity of the phenomenon (reviews by Friedman et al., 1965; Plaut & Friedman, 1981; Rogers et al., 1979). Stressor influences on susceptibility to infectious agents depend on the species of experimental animal, the type of stimulation, the timing of acute stressor administration relative to the infectious challenge, and the infectious agent. This work underscores the importance of identifying the behavioral and biological pathways that link psychosocial factors to disease susceptibility including identifying the parameters of immunity that are important in the face of different pathogens. Some of the problems we find in applying these results to understanding the

influence of social stressors on human susceptibility include that the stressors were relatively short-lived, primarily involved physical stimulation, and were qualitatively unlike those that either human or rodent would confront outside of the laboratory. The lack of generalization of results across strains of mice and rats also suggests that rodent models are not appropriate for answering questions about psychosocial influences on human infectious susceptibility.

2. Stress and Activation of Latent Viral Infections

There is growing evidence that stressors may trigger *reactivation* of herpes viruses and hence, recurrence of disease among those with previous exposure to herpes. Indirect support for stressor-triggered reactivation comes from a series of studies indicating increased antibodies to three herpesviruses (HSV-1, CMV, EBV) under stress (e.g., Glaser et al., 1985, 1987), while direct support derives from prospective studies of unpleasant moods on oral (Friedmann, Katcher, & Brightman, 1977; Katcher et al., 1973) and genital herpes (Goldmeier & Johnson, 1982; McLarnon & Kaloupek, 1988).

D. Other Factors Influencing Susceptibility to Infection

Stress is not the primary etiologic agent in infectious disease, but rather, may be one of many contributors. The primary factor in susceptibility is prior exposure and consequent development of immunity. This immunity is partly attributable to the production of antibodies that occurs when persons are exposed to an infectious agent. Some antibodies remain in circulation and help fight the same infectious agent upon later exposure. Presence of antibodies also provides evidence of prior exposure. Exposure to an infectious agent also sensitizes a population of white blood cells (lymphocytes) to recognize and aid in destroying that agent upon subsequent exposure.

Other factors influence risk for infectious disease (see Jackson, Dowling, et al., 1960; Jemmott & Locke, 1984; Plaut & Friedman, 1981; Kiecolt-Glaser & Glaser, 1988a). These factors include nutritional status of the host, previous history of illness, presence of other disease, genetic-immune factors, age, race, gender, pregnancy, rhythms (e.g., circadian, menstrual phase, annual), and seasons of the year (e.g., temperature, light exposure). Some of these factors (e.g., race and gender) may be correlated with both stress and infection and consequently provide alternative (spurious) explanations for correlations between stress and infectious disease. Each factor may also make significant independent contributions to unexplained error variance. The more of these factors controlled for in any study, the greater the probability of isolating effects of stress in the context of multiple environmental, social, and biological predictors (see Plaut & Friedman, 1981; Schleifer et al., 1986).

III. THE COMMON COLD STUDIES

In our own work, we pursue the question of whether stress places people at greater risk for infectious disease, and at the same time attempt to identify the behavioral and biological pathways through which such relations operate. For stressful events to influence susceptibility, they are presumed to be appraised as stressful (as exceeding ability to cope), and to consequently elicit an emotional response. This emotional response is thought to trigger either behavioral (e.g., increased smoking) or neuroendocrine (e.g., increases in epinephrine, norepinephrine, or cortisol) responses thought to influence the immune system's ability to respond to a challenge. The work we describe was designed to examine the psychological, behavioral, and biological pathways thought to link stressful events to illness susceptibility, while carefully controlling for a variety of other factors that might influence risk for infectious disease.

The data described here are from a trial conducted at Britain's Medical Research Council's Common Cold Unit between 1986 and 1989 (Cohen, Tyrrell, & Smith, 1991, 1993). In this study, we assessed stressful life events, perceived stress, and negative affect *before* experimentally exposing subjects to a common cold virus. We then carefully monitored subjects for the development of infection and clinical illness. By intentionally exposing people to an upper respiratory virus, we were able to control for the possible effects of stressful events on exposure to infectious agents (as opposed to their effects on host resistance). In the remainder of this chapter, we examine the relation between each of the three stress scales and risk for clinical colds, evaluate potential pathways through which each might influence susceptibility to infectious disease, and discuss differences in relations between individual scales and illness susceptibility in terms of the components of psychological stress that each of the scales assess.

A. Methods

The subjects were 154 men and 266 women volunteers 18 to 54 years old. All reported no chronic or acute illness or regular medication regimen and were judged in good health following examination. During their first two days in the clinical unit, they were given a thorough medical examination, completed psychological stress, personality, and health practice questionnaires and had blood drawn for immune and cotinine assessments. Subsequently, volunteers were exposed via nasal drops to a low infectious dose of one of five respiratory viruses: rhinovirus types 2 ($n = 86$), 9 ($n = 122$), 14 ($n = 92$), respiratory syncytial virus ($n = 40$), and coronavirus type 229E ($n = 54$). An additional 26 volunteers received saline. For 2 days before and 7 days after viral challenge, volunteers were quarantined in large apartments (alone or with one or two others). Starting 2 days before viral

challenge and continuing through 6 days postchallenge, each volunteer was examined daily by a clinician using a standard respiratory sign-symptom protocol. Examples of items on the protocol include sneezing, watering of eyes, nasal stuffiness, sore throat, hoarseness, and cough. The protocol also included an objective count of the number of tissues used daily by a volunteer and body temperature (oral) assessed twice each day. Samples of nasal secretions were also collected daily to assess whether volunteers were infected by the experimental virus. Approximately 28 days after challenge a second serum sample was collected to assess changes in viral-specific antibody. All investigators were blind to volunteers' psychological status and to whether they received virus or saline.

1. Infections and Clinical Colds

To be infected means that the challenge virus replicates within the body. This is detected directly by culturing nasal secretion samples (viral isolation) or indirectly through establishing significant increases in viral-specific antibody. A volunteer was deemed *infected* if virus was isolated in nasal secretion after viral challenge or there was a significant rise in pre- to post-challenge viral specific serum antibody. Eighty-two percent (325) of the volunteers receiving virus were infected.

A person can be infected without developing clinical illness. The criteria for *clinical illness* were *both* infection and a positive clinical diagnosis. At the end of the trial, the clinician judged the severity of each volunteer's cold on a scale ranging from nil (0) to severe (4). Ratings of mild cold (2) or greater were considered positive clinical diagnoses. Thirty-eight percent (148) developed clinical colds. *None* of the 26 saline controls developed colds. The subjects also rated the severity of their colds on the same scale. The clinical diagnosis was in agreement with the subject's rating in 94% of the cases.

2. Psychological Stress

We noted earlier that when demands imposed by events exceed ability to cope a psychological stress response is elicited and that this response is composed of negative cognitive and emotional states. In order to assess the various components of this process, three kinds of measures of psychological stress were used: (1) number of major stressful life events judged by the respondent as having a negative impact, (2) perception that current demands exceed capabilities to cope, and (3) current negative affect. The major stressful life events scale consisted of events that might happen in the life of the respondent (41 items) or close others (26 items). The scale score was the number of negative events reported as occurring during the last year. The Perceived Stress Scale was used to assess the degree to which situations in life are perceived as stressful. Items in the scale were designed to tap how unpredictable, uncontrollable, and overloading respondents find

their lives. Finally, the negative affect scale included 15 items from Zevon and Tellegen's list of negative emotions. We also present data based on analyses using the psychological stress index created by quartiling each scale and summing quartile ranks for each subject.

3. Standard Control Variables

Each analysis controls (covaries) for the possible effects of a series of variables that might provide alternative explanations for a relation between stress and illness. These include prechallenge serostatus for the experimental virus, age, gender, education, allergic status, weight, season, number of others the volunteer was housed with, whether an apartment mate was infected, and challenge virus.

4. Health Practice Measures

We also conduct separate analyses that assess the roles of health practices as possible pathways linking stress and susceptibility. Measures included smoking (serum cotinine), drinking alcohol, exercise, quality of sleep, and diet.

5. Personality Measures

Because psychological stress could reflect stable personality styles rather than responses to environmental stressors, self-esteem and personal control (two personality characteristics closely associated with stress) were assessed prior to viral challenge. A third personality characteristic, introversion–extraversion, was also assessed.

B. Results

1. Stress and Susceptibility to Clinical Illness

High-stressed persons have higher rates of colds irrespective of the stress scale. Figure 1 depicts this relation controlling for whether a roommate was infected. To determine whether any of these effects might be attributable to relations between stress and health practices, we ran an additional set of conservative analyses including smoking rate, drinking rate, diet, exercise, and sleep quality in the equations along with the 10 standard control variables. The addition of health practices did not significantly alter the results. To determine whether these relations might be attributable to the stress scales actually reflecting personality characteristics, we ran an additional analysis in which the three personality factors were added to the equation. Again, the relations between stress and illness were independent of these personality characteristics. In a series of final analyses, the three stress scales were entered into equations simultaneously (in pairs) in order to assess whether they were independently associated with illness.

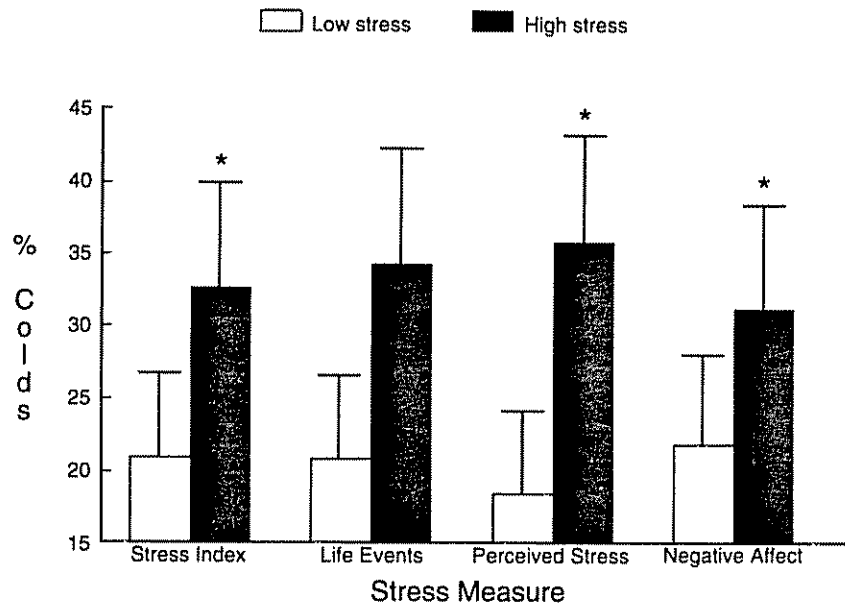


FIGURE 1 Observed associations between each of the stress measures and rates of clinical colds for the sample without infectious roommates. Standard errors are indicated. Significant effects ($p < .05$) are marked with an asterisk. (Reprinted from *Journal of Personality and Social Psychology*, 1993, 64 with permission of the American Psychological Association.)

These analyses indicated that the relation between life events and colds was independent of the relation between both perceived stress and clinical illness and negative affect and clinical illness (Cohen, Tyrrell, & Smith, 1993).

2. Are Stress Effects Consistent across the Five Viruses?

The analyses described so far have collapsed across viruses (including statistical controls for virus in the regression equation). However, a test of whether the effects of stress were consistent across the viruses (interaction term stress by virus type) indicated that they were. The influence of stress on each virus is depicted in Figure 2. This suggests the possibility that the relation between psychological stress and upper respiratory illness is non-specific, i.e., not dependent on the pathogenesis of the specific virus. Figure 2 also suggests that a dose-response relation occurred in all cases, with each increase in stress associated with an increase in colds. (A detailed analysis of the dose-response issue is reported in Cohen, Tyrrell, & Smith, 1991).

3. Is Stress Associated with Increased Infection or Increased Illness among Infected Persons?

Stress-associated increases in clinical illness could be attributable to an association between stress and increased probability of infection (viral repli-

cation) or to an association between stress and increased probability of infected persons developing clinical symptoms. Additional analyses addressed this issue. The first analysis assessed whether the reported relations between the various stress measures and clinical colds were partly or wholly attributable to an association between these scales and increased infection. As apparent from Figure 3, infection rates were higher for those above the median of all four measures. However, these differences were reliable for the stress index, perceived stress, and negative affect but not for stressful life events. The second analysis assessed whether the reported relations between the various stress measures and clinical colds were partly or wholly attributable to associations between stress and becoming sick (developing clinical symptoms) *following* infection. Because these analyses included only persons who were infected, the results are independent of earlier analyses predicting infection. As apparent from Figure 4, only life events approached reliable prediction of colds among infected persons.

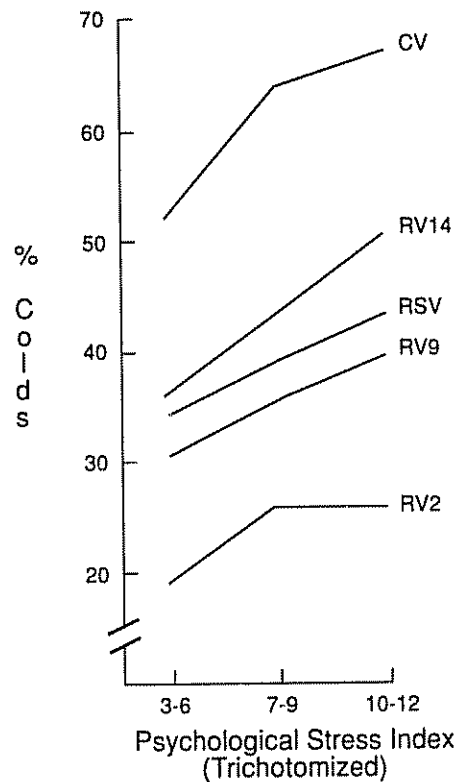


FIGURE 2 Observed associations between the psychological stress index and rates of clinical colds, separately for each virus.

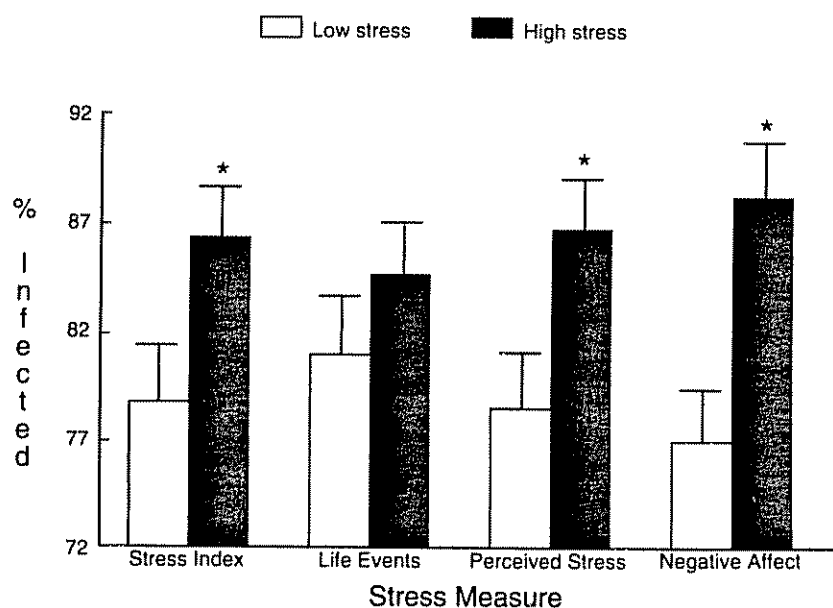


FIGURE 3 Observed associations between each of the stress measures and rates of infection. Standard errors are indicated. Significant effects ($p < .05$) are marked with an asterisk.

C. Discussion

The three stress scales are similar in that increases in each scale are associated with increases in clinical illness. In all cases, these relations could not be explained by factors thought to be associated with stress including age, gender, education, weight, allergic status, or health practices, the virus the subject was exposed to, or environmental characteristics associated with the design of the study. The relations were also not explicable in terms of either stress-induced differences in health practices, or associations between stress and the three personality characteristics we measured: self-esteem, personal control, and introversion-extraversion.

The consistency of the stress-illness relation among three very different viruses—rhinovirus, coronavirus, and respiratory syncytial virus (as well as among rhinovirus types)—was impressive. This observation suggests that stress is associated with the suppression of a general resistance process in the host, leaving persons susceptible to multiple infectious agents (or at least agents attacking the upper respiratory tract), or that stress is associated with the suppression of many different immune processes with similar results.

As interesting as the similar relation between each stress scale and clinical illness is, these relations were not all mediated by the same biological process. Negative life events were associated with greater rates of clinical

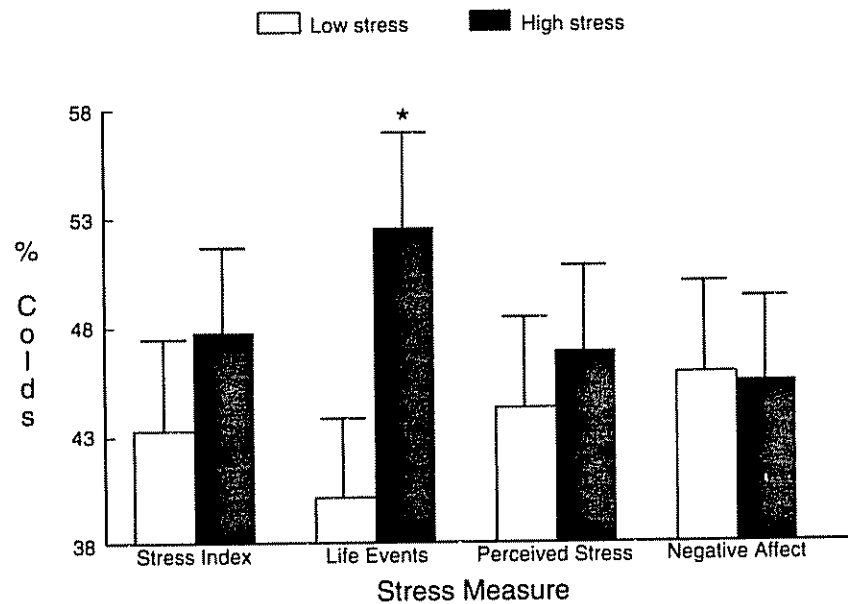


FIGURE 4 Observed associations between each of the stress measures and rates of colds among infected subjects. Standard errors are indicated. Significant effects ($p < .05$) are marked with an asterisk

cal illness and this association was primarily mediated by increased symptoms among infected persons. Perceived stress and negative affect were also related to clinical illness, but their associations with increased risk were primarily attributable to increased infection. These differences suggest that (1) the negative life events instrument measures something different than perceived stress and negative affect scales, and (2) that the constructs they tap have somewhat different consequences for the pathogenesis of infectious illness.

Psychological stress theory assumes that objective events influence disease outcomes through the negative cognitive and affective responses they elicit. In our study, life events predicted illness even when the possible effects of perceived stress and negative affect were controlled for. That these scales have independent relations with illness and that these relations are mediated by different processes challenges the assumption that perceptions of stress and negative affect are necessary for stressful life events to influence disease risk.

However, the most important conclusion of this study is that all of these instruments indicate what up to now has been somewhat speculative, that psychological stress is associated with increased susceptibility to biologically verified infectious disease processes.

IV. FUTURE PROSPECTS

It is likely that the next few years will result in a clearer understanding of the relations between psychosocial factors and immunity, the mechanisms that link psychosocial influence to immune change, and the range of immune function that is subject to alteration. Initial work will also be done on the characteristics of host resistance that influence susceptibility to a range of viral diseases and reactivation of latent viral infections.

A. What Psychosocial Factors Influence Immune Function?

The thrust of most research up until now has been on the effects of stress on immunity. Stress has been defined broadly and has included environmental events such as taking examinations and bereavement, affective disorders such as depression, and self-reports of stress and negative affect. Current work is moving toward clearer understanding of the characteristics of situations that influence immune function. It is also examining the kind of psychologic and psychophysiologic responses to situations requisite for immune change. This includes identifying the nature, domain, and timing (relative to immune change and infectious susceptibility) of stressors that influence immunity. It also includes differentiating various types of affective responses (e.g., anxiety, depression, anger) to stressors and identifying the types of affect that play a role in stressor-immune relations. There is also an expansion of psychosocial factors under consideration including closer examination of characteristics of the individual that might protect them from the potential influences of stressors on immunity such as social support systems and personality characteristics. Personality is also being studied as an independent influence on immune status and infectious susceptibility.

B. Which Parameters of Immunity Are Subject to Psychosocial Influence?

The existing literature focuses primarily on the effects of psychosocial factors on mitogen-stimulated lymphocyte proliferation, natural killer cell activity, and enumerations of peripheral white blood cells. This focus derives partly from historical use of these indicators in human immunology. Contemporary research is choosing immune outcomes to study based on more specific questions regarding the role of immunity in disease susceptibility and progression. As a result, future studies will contain a much broader range of immune measures, for example, PMN superoxide production, bacterial killing, phagocytosis, cytokine production, lymphocyte production of interferon, and immunoglobulin production by individual B lymphocytes.

C. Which Parameters of Immunity Are Critical in Susceptibility to Infection and to Viral Reactivation?

The ability to link our knowledge about psychosocial influences on immunity to understanding and predicting psychosocial influences on disease is severely limited by a lack of data on assessing host resistance. Are there specific psychosocial-induced immune changes that place persons at risk for a range of infectious diseases? Alternatively, can we specify psychosocial-induced immune changes that predict susceptibility to specific diseases or reactivation of specific latent viruses? In the next few years, we hope to learn some about the role of immunity in susceptibility to a small range of viral infections. The eventual goal will be to develop a broad understanding of the nature of both pathogen specific and nonspecific host resistance.

D. What Are the Hormonal Mechanisms That Link Psychosocial Factors to Immune Function?

Although there is a good basis for assuming that psychosocial influences on immunity and disease susceptibility are mediated by circulating hormones, work in humans in this area is sparse. It is becoming clear that hormone mediation in humans is different than rodents, however, we still know very little about which specific hormones influence which specific immune functions. The next few years should see substantial increases in experimental laboratory studies, field studies, and nonhuman primate analog experiments demonstrating stress–hormone–immune links. These studies will result in a better understanding of how psychosocial factors influence immunity as well as information in regard to the potential role of pharmacological interventions in altering psychosocial–immune relations.

E. What Are the Behavioral Mechanisms That Link Psychosocial Factors to Immunity?

A weakness in much of the existing research on psychosocial influences on immunity is the lack of attention to potential behavioral pathways. For example, we know that stress often influences a range of health practices such as smoking, drinking alcohol, exercise, diet, and sleep quality. It is possible that these behaviors constitute major pathways in linking stress (and other psychosocial factors) to both immune change and alterations in susceptibility to infection. It is likely that much of the research conducted during the next few years will place greater emphasis on accurately assessing behavioral as well as hormonal pathways.

V. SUMMARY

There is substantial evidence for the plausibility of psychosocial influences on infectious disease in humans as well as evidence for a role of stress in determining susceptibility for a small number of infectious agents. However, we still know little about the characteristics of psychosocial factors that increase or decrease risk of disease onset and progression and of the nature of behavioral, endocrine, and immune changes that are responsible for psychosocial-induced changes in disease risk. Until there is more empirical evidence for specific mechanisms linking psychosocial factors to infectious disease, we will have little real understanding of the extent to which evidence deriving from current work generalizes to other disease models.

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