

# Stress, Immunity, and Susceptibility to Upper Respiratory Infection

SHELDON COHEN, GREGORY E. MILLER

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## I. INTRODUCTION

Studies examining whether stress confers increased susceptibility to infectious disease date back to the 1950s. Considerable evidence has accumulated since that time in support of a relationship between stress and the incidence of *self-reported* colds and influenza (reviewed by Cohen & Williamson, 1991). The most convincing work on stress and infectious disease, however, has come from studies that provide biological verification of illness. For example, prospective epidemiological studies have demonstrated that family stress is associated with a higher incidence of serologically verified upper respiratory infection (Clover, Abell, Becker, Crawford, & Ramsey, 1989; Graham, Douglas, & Ryan, 1986; Meyer & Haggerty, 1962). In contrast, early viral-challenge studies, where volunteers completed psychological stress measures and were subsequently administered an experimental pathogen, yielded inconsistent findings concerning the association between stress and infectious susceptibility (Broadbent, Broadbent, Phillpotts, & Wallace,

1984; Greene, Betts, Ochitill, Iker, & Douglas, 1978; Locke & Heisel, 1977; Totman, Kiff, Reed, & Craig, 1980). However, recent studies employing larger sample sizes and more sophisticated methodologies provide strong evidence for a relationship between increased stress and illness risk (Cohen, Tyrrell, & Smith, 1991; Cohen et al., 1998; Cohen, Doyle, & Skoner, 1999; Stone et al., 1993).

If psychological stress does heighten vulnerability to infectious illness, what are the mechanisms through which this might occur? When the demands imposed by life events exceed a person's ability to cope, a psychological stress response is elicited (Lazarus & Folkman, 1984). The stress response consists of negative cognitive states such as helplessness and negative emotional states such as sadness or fear. These states set into motion a series of biological and behavioral changes that alter immune function and as a consequence may put persons at higher risk for developing infection and illness when exposed to an infectious pathogen. For instance, stress may influence immunity via central nervous system (CNS) innervation of lymphoid organs or through neuroendocrine-immune pathways. Direct neural pathways linking the CNS to the immune system have been identified (Felten et al., 1987; Felten & Felten, 1994). In the case of hormonal pathways, catecholamines secreted by the adrenal-medulla in response to stress and stress-triggered pituitary-mediated hormones such as cortisol and prolactin have been associated with modulation of immune function (Felten & Felten, 1994; Rabin, Kusnecov, Shurin, Zhou, & Rasnick,

1995) Moreover, receptors for a number of hormonal products have been found on lymphocytes and ligation of these receptors induces changes in lymphocyte function (see Blalock, 1994).

Behavioral changes that occur as adaptations or coping responses to psychological stress may also influence immunity. For example, persons experiencing stress often engage in poor health practices, e.g., smoking, poor diets, and poor sleeping habits (Cohen & Williamson, 1988; Conway, Vickers, Ward, & Rahe, 1981), that may have immunomodulatory effects (Kiecolt-Glaser & Glaser, 1988). Aggressive or affiliative behaviors triggered by prolonged psychological stress may also influence immunity. In other words, it may be the coping behaviors themselves, and not the precipitating stressor, that trigger sympathetic or endocrine responses (Cohen, Evans, Stokols, & Krantz, 1986; Manuck, Harvey, Lechleiter, & Neal, 1978).

Accumulating evidence on the role of the social environment and health has raised questions about potentially positive psychosocial effects on host resistance. Prospective studies have documented that people who participate in multiple social domains (e.g., family, friend, work, group membership) live longer (reviewed by Berkman, 1995), are more likely to survive myocardial infarction (reviewed by Berkman, 1995; cf. Orth-Gomer, Rosengren, & Wilhelmsen, 1993), are less likely to report being depressed (reviewed by Cohen & Wills, 1985), and are less likely to suffer a recurrence of cancer (reviewed by Helgeson, Cohen, & Fritz, 1998) than their more isolated counterparts. The health risks of being isolated are comparable in magnitude to the risks associated with cigarette smoking, blood pressure, and obesity and remain even after controlling for these and other traditional risk factors.

Although there is little evidence on the role of social behaviors in host resistance to infectious agents, there are several reasons to hypothesize that individuals with more diverse social networks may be at reduced risk for the development of upper respiratory infections (see Cohen, 1988; Cohen, Gottlieb, & Underwood, in press). First, social relationships may foster behaviors that promote resistance to infection, such as regular exercise and abstinence from tobacco. Second, when stressful life events occur, social relationships may serve a buffering function that protects individuals from the emotional and physiological sequelae associated with stress. Several studies have demonstrated that the presence of a supportive other can blunt autonomic nervous system and hypothalamo-pituitary-adrenal axis responses to stress (e.g., Kamarck, Manuck, & Jennings, 1990;

Kirschbaum, Klauer, Sigrun-Heide, & Hellhammer, 1995).

In the remainder of this chapter we describe our own research on stress, social participation, and susceptibility to upper respiratory infection. In these studies, we assess the psychosocial characteristics of healthy volunteers and subsequently expose them to a virus that causes a common cold. Approximately 40% of those exposed develop a verifiable illness. Hence we can ask whether their psychosocial status preceding exposure predicts whether their bodies are able to resist infection and illness. This paradigm eliminates the possibilities that associations we find between psychosocial characteristics and susceptibility are attributable to *previous exposure* to the virus (we assess and control for pre-challenge antibody), to *differential exposure to the virus* (we expose volunteers to controlled doses of virus), to *illness causing changes in psychosocial predictors* (we assess psychosocial factors before viral exposure in healthy volunteers), or to *illness causing changes in psychological, behavioral, and biological processes we pursue as links between psychosocial factors and disease susceptibility* (we assess these factors before viral exposure as well).

## II. THE BRITISH COMMON COLD STUDY: PSYCHOLOGICAL STRESS AND COLDS

Our initial study was carried out at the Medical Research Council's Common Cold Unit between 1986 and 1989. Detailed descriptions of the methodology used in this investigation have been published elsewhere (Cohen et al., 1991; Cohen, Tyrrell, & Smith, 1993). Briefly, 154 men and 266 women between the ages of 18 and 54 volunteered for the study. All were judged to be in good health following a physical examination, defined as having no acute or chronic medical condition and no regular medication regimen. During their first 2 days on the clinical unit, volunteers were given a thorough medical examination and completed psychological stress, personality, and health practice questionnaires. Subsequently, volunteers were exposed via nasal drops to a low infectious dose of one of five respiratory viruses: rhinovirus types 2 ( $n = 86$ ), 9 ( $n = 122$ ), and 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 as an indirect measure of infection. All investigators were blind to volunteers' psychological status and to whether they received virus or saline.

## A. Measures

### 1. Psychological Stress

Recall that when environmental demands outstrip an individual's ability to cope, a stress response is triggered, consisting of negative emotional and cognitive states. To capture the various components of this process, we had volunteers complete questionnaires assessing (a) the number of major stressful life events they judged as having a negative impact, (b) the perception that current demands exceeded their ability to cope, and (c) their 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 Perceived Stress Scale (Cohen & Williamson, 1988) was used to assess the degree to which situations in life were perceived as stressful. Items in the scale were designed to tap how unpredictable, uncontrollable, and overloading respondents found their lives. The negative affect scale included 15 items from the Zevon and Tellegen (1982) list of negative emotions. We also created an index of psychological stress that was based on all three of the scales described above. This was accomplished by quartiling each scale and summing quartile ranks for each subject, resulting in a scale with scores ranging from 3 to 12.

### 2. Clinical Colds

Volunteers were considered to have a cold if they were *both* infected and meeting illness criteria. Infection status was determined directly by culturing nasal secretion samples for viral proteins or indirectly through establishing fourfold increases in viral-specific antibody from baseline to 28 days postexposure. The illness criterion was based on clinician judgement of the severity of each volunteer's cold at the end of the trial, 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 (infection + illness). None of the 26 saline controls developed colds.

### 3. Health Practice Measures

We also examined whether health practices operated as a pathway through which stress contributed to disease susceptibility. Health practice measures included smoking status, alcohol consumption, exercise frequency, subjective sleep quality, and diet.

### 4. 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.

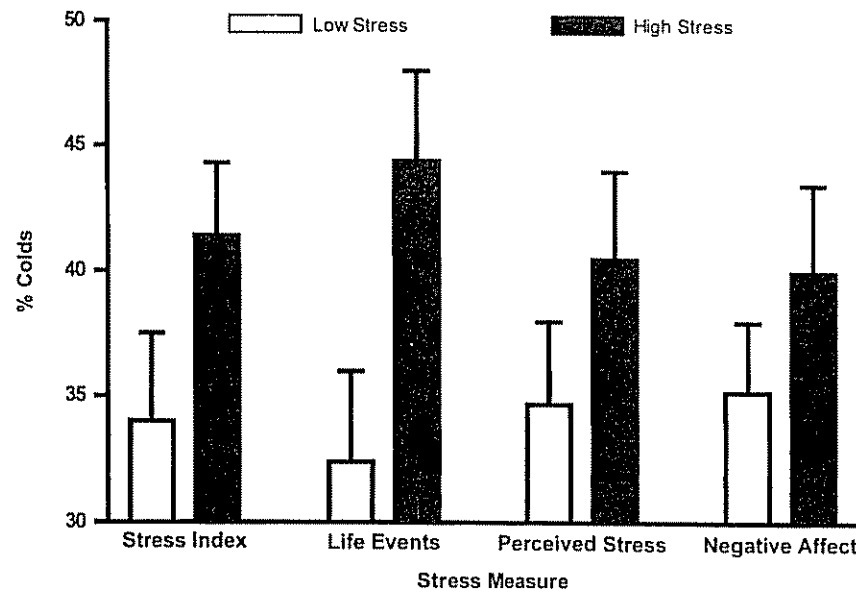
### 5. Standard Control Variables

The analyses presented below include statistical controls for a set of variables that could provide alternative explanations for any relationship between stress and illness. These standard control variables include age, gender, education, weight, allergic status, season of the year during which the trial was conducted, the number of others the subject was housed with during the trial, whether housemates were infected or not, type of experimental virus the subject was infected with, and prechallenge serostatus for the experimental virus.

## B. Results

### 1. Stress and Susceptibility to Clinical Illness

As Figure 1 illustrates, subjects with more stress had higher rates of colds, irrespective of whether stress was measured as life events, perceived stress, or negative affect or by using the stress index. 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 and the stress index. This procedure tests whether stress is associated with greater susceptibility after the possible effects of these variables are subtracted. The addition of health practices did not significantly alter the results. To determine whether these relations might be attributable



**FIGURE 1** Observed association between each of the stress measures and rates of clinical colds. Standard errors are indicated [Figure from Cohen, S., Tyrrell, D. A. J., & Smith, A. P. (1993). Negative life events, perceived stress, negative affect, and susceptibility to the common cold *Journal of Personality and Social Psychology*, 64, 135. Reprinted with permission from the American Psychological Association]

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.

### 2. Are Stress Effects Consistent across the Five Viruses?

The analyses described thus far have collapsed across viruses. However, a test of whether the effects of stress were consistent across the viruses (stress by virus type interaction term) 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 nonspecific, i.e., not dependent on the pathogenesis of the specific virus. Figure 2 also suggests the dose-response type relation that 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 et al. (1991).)

## C. Discussion

We found that higher levels of stress—whether measured as life events, perceived stress, or negative affect—were 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, the virus that 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 across 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. It is also possible that stress is associated with some general change in the host, such as the ability to produce mucus or the quality of mucus production.

## III. THE PITTSBURGH COMMON COLD STUDY: STRESS, SOCIAL NETWORKS, AND COLDS

Although the study described above yielded compelling evidence for a relationship between stress and

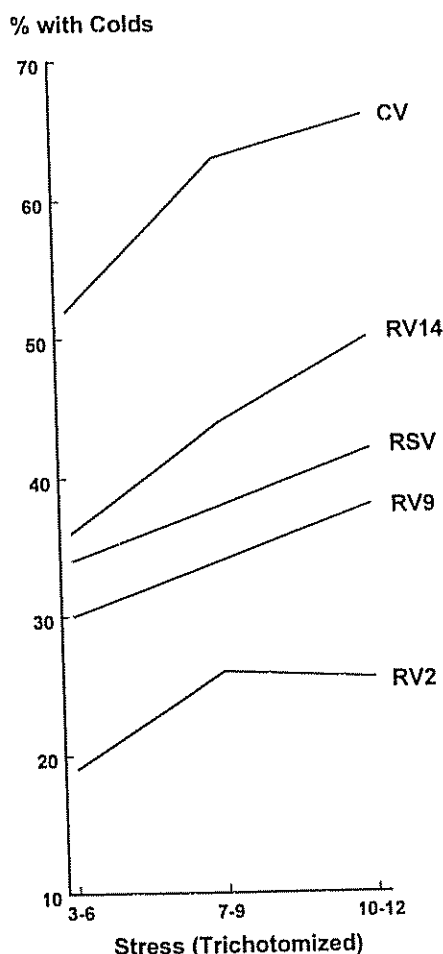


FIGURE 2 Association between the psychological stress index and the rate of clinical colds for each of the five viruses. CV, coronavirus; RSV, respiratory syncytial virus; RV, rhinovirus

susceptibility to upper respiratory infection, it provided little information about the characteristics of stressors that place individuals at risk for illness. The objective of our second study was to gather more information about this issue. We were interested in answering questions such as: Do acutely stressful events have the same impact on susceptibility as more chronic, ongoing stressors? Do certain classes of stressors have a more potent impact than others? Does illness risk vary as a function of the duration of a stressor? The Pittsburgh study also provided us with an opportunity to examine the role of social participation in illness susceptibility. We were interested in examining both the direct effects of social participation on risk for colds and the extent to which having social ties could buffer volunteers from the increased susceptibility associated with stressful life events.

This study was carried out in Pittsburgh, Pennsylvania, between 1993 and 1996. Descriptions of the methods used have been published elsewhere

(Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997; Cohen et al., 1998). Briefly, 276 adults (125 men and 151 women) between the ages of 18 and 55 participated in the study. All volunteers initially came to the hospital for medical eligibility screenings and were judged to be in good health. Social networks, select health practices (smoking, alcohol consumption, exercise, sleep quality, diet), demographic factors, body weight, and height were also assessed at the screening and used as baseline data for those who were found to be eligible. Eligible subjects returned to the hospital both 4 and 5 weeks after screening to have blood drawn for assessment of a marker of immune function—natural killer cell activity—that was based on both blood draws, and antibody to the experimental virus based on the second blood draw. A personality questionnaire was administered twice, once at each blood draw. Volunteers returned an additional time during the period after initial screening but before being exposed to the virus to complete an intensive stressful life events interview.

Subjects were quarantined within 1 week following the second blood draw. Baseline assessment of self-reported respiratory symptoms and two objective indicators of illness (nasal mucociliary clearance, and nasal mucus production) were assessed during the first 24 h of quarantine (before viral exposure). Urine samples for the assessment of cortisol, epinephrine, and norepinephrine were also collected at this time. At the end of the first 24 h of quarantine, volunteers were given nasal drops containing a low infectious dose of one of two types of rhinovirus (RV39 [ $n = 147$ ] or Hanks [ $n = 129$ ]). The quarantine continued for 5 days after exposure. During this period volunteers were housed individually, but were allowed to interact with each other at a distance of 3 feet or more. Nasal secretion samples for verifying infection by virus culture were collected on each of the 5 days. On each day, volunteers completed a respiratory symptoms questionnaire and were tested for objective markers of illness. Approximately 28 days after challenge, another blood sample was collected for verifying infection by determination of changes in antibody to the challenge virus. All investigators were blinded to subjects' status on social network, personality, endocrine, health practice, immune, and pre-challenge antibody measures

## A. Measures

### 1. Social Stress

A semistructured interview, the Bedford College Life Events and Difficulties Schedule (LEDS) was

used to assess life events (Brown & Harris, 1989; Harris, 1991). The LEDS uses strict criteria for whether or not an event occurs, classifies each event on the basis of severity of threat and emotional significance, and allows dating of the onset and resolution of each event and hence a determination of event duration. Raters blind to the individual's subjective response to an event are provided with extensive information regarding each event and the context in which it occurred. They rate the threat and emotional significance of events based on the likely response of an average person to an event occurring in the specified context. A person is considered under stress if they have an event that is rated as moderately or severely threatening.

## 2. Social Participation

Social network participation was assessed by questionnaire. The Social Network Index assesses participation in 12 types of social relationships (Cohen et al., 1997). These include relationships with a spouse, parents, parents-in-law, children, other close family members, close neighbors, friends, workmates, schoolmates, fellow volunteers (e.g., charity or community work), members of groups without religious affiliations (e.g., social, recreational, professional), and members of religious groups. One point is assigned for each kind of relationship (possible score of 12) for which respondents indicate that they speak (in person or on the phone) to someone in that relationship at least once every 2 weeks. The total number of persons with whom they speak at least once every 2 weeks (number of network members) was also assessed.

## 3. Clinical Colds

Volunteers were considered to have a cold if they were *both* infected and meeting illness criteria. They were classified as infected if the challenge virus was isolated on any of the five postchallenge study days or there was a substantial rise (fourfold increase in antibody titer) in serum antibody level to the experimental virus. The illness criterion in this trial was based on selected *objective* indicators of illness—the amount of mucus produced during quarantine and mucociliary clearance function. By basing the definition of illness entirely on objective indicators, we were able to exclude interpretations of our data based on psychological influences on symptom presentation. Mucus weights were determined by collecting used tissues in sealed plastic bags. After correcting for the weight of the bag and tissue, and the mucus weight at baseline, the postchallenge weights were summed across the 5 days to create an adjusted total mucus

weight score. Nasal mucociliary clearance function refers to the effectiveness of nasal cilia in clearing mucus from the nasal passage toward the throat. Clearance function was assessed as the time required for a dye administered into the nose to reach the throat. Each daily time was adjusted for baseline and the adjusted average time in minutes was calculated across the postchallenge days of the trial. To meet clinical illness criteria, subjects had to have a total adjusted mucus weight of at least 10 g or an adjusted average mucociliary nasal clearance time of at least 7 min.

## 4. Standard Control Variables

Standard control variables were again used to examine alternative explanations for any relationship between psychosocial factors and illness. These included age, gender, ethnicity, education, body mass index (weight in kilograms divided by the square of height in meters), season during which the trial was conducted, type of experimental virus, and prechallenge antibody titers to the experimental virus.

## 5. Personality

Because either stress or social participation might merely be markers of stable personality styles, we assessed the "Big Five" personality factors (Goldberg, 1992). These factors are thought to represent the basic structure of personality (e.g., Goldberg, 1992). The factors are commonly described as: introversion-extraversion, agreeableness, conscientiousness, emotional stability, and openness.

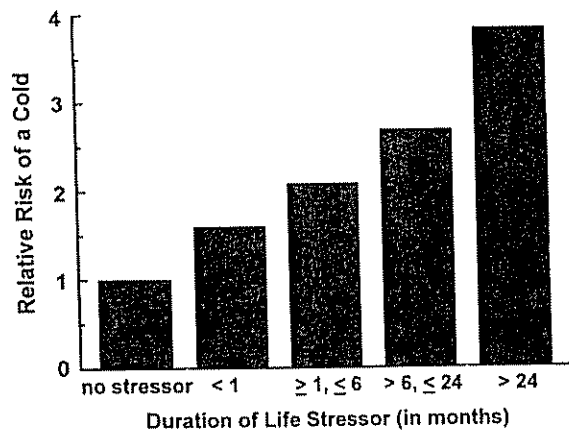
## B. Results

### 1. Acute Stressful Life Events, Chronic Difficulties, and Susceptibility

The longer the stressful life event, the greater the risk for developing a clinical illness (Figure 3). Moreover, this association could be accounted for primarily by two types of events: enduring (1 month or longer) interpersonal problems with family and friends and enduring work (under- or unemployment; Figure 4). These effects held across two rhinoviruses and were equal for persons with and without neutralizing antibody to the virus prior to inoculation.

### 2. Social Networks and Susceptibility

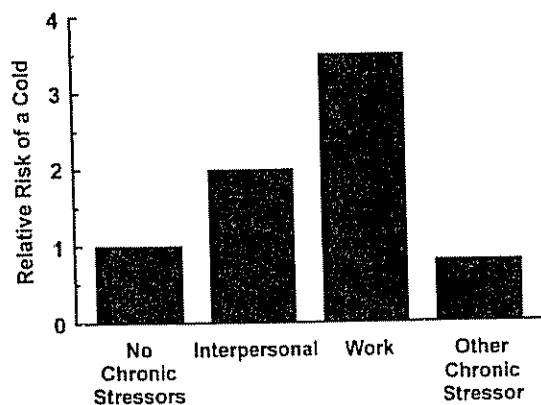
As apparent from Figure 5, the rate of colds decreased as social network diversity increased. The adjusted relative risks of developing a cold were 4.2,



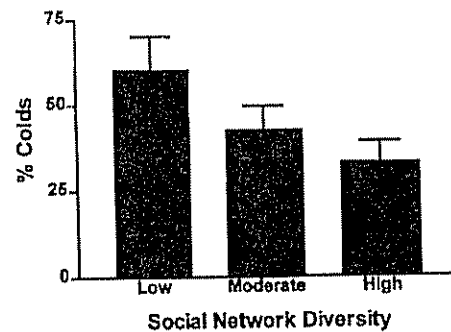
**FIGURE 3** Relative risk (odds ratio adjusted for standard controls) of developing a cold contrasting persons with stressors of varying duration with those without any stressor. Participants are grouped by their longest stressor [Figure from Cohen, S., Frank, E., Doyle, W. J., Skoner, D. P., Rabin, B. S., & Gwaltney, J. M., Jr (1998) Types of stressors that increase susceptibility to the common cold in healthy adults *Health Psychology, 17*, 219. Reprinted with permission from the American Psychological Association]

1.9, and 1 respectively. There were no interactions between the standard control variables and social network diversity in predicting colds. Hence, the relations were similar for the two virus types, for different preexposure antibody levels, age, gender, race, education, and body mass, and across the two seasons.

Total number of network members was not associated with colds. Moreover, entering number of network members into the first step of the regression



**FIGURE 4** Relative risk (odds ratio adjusted for standard controls) of developing a cold contrasting persons with interpersonal, work, and other chronic stressors with those having no chronic stressors. [Figure adapted from Cohen, S., Frank, E., Doyle, W. J., Skoner, D. P., Rabin, B. S., & Gwaltney, J. M., Jr (1998) Types of stressors that increase susceptibility to the common cold in healthy adults *Health Psychology, 17*, 219. Reprinted with permission from the American Psychological Association]



**FIGURE 5** Observed incidence of colds by social network diversity. Low diversity is described as one to three types of social relationships, moderate four to five; and high six or more. Standard errors are indicated. [Figure adapted from Cohen, S., Doyle, W. J., Skoner, D. P., Rabin, B. S., & Gwaltney, J. M., Jr (1997) Social ties and susceptibility to the common cold *Journal of the American Medical Association, 277*, 1943]

equation along with standard controls did not reduce the association between diversity and colds. Hence the diversity of the network is more important than the number of network members and its association with colds is independent of the number of members.

The association of social participation and susceptibility was independent of the association between chronic stressors and susceptibility. Moreover, the interaction between chronic stress and network diversity did not achieve statistical significance, indicating that network diversity did not function as a stress buffer, but rather had a direct (irrespective of stress level) association with cold susceptibility.

### 3. Pathways Linking Social Networks and Stressful Life Events to Susceptibility

Preliminary analyses indicated that those with low levels of social participation were more likely to be smokers and less likely to exercise. Similarly, those with enduring chronic stressors were more likely to be smokers. There were also marginal associations between having a chronic stressor and less exercise and poorer sleep efficiency. All of these health practices were also associated with susceptibility to colds, with smokers, those getting less exercise, and those with poor sleep quality all at greater risk. However, these health practices could explain only a small fraction of the relation between these psychosocial characteristics and susceptibility to infectious illness. Although higher levels of epinephrine and norepinephrine were associated with greater risk for developing a cold, neither of these hormones (nor cortisol) was associated with social network or

chronic stress indices. Hence, neither could operate as pathways linking these variables to illness susceptibility. Our measure of immune function, natural killer cell cytotoxicity, was not associated with either psychosocial characteristics or cold risk.

#### 4. Personality as an Alternative Explanation

Of the Big five factors, we found that only introversion-extraversion was associated with susceptibility to colds. Those with scores below the median ("introverts") were at 2.7 times greater risk. Although none of the personality factors were associated with chronic stress, introversion was associated with lower levels of social network diversity. However, the relation between network diversity and colds occurred above and beyond (independent of) the association of introversion and colds.

### C. Discussion

This study provided additional evidence that psychological stress contributes to susceptibility to upper respiratory infection (see Cohen et al., 1991, 1993; Graham et al., 1986; Meyer & Haggerty, 1962; Stone et al., 1993). It also provided information about the characteristics of stressors that are likely to heighten risk for illness. Although acutely stressful life events did not confer increased susceptibility, enduring stressors lasting 1 month or longer were associated with a higher incidence of clinical colds. The relationship between chronic stress and illness was independent of volunteers' age, gender, ethnicity, education, body mass, and prechallenge virus-specific antibody levels. It also was independent of the season during which the challenge was conducted and the type of experimental virus administered.

The link between chronic stress and illness risk was primarily attributable to chronic problems in the interpersonal or work domains. Volunteers experiencing chronic interpersonal stressors such as conflicts with friends, family, or spouses were at nearly three times the risk of developing a cold as those without enduring stressors. Volunteers who were chronically underemployed or unemployed were almost five times as likely to become ill in comparison with volunteers without a chronic stressor. Because many types of chronic stressors had a low base rate in our sample, these findings should not be taken to mean that interpersonal or work stressors are the only types of enduring difficulties that heighten illness risk. Instead, our findings suggest that when these stressors occur, they can have potent influences on

susceptibility. The magnitude of this influence seems to depend in part on the duration of the stressor itself. The longer the duration of the stressor, the greater the risk for illness.

This study also demonstrated that social isolation constitutes a major risk factor for the development of illness. Volunteers who were relatively socially isolated (one to three relationships) were 4.2 times more likely to develop illness than those with very diverse networks (six or more relationships). Interestingly, it was the diversity of participants' social networks, rather than the total number of relationships that they had, that predicted susceptibility. This suggests that it is something about occupying a variety of social roles (e.g., spouse, parent, co-worker, friend) that promotes resistance to infection. How this occurs is not clear, although the present study suggests that it is *not* likely to be through a stress-buffering mechanism.

What can account for the relations between chronic stress, social participation, and susceptibility to infectious illness? Our results left us with few ideas. Neither health practices nor endocrine or immune assessments provided an explanation. Because the health practice measures were all related to susceptibility in the expected manner, we are confident that we did a good job of assessing this pathway. As a consequence, it seems unlikely that these health practices play a major role in linking social environments to resistance to infectious illness. Although we assessed the health practices that we thought would be most likely to provide a pathway, it is possible that other practices such as caffeine intake, use of mouthwash, or regular hand washing, might link stress or social participation to illness susceptibility.

Elevated epinephrine and norepinephrine were also associated with increased risk for illness. Because epinephrine and norepinephrine were assessed during the 24 h before viral exposure, it is possible they were indicating a stress type reaction to the beginning of quarantine rather than a basal level of response to volunteers' background environments.

Natural killer cell activity was not associated with either the psychosocial variables or risk for illness. We chose natural killer cell activity as our primary marker of immune function for two reasons. First, natural killer cells are surveillance cells that identify infected (and otherwise altered cells) and kill them. In theory, higher levels of natural killer cell activity should help limit infection and hence prevent illness. Second, there is evidence that chronic psychological stress is associated with suppression of NK activity (reviewed in Herbert & Cohen, 1993). However, NK activity did not operate as a pathway linking stress or social



participation to illness susceptibility in our study. Measuring immunity in peripheral blood is not always the most appropriate procedure and may be the problem here (Cohen & Herbert, 1996). In theory, NK activity in the lung might be the essential issue in the case of respiratory infections. It is also possible the NK activity in the blood might make a difference, but that the ability of the immune system to compensate for deficits in single subsystems obscures any relation. At any rate, we found no evidence for immune mediation of the relations between stress and infectious illness or social participation and infectious disease. Again, we think that this may be attributable to problems in measurement.

#### IV. PITTSBURGH INFLUENZA STUDY: CYTOKINES AS MEDIATORS

Up until now, the major outcome in our studies has been whether persons exposed to a virus develop a clinical illness. Clinical illness has been defined as a combination of infection by the virus (assessed by viral shedding or increased viral-specific antibody) and symptom expression (doctor diagnosed or verified by objective markers such as mucus weights). Our recent work has moved toward providing a more refined understanding of how psychosocial factors influence disease susceptibility. To do this, one needs to distinguish between the role that psychosocial factors play in susceptibility to infection and the role that they play in expression of illness among infected persons. (In our earlier trials, approximately 80% of exposed subjects develop infection, but only 40% are diagnosed as clinically ill.) We have started to address this issue by developing a challenge model that allows examination of illness expression among infected persons. To accomplish this, we used an influenza A virus that results in infection in 95% or more of subjects without previous exposure (i.e., without neutralizing antibody) to the virus. We then examine the extent to which psychosocial factors predict illness expression among infected subjects.

A major focus of this trial was to test the possibility that proinflammatory cytokines might play a role in illness expression. Recent advances in the understanding of how cytokines function in upper respiratory infection offers a promising new direction for this research. Psychological stressors have been shown to activate the production of proinflammatory cytokines such as IL-1, IL-6, IFN- $\gamma$ , and TNF- $\alpha$  (Ackerman, Martino, Heyman, Moyna, & Rabin, 1998). Local increases in the concentrations of one of these cytokines, IL-6, have been linked to greater cold symptomatology

among persons with verified upper respiratory infection (Gentile, Doyle, Whiteside, Hayden, & Skoner, in press; Hayden et al., 1998). Since the secretion of cytokines in response to infection is thought to be mediated by glucocorticoids (Dobbs, Feg, Beck, & Sheridan, 1996), it is conceivable that stress could exacerbate cold symptomatology through a cortisol-triggered upregulation of proinflammatory cytokine production.

We recently conducted a relatively small trial to test the viability of studying illness expression per se and examining the role of cytokines in the link between stress and expression. This trial was designed to determine whether psychological stress was associated with the expression of symptoms and production of mucus in infected subjects (Cohen et al., 1999) and whether stress-associated elevations in cytokine production in response to a virus might explain an association between stress and illness expression. After completing a measure of psychological stress (the Perceived Stress Scale (PSS)), 55 subjects were experimentally infected with the A Kawasaki Influenza virus. Subjects were monitored in quarantine for 8 days (baseline and 7 days after inoculation) for upper respiratory symptoms, mucus production, and nasal lavage levels of interleukin (IL)-6.

As in previous trials we included standard controls for age, season of the year, gender, race, and body mass. The association between perceived stress and symptoms, mucus weights, and IL-6 are presented in Figures 6, 7, and 8. Higher psychological stress

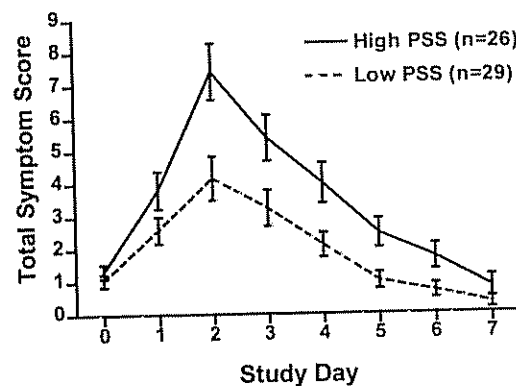
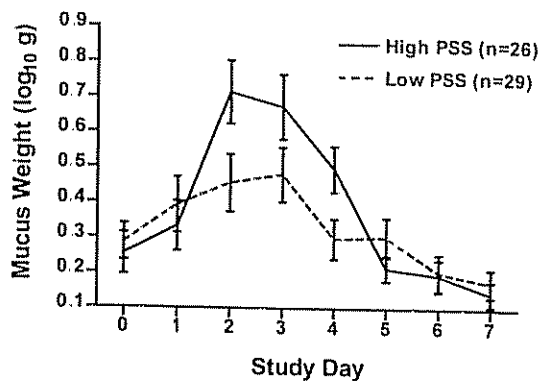
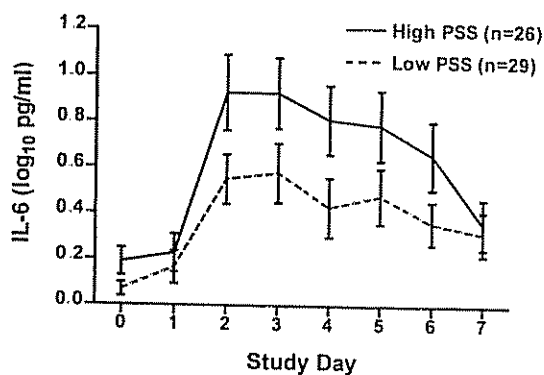


FIGURE 6 The association between psychological stress (low, below median, high, above median) and symptoms of upper respiratory illness among subjects infected with an influenza A virus. Viral inoculation occurred at the end of day 0. Standard errors are indicated [Figure from Cohen, S., Doyle, W. J., & Skoner, D. P. (1999). Psychological stress, cytokine production, and severity of upper respiratory illness. *Psychosomatic Medicine*, 61, 177. Reprinted with permission from the American Psychosomatic Society.]



**FIGURE 7** The association between psychological stress (low, below median, high, above median) and mucus weights among subjects infected with an influenza A virus. Viral inoculation occurred at the end of day 0. Standard errors are indicated. [Figure from Cohen, S., Doyle, W. J., & Skoner, D. P. (1999). Psychological stress, cytokine production, and severity of upper respiratory illness. *Psychosomatic Medicine*, 61, 177. Reprinted with permission from the American Psychosomatic Society.]

assessed prior to the viral challenge was associated with greater symptom scores, greater mucus weights, and higher IL-6 lavage concentrations in response to infection. The IL-6 response was temporally related to both markers of illness expression, and mediation analyses indicated that these data were consistent with IL-6 acting as a major pathway through which stress was associated with increased symptoms of illness. However, this is correlational data and must be interpreted with care. This pattern of data is also consistent with rises in IL-6 occurring in response to tissue damage associated with illness symptoms or IL-6 responding in concert with other unassayed pro-



**FIGURE 8** The association between psychological stress (low, below median, high, above median) and IL-6 in nasal secretions among subjects infected with an influenza A virus. Viral inoculation occurred at the end of day 0. Standard errors are indicated. [Figure from Cohen, S., Doyle, W. J., & Skoner, D. P. (1999). Psychological stress, cytokine production, and severity of upper respiratory illness. *Psychosomatic Medicine*, 61, 178. Reprinted with permission from the American Psychosomatic Society.]

inflammatory chemicals that might play the causal role here.

## V. CONCLUSIONS

These studies that we have presented convincingly demonstrate that psychological stress is associated with increased vulnerability to the common cold. This relationship emerges whether stress is measured as life events, perceived stress, or negative emotional states. It also emerges across seven different experimental viruses, suggesting that stress dampens resistance in a way that renders the host vulnerable to a variety of infectious agents that invade the respiratory tract. The characteristics of stressors that influence illness risk also have been clarified to some extent. More enduring stressors such as underemployment and conflicts with family or friends confer increased susceptibility, while acutely stressful life events do not. The mechanisms by which this occurs are not yet clear. Our work suggests that stress-elicited changes in health behaviors such as smoking or exercise are not responsible. Moreover, thus far we have been unable to identify endocrine mediators of the relationship between stress and illness. As we noted above, this may be attributable to measurement problems. We have, however, had some initial success in our attempt to identify immune pathways with our evidence that IL-6 response to infection overlaps with stress and illness expression. We are continuing to examine the potential role of proinflammatory cytokines and hope that this work will provide a more complete understanding of the pathways which link psychological stress with vulnerability to upper respiratory infection.

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