Journal of Personality and Social Psychology
1993, Vol. 64, No. 1, 131-140

0022-3514/93/$3.00

Negative Life Events, Perceived Stress, Negative Affect, and Susceptibility to the Common Cold

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After completing questionnaires assessing stressful life events, perceived stress, and negative affect, 394 healthy Ss were intentionally exposed to a common cold virus, quarantined, and monitored for the development of biologically verified clinical illness. Consistent with the hypothesis that psychological stress increases susceptibility to infectious agents, higher scores on each of the 3 stress scales were associated with greater risk of developing a cold. However, the relation between stressful life events and illness was mediated by a different biologic process than were relations between perceived stress and illness and negative affect and illness. 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.

It is commonly believed that life stressors increase susceptibility to infectious disease. When demands imposed by events exceed ability to cope, a psychological stress response is elicited (Lazarus & Folkman, 1984). This response is composed of negative cognitive and emotional states. In turn, these states are thought to alter immune function through autonomic nerves that connect the central nervous system to immune tissue (D. L. Felten, Felten, Carlson, Olschowka, & Livnat, 1985; S. Y. Felten & Olschowka, 1987), through the action of hormones whose release is associated with negative affectivity (Shavit, Lewis, Terman, Gale, & Liebeskind, 1984), or through stress-elicited changes in health practices such as smoking and alcohol consumption (Cohen & Williamson, 1991; Kiecolt-Glaser & Glaser, 1988).

Direct connections between stress and various functions of the immune system have been found in both field (e.g., Kiecolt-Glaser & Glaser, 1991) and laboratory settings (e.g., Manuck, Cohen, Rabin, Muldoon, & Bachen, 1991; Naliboff et al., 1991). However, it is unclear whether the immune changes related to stress in these studies are of the type or magnitude that would influence susceptibility to infection (Jemmott & Locke, 1984; Laudenslager, 1987). There is also research directly assessing the relation between stress and upper respiratory infections in community samples (see review in Cohen & Williamson, 1991). Several of these studies provide evidence that social stressors increase risk for verified upper respiratory disease (Graham, Douglas, & Ryan, 1986; Meyer & Haggerty, 1962). This work, however, did not control for the possible effects of stressful events on exposure to infectious agents (as opposed to their effects on host resistance) or provide evidence about other behavioral and biologic mechanisms through which stress might influence susceptibility to infection. Moreover, the literature on this topic is not entirely consistent with several studies failing to find a relation between stress and respiratory disease (Alexander & Summerskill, 1956; Cluff, Cantor, & Imboden, 1966).

Viral-challenge studies, in which volunteers who complete stress scales are intentionally exposed to a cold or influenza virus, have provided only weak support for a relation between stress and susceptibility to upper respiratory infections (Broadbent, Broadbent, Phillpotts, & Wallace, 1984; Totman, Kiff, Reed, & Craig, 1980; Greene, Betts, Ochitill, Iker, & Douglas, 1978; Locke & Heisel, 1977). This work, however, suffers from a wide range of methodological flaws (Cohen & Williamson, 1991). Individual studies suffer from insufficient sample sizes, concurrent administration of drugs, lack of information on overall rates of infection in response to the dose of virus administered, and lack of controls for important predictors of susceptibility such as preexisting antibodies to the infectious agent, gender, and age (see Jackson et al., 1960). They also fail to control for the possible role of stress-elicited changes in health practices such as smoking and alcohol consumption.

Part of the problem in establishing a relation between stress and new cases of disease is that there is little agreement within or across disciplines on how stress should be defined or measured. As addressed earlier, this article is concerned with *psychological stress,* that is, negative cognitive and emotional states elicited when persons perceive that their demands exceed their

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This research was supported by grants from the National Institute of Allergies and Infectious Disease (A123072) and the Office of Naval Research (N00014-88-K-0063), by a Research Scientist Development Award to Sheldon Cohen from the National Institute of Mental Health (MH00721), and by the Medical Research Council's Common Cold Unit.

We are indebted to S. Bull, R. Dawes, J. Greenhouse, J. Middleton, H. Parry, M. Sargent, J. Schlarb, S. Trickett; the medical, nursing, and technical staff of the Common Cold Unit; and the volunteers for their contribution to the research.

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ability to cope (Lazarus & Folkman, 1984). However, even within this constrained area, there is considerable controversy as to how such a state should be assessed (e.g., Cohen, 1986; Dohrenwend & Shrout, 1985; Lazarus, DeLongis, Folkman, & Gruen, 1985). In an article published in a medical journal (Cohen, Tyrrell, & Smith, 1991), we reported that psychological stress, operationally defined as an index including negative life events, perceived stress, and negative affect, predicted susceptibility to colds among 394 initially healthy persons we intentionally exposed to upper respiratory viruses. We justified the use of the stress index on the basis of a factor analysis indicating that the three measures formed a single principal component, providing evidence that the scales measure a common underlying concept. By using a single index, we were able to substantially reduce the number of analyses and hence Type I error. The psychological stress index provided a robust and valid measure in that it showed a linear relation with risk for developing colds, and in that the relation between the stress index and susceptibility was unaffected by controls for a series of environmental, psychological, behavioral, and immunological factors. However, combining the three scales masked information that examination of the individual scales might tell us about the stress process. Although the scales are correlated with one another, each taps a somewhat different component of the psychological stress experience.

In this article, we present further data from our prospective study of persons intentionally exposed to upper respiratory viruses. Healthy persons were administered the three stress scales, three personality scales, and measures of health practices, and then they were experimentally exposed to one of five cold viruses or placebo. The association between stress and the development of biologically verified clinical disease was examined with use of a control for baseline (prechallenge) antibodies to the challenge virus, the identity of the challenge virus, allergic status, weight, the season, the number of subjects housed together, the infectious status of any subjects sharing housing, and various demographic factors. We examine the relation between each of the three separate stress scales and risk for clinical colds, evaluate potential pathways through which each might influence susceptibility, and discuss the differences in terms of the components of psychological stress that each of the scales assess.

Method

The subjects were 154 men and 266 women who volunteered to participate in trials at the Medical Research Council's Common Cold Unit (CCU) in Salisbury, England. All reported no chronic or acute illness or regular medication regimen on their applications and were judged in good health following clinical and laboratory examination on arrival at the unit. Pregnant women were excluded. Volunteers' ages ranged from 18 to 54 years, with a mean of 33.6 and standard deviation of 10.6. Twenty-two percent did not complete their secondary education, 51% completed secondary education but did not attend a university, and 27% attended a university for at least 1 year. Volunteers were reimbursed for their traveling expenses and received free meals and accommodations. The trial was approved by the Harrow District Ethical Committee and informed consent was obtained from each volunteer after the nature and possible consequences of the study were fully explained.

Procedure

During their first 2 days at the CCU, volunteers were given a thorough medical examination, completed a series of self-reported behavioral protocols including psychological stress, personality, and health practice questionnaires, and had blood drawn for immune and cotinine assessments. Subsequently, volunteers were exposed using nasal drops, to a low infectious dose of one of five respiratory viruses: rhinovirus types 2 (RV2; $n = 86$), 9 (RV9; $n = 122$), and 14 (RV14; $n = 92$), respiratory syncytial virus (RSV; $n = 40$), and coronavirus type 229E (CV; $n = 54$). An additional 26 volunteers received saline. One or two viruses were used in each individual trial, and volunteers were randomly assigned to virus and saline conditions. Viral doses were intended to simulate those that occur in person-to-person transmission, and they resulted in illness rates of between 20% and 60%. For 2 days before and 7 days after viral challenge, volunteers were quarantined in large apartments (alone or with 1 or 2 others). Starting 2 days before viral challenge and continuing through 6 days after the challenge, each volunteer was examined daily by a clinician using a standard respiratory sign–symptom protocol (Beare & Reed, 1977). Examples of items on the protocol include sneezing, watering of eyes, nasal stuffiness, nasal obstruction, postnasal discharge, sinus pain, sore throat, hoarseness, cough, and sputum. 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. Approximately 28 days after the viral challenge a second serum sample was collected by volunteers' own physicians and shipped back to the CCU. All investigators were blind to volunteers' psychological status and to whether they received virus or saline.

Psychological Stress

Three kinds of measures of psychological stress were used: (a) number of major stressful life events judged by the respondent as having a negative impact, (b) perception that current demands exceed capabilities to cope, and (c) 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 events were a subset of those appearing in the List of Recent Experiences (Henderson, Byrne, & Duncan-Jones, 1981) and were chosen because of their potential for negative impact and the relatively high frequency of occurrence in population studies. Respondents were asked which of the items had occurred during the last 12 months. They were asked to rate each event they reported as having either a positive or negative impact on their lives. A few items such as death of a spouse or child were assumed to be consensually negative, and the respondent was not asked for an impact rating. The scale score was the number of negative events (either consensual or respondent rated) reported by the subject. Because the scores were highly skewed (57% reported two or fewer events, range was 0–14), with some irregularities in the smoothness of the distribution, we used two different approaches to life-event analyses. In the first, we retained the continuous scaling by using a $\log_{10}$ transformation of the raw data. In the second, we transformed life events into a dichotomized variable: two or fewer events versus more than two events. The 10-item Perceived Stress Scale (PSS-10; Cohen & Williamson, 1988) was used to assess the degree to which situations in life are perceived as stressful (reliability in this sample, $\alpha = .85$). Items in the PSS-10 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 (1982) list of negative emotions. The items included distressed, nervous, sad, angry, dissatisfied with self, calm (reverse scored), guilty, scared, angry at yourself, upset, irritated, depressed, hostile, shaky, and content (reverse scored). A 5-point (0–4) Likert-type response format was used to report affect intensity during the last week ($\alpha = .84$). Both the PSS-10

and negative affect scores were approximately normally distributed, and their raw (continuous) scores were used as predictors in the regression analyses. Stressful life events were correlated .35, $p < .001$, and .35, $p < .001$, with PSS-10 and negative affect, respectively. Negative affect was correlated .65, $p < .001$, with the PSS-10. Point biserial correlations between dichotomized stressful life events and PSS-10 and life events and negative affect were .32, $p < .001$, and .32, $p < .001$, respectively.

For comparison, we also present data based on analyses using the psychological stress index used in our earlier article (Cohen, Tyrrell, & Smith, 1991). All three stress scales formed a single principal component, with loadings of .66, .86, and .86, respectively, providing evidence that the scales measure a common underlying concept. Hence we formed an index combining the three measures as an indicator of psychological stress. Because life events were not normally distributed, an index based on normalized scores was not appropriate. Instead, the index was created by quartiling each scale and summing quartile ranks for each subject (1 for lowest quartile and 4 for highest), resulting in a stress index ranging from 3 to 12. The quartiles were 0, 1–2, 3–4, and 5–14 for the life-events scale; 0–10, 11–14, 15–18, and 19–33 for the PSS-10; and 0–7, 8–13, 14–20, and 21–49 for the negative affect scale. Index scores were approximately normally distributed.

Infections and Clinical Colds

Infectious diseases result from the growth and action of microorganisms or parasites in the body (see Cohen & Williamson, 1991). Infection is the multiplication of an invading microorganism. It is possible for a person to be infected (for the microorganism to replicate) without developing clinical symptoms. Clinical disease occurs when infection is followed by the development of symptomatology characteristic of the disease.

Biological verification of infection can be accomplished by establishing that an infectious agent is present or replicating in tissue, fluid, or both. We use two common procedures for detecting a replication of a specific virus. In the viral isolation procedure, nasal secretions are cultured (put in a medium that stimulates virus replication). If the virus is present in nasal secretions, it will grow in the medium and can be detected. Alternatively, we can indirectly assess the presence of a replicating virus by looking at changes in serum antibody levels to that virus. Antibodies are protein molecules that attach themselves to invading microorganisms and mark them for destruction or prevent them from infecting cells. An invading microorganism (i.e., infection) triggers the immune system to produce antibody. (*Antibody* is also called *immunoglobulin* [Ig]). Because each antibody recognizes only a single type of microorganism, the production of antibody to a specific infectious agent is evidence for the presence and activity of that agent.

Assays for viral isolation and viral-specific antibody levels. Nasal wash samples for viral isolation were collected before inoculation and on Days 2–6 after viral inoculation. They were mixed with broth and stored in aliquots at −70°C. Rhinoviruses were detected in O-Hela cells, respiratory syncytial virus in Hep2 cells, and coronavirus in the C-16 strain of continuous human fibroblast cells. When a characteristic cytopathic effect was observed, the tissue culture fluids were passaged into further cultures and identity tests on the virus were performed. Rhinoviruses and coronaviruses were confirmed by neutralization tests with specific rabbit immune serum, and respiratory syncytial virus by immunofluorescent staining of culture cells.

Levels of neutralizing antibodies and of specific antiviral immunoglobulin A (IgA) and immunoglobulin G (IgG) were determined before and 28 days after the viral challenge. Neutralizing antibodies (for rhinoviruses only) were determined by neutralization tests with homologous virus (Al Nakib & Tyrrell, 1988). Results were recorded as the highest dilution showing neutralization, and a fourfold rise was regarded as significant. Suitable neutralizing tests were not available for RSV and CV.

Viral specific IgA and IgG levels for rhinoviruses (Barclay & Al Nakib, 1987), CV (Callow, 1985), and RSV (Callow, 1985) were determined by enzyme-linked immunosorbent assays. This test detects antibody which correlates with neutralization titers, is associated with resistance to infection, and increases in response to infection (Al Nakib & Tyrrell, 1988).

Operational definitions of infection and clinical colds. A volunteer was deemed infected if a virus was isolated after the challenge or if there was a significant rise in viral-specific serum antibody after the challenge, that is, a fourfold increase in neutralizing antibody (rhinoviruses only) or an IgG or IgA increase of two standard deviations greater than the mean of nonchallenged volunteers (all viruses). Eighty-two percent (325) of the volunteers receiving virus were infected. Nineteen percent (5) of the volunteers receiving saline were infected. We attributed infections among the saline group to volunteer transmission of virus to others housed in the same apartment. A control for person-to-person transmission is included in the data analysis.

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. Volunteers also judged the severity of their colds on the same scale. Clinician diagnosis was in agreement with self-diagnosis for 94% of the volunteers. Volunteers were defined as having developed *clinical colds* if they were both infected and diagnosed by the clinician as having a clinical cold. Of the 394 volunteers participating in the trials, 38% (148) developed clinical colds. None of the 26 saline controls developed colds.

Seven persons with positive clinical diagnoses but no indication of infection were excluded from the sample because we assumed the illness was caused by pretrial exposure to another virus. Analyses including them (by definition no clinical cold and no infection) resulted in identical conclusions.

Body Temperature and Mucus Weights

Because clinical diagnoses can be influenced by how subjects present their symptoms, we independently evaluated the associations between each stress measure and two clinical signs not subject to self-presentation bias: body temperature and mucus weights. Body temperature (degrees centigrade) was taken each morning and afternoon with an oral thermometer. An average daily temperature ([morning + afternoon]/2) was calculated for the day before and each day following the viral challenge. Mucus weights were determined by collecting tissues used by subjects in sealed plastic bags. The bags were weighed, and the weight of the tissues and the bags was subtracted. Daily mucus weights (in grams) were calculated for both before and after the viral challenge. The prechallenge measure was based on the mucus weight on the day before challenge. The postchallenge measures were based on the weights from Days 1 to 5 after the challenge. To obtain an approximately normally distributed variable, we used the $\log_{10}$ of both pre- and postchallenge mucus weights in the analyses.

Standard Control Variables

We used a series of control 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.

Prechallenge serostatus refers to whether a subject had antibody to the virus before experimental exposure, that is, was previously exposed

to the virus. Serostatus was defined as positive when a volunteer had a neutralizing prechallenge antibody titer greater than 2 for rhinoviruses and a prechallenge antibody level greater than the sample median for CV and RSV. Forty-three percent of volunteers were seropositive before the challenge, including 55% for RV2, 48% for RV9, 20% for RV14, 50% for RSV, and 50% for CV.

Age and gender were based on self-report. Because age was not normally distributed it was scored categorically on the basis of a median split: 18–33 or 34–54. Scores on education were based on a 9-point self-report scale ranging from *no schooling* (0) to *doctoral degree* (8). Allergic status was based on physician interview questions regarding allergies to food, drugs, or other allergens. Persons reporting any allergy were defined as *allergic*. A ponderal index (weight/height^3) was used to control for volunteers' weight. We used the number of hours of daylight on the first day of the trial as a continuous measure of the season. Number of daylight hours was correlated .80 ($p < .001$) with the average temperature on the same day. A control for the possibility that person-to-person transmission rather than the virus inoculation might be responsible for infection or clinical colds was also included. Because person-to-person transmission would only be possible if an apartment mate was infected by the viral challenge, the control variable indicated whether any housing mate was infected. Finally, *challenge virus* is a categorical variable representing the experimental virus to which a volunteer was exposed.

Health Practice Measures

Health practices including smoking, drinking alcohol, exercise, quality of sleep, and dietary practices were assessed as possible pathways linking stress and susceptibility. Cotinine as assessed in serum by gas chromatography was used as a biochemical indicator of smoking rate because it provides an objective measure of nicotine intake that is not subject to self-report bias (Feyerabend & Russell, 1990; Jarvis, Tunstall-Pedoe, Feyerabend, Vesey, & Saloojee, 1987). We used the $\log_{10}$ of the average of the two (before and 28 days after challenge) cotinine measures as an indicator of smoking rate. (The correlation between the two measures was .95, $p < .001$, $N = 348$). The correlation between the $\log_{10}$ average cotinine and the $\log_{10}$ self-reported number of cigarettes smoked per day was .96 ($p < .001$, $N = 372$).

The remaining health practices were assessed by questionnaire before the viral challenge (see Cohen et al., 1991). Average number of alcoholic drinks per day was calculated using separate estimates of weekday and weekend drinking. A half pint, bottle, or can of beer, glass of wine, and shot of whisky contain approximately equal amounts of alcohol and were each treated as a single drink. We use the $\log_{10}$ of average number of drinks per day as an indicator of drinking. The exercise index included items on the frequency of walking, running, jogging, swimming, aerobics, and work around the house. The quality of sleep index included items on feeling rested, difficulty falling asleep, and awakening early; and the dietary habit index was made up of items designed to assess concern with a healthy diet and included frequencies of eating breakfast, fruits, and vegetables.

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 before the viral challenge. Self-esteem was measured by the self-regard and social confidence subscales of the Feelings of Inadequacy Scale (Fleming & Watts, 1980; $\alpha = .89$), and personal control by the personal efficacy and interpersonal control subscales of the Spheres of Control Scale (Paulhus, 1983; $\alpha = .76$). A third personality characteristic, introversion–extraversion was also assessed because of an existing literature suggesting that introverts were at higher risk for infection (Broadbent et al., 1984; Totman et al., 1980). It was assessed by the Eysenck Personality Inventory (Eysenck & Eysenck, 1964; $\alpha = .80$).

Statistical Analysis

As expected, none of the saline control subjects developed colds and hence the analyses include only persons receiving a virus. The primary analysis tests whether each of the psychological stress measures is associated with greater rates of clinical colds. Secondary analyses assess the importance of the two components of the definition of a clinical cold, infection and illness (clinical symptomatology), in accounting for an association of stress and clinical colds. Specifically, we determined whether the relation between stress and colds was attributable to increases in infection or to increases in diagnosed colds among infected persons.

Logistic regression was used to predict these dichotomous outcomes (Hosmer & Lemeshow, 1989). We used a regression procedure that provides estimated regression coefficients for each independent variable adjusted for all other variables in the equation. Probability values are based on the change in log-likelihood that would result if each variable were entered as the last variable in a stepwise regression. This is analogous to testing whether a variable accounts for a significant increment in explained variance in a linear regression model.

We report a sequential series of analyses. In the first analysis, only the psychological stress measure was entered as a predictor. In the second, we entered the standard control variables along with the stress measure and tested whether there was a significant change in log-likelihood when the stress index was added to the equation. Education, weight, season, and number of apartment mates were entered as continuous variables and the remainder of the standard controls as dummy (categorical) variables (Hosmer & Lemeshow, 1989).

Additional analyses tested possible roles of health practices and personality variables in the relation between stress and clinical colds. In all cases, we added these variables to a regression equation that included standard controls, and we report the adjusted coefficient and the probability value based on the change in log-likelihood when the stress measure is added to the equation. These analyses are extremely conservative, testing the significance of the stress measures after adding as many as 16 control variables.

Repeated measures analysis of covariance was used in supplementary analyses of continuous outcomes: postchallenge mucus weights and body temperature. In each case, prechallenge scores and standard control variables were used as covariates.

Results

Stress and Susceptibility to Clinical Illness

Figure 1 presents separate rates of clinical colds for those above and below the median of each stress measure. Rates for the psychological stress index are also presented for comparison (Cohen et al., 1991). As apparent from the figure, highly stressed persons have higher rates of colds irrespective of the stress scale, although this difference is statistically reliable only with the psychological stress index and stressful life events. Both the index and life events predicted colds when they were the only predictor in the equation ($b = .10$, $p < .02$ for the index; $b = .74$, $p < .04$ for continuous life events variable; and $b = .51$, $p < .02$ for dichotomous life events), as well as when the 10 control variables were entered into the equation ($b = .10$, $p < .04$

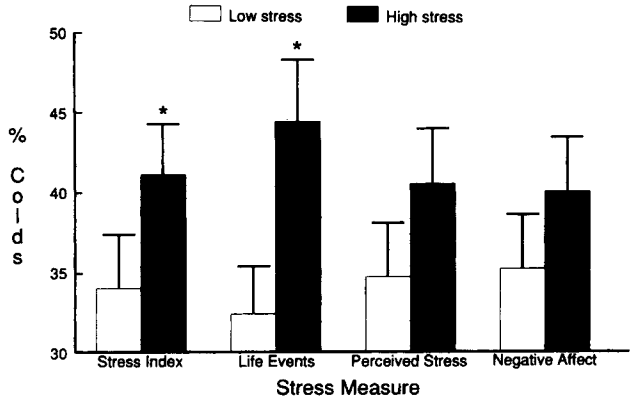

Figure 1. Observed associations between each of the stress measures and rates of clinical colds for the entire sample (N = 394). (Standard errors are indicated by vertical lines. *$p < .05$.)

for the index; $b = .75$, $p = .06$ for continuous and $b = .46$, $p < .05$ for dichotomous life events).

To determine whether any of the effects reported above 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 of any of the equations described earlier ($b = .12$, $p < .02$ for the index; $b = .73$, $p = .08$ for continuous and $b = .46$, $p = .06$ for dichotomous life events).

In the analyses presented so far, each of the stress measures was evaluated in separate equations. However, the data suggest the possibility that the effects of life events were independent of the effects of the other two measures. Because of the high correlation of perceived stress and negative affect, all three stress measures could not be entered into the same equation. Instead, we fit two models to the clinical cold data. In the first we entered life events, perceived stress, and their residualized interaction and in the second we entered life events, negative affect, and their residualized interaction. Life events was the only reliable predictor even approaching significance in any of the equations. For the equation with perceived stress, $b = .68$ and $p = .08$ when the continuous variable was used, and $b = .47$ and $p < .04$ when the dichotomous variable was used. For the equation with negative affect, $b = .74$ and $p = .05$ when the continuous variable was used, and $b = .50$ and $p < .03$ when the dichotomous variable was used. The reliable effect of life events in these models indicates that the component of stressful life events that predicts clinical illness is independent of what is measured by the two remaining scales. The lack of reliable interactions also suggests that the influence of life events is independent of the level of either perceived stress or negative affect.

In our previous article, we found that being housed with another person who became infected (and thus infectious) partly obscured the effects of stress on colds. This occurred because persons with infectious roommates may be reexposed to the virus after viral challenge. This was in contrast to persons without infectious roommates who received a single dose-controlled exposure. Hence, we ran a set of additional regression equations predicting clinical colds including only the 91 subjects without infectious roommates (28 of these people had no roommates). Although these analyses resulted in a substantial loss of statistical power, they provided some information on how the separate scales fare when a major source of noise is eliminated from the analyses. Each equation included the standard control variables and the five health practices. As in the analyses including all subjects, clinical illness rates were higher for those with higher levels of stress as assessed by all of the measures (see Figure 2). These relations were statistically reliable in the cases of the stress index ($b = .32$, $p < .02$), perceived stress ($b = .14$, $p < .02$), and negative affect ($b = .09$, $p < .03$), but marginally reliable at best in the case of life events ($b = .58$, *ns* for the continuous variable; $b = 1.12$, $p = .08$ for the dichotomous variable).

Stress and Infection

Recall that to be infected means that the challenge virus replicates within the body. This is detected directly in culture (viral isolation) or indirectly through establishing significant increases in viral-specific antibody. A person can be infected without developing clinical illness. The following analyses include all subjects and assess whether the reported relations between the various stress measures and clinical colds are partly or wholly attributable to an association between these scales and increased infection.

Table 1 presents rates of infection for those below and above the median for each of the three stress measures as well as the stress index. As apparent from the table, while infection rates are higher for those above the median on all four measures, these differences are reliable for the stress index ($b = .15$, $p < .01$; $b = .17$, $p < .01$ with standard controls; $b = .18$, $p < .01$ with health practices), perceived stress ($b = .05$, $p < .03$; $b = .04$, $p = .05$ with standard controls; $b = .05$, $p = .06$ with health practices), and negative affect ($b = .04$, $p < .01$; $b = .05$, $p < .01$ with standard controls; $b = .06$, $p < .01$ with health practices), but not for either continuous or dichotomous life events.

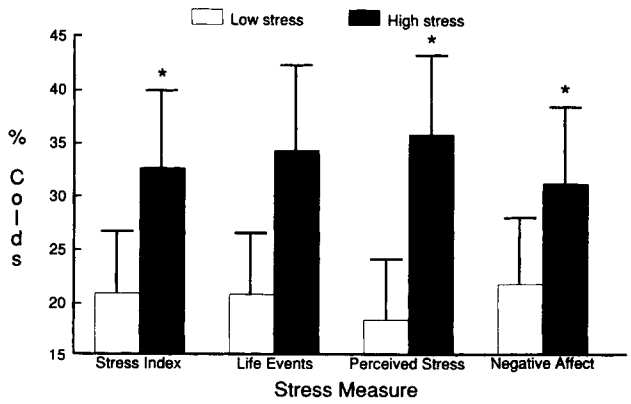

Figure 2. Observed associations between each of the stress measures and rates of clinical colds for the sample without infectious roommates (n = 91). (Standard errors are indicated by vertical lines. *$p < .05$.)

Table 1
Observed Percentage of Infection and Clinical Colds Among Infected Subjects by Scores on the Stress Index and by Scores on the Three Individual Measures of Stress for the Entire Sample and for the Subsample Without Infectious Roommates

Score	Entire sample		Sample without infectious roommates	
	% infected (n = 394)	% colds among infected subjects (n = 325)	% infected (n = 91)	% colds among infected subjects (n = 68)
Stress index				
Low	78.7	43.2	72.9	28.6
High	86.3**	47.7	76.7*	42.4
No. of stressful life events				
Low	80.9	40.1	73.6	28.2
High	84.6	52.5**	76.3	44.8
Perceived stress scale				
Low	78.4	44.2	69.4	26.5
High	86.7**	46.8	81.0**	44.1
Negative affect				
Low	76.9	45.8	67.4	32.3
High	88.2**	45.4	82.2**	37.8

* $p < .10$ in model without controls. ** $p < .05$ in model without controls.

Are the relations between perceived stress and infection and negative affect and infection independent of life events? When life events is entered into an equation with perceived stress and their residualized interaction, only the relation between perceived stress and infection approaches significance ($b = .04$, $p = .06$ for continuous variable; $b = .05$, $p < .05$ for the dichotomous variable). Similarly, when entered into a regression with negative affect and their residualized interaction, only negative affect is reliable ($b = .04$, $p < .02$ for the continuous variable; $b = .04$, $p < .02$ for the dichotomous variable). This suggests that the components of perceived stress and negative affect that predict clinical illness are mostly independent of what is measured by the life events scale.

Results from analyses of the 91-subject subsample were similar to those found in the entire sample. In a regression equation including standard controls and health practices, both perceived stress ($b = .16$, $p < .02$) and negative affect ($b = .13$, $p < .01$) were associated with infection. The stress index was marginally related ($b = .27$, $p = .07$). Life events (both continuous and dichotomous) were not.

Stress and Clinical Symptomatology Among Infected Persons

To be defined as clinically ill, persons must exhibit both infection and clinical symptoms. The following analyses were designed to assess 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) after infection. Because these analyses included only persons who were infected, the results are independent of earlier analyses predicting infection.

Table 1 presents rates of clinical colds among infected persons for those above and below the median on each stress measure as well as the stress index. As apparent from the table, only life events approached reliable prediction of colds among infected persons (for continuous variable, $b = .68$, $p = .08$; $b = .62$, $p = .16$ with standard controls; $b = .58$, $p = .21$ with standard controls and health practices; for dichotomous variable $b = .50$, $p < .03$; $b = .44$, $p = .08$ with standard controls; $b = .46$, $p = .08$ with standard controls and health practices).

Was the relation between life events and colds among infected persons independent of perceived stress and negative affect? Stressful life events still predicted clinical illness in both equations including perceived stress and their interaction ($b = .74$, $p = .08$ for continuous variable; $b = .51$, $p < .04$ for dichotomous variable) and equations including negative affect and their interaction ($b = .82$, $p = .06$ for continuous variable; $b = .56$, $p < .02$ dichotomous variable). This suggests that the component of stressful life events that predicts clinical illness among infected persons is independent of what is measured by the two remaining scales.

In the analyses presented so far, the diagnosis of illness was based on clinical judgment. Additional analyses investigated the associations of life events with two purely objective measures of disease manifestation: mucus weight and average body temperature. Only persons defined as infected were included. These analyses were repeated measure analyses of covariance. The covariate in the mucus weight analysis was the mucus weight on the day before viral challenge and in the temperature analysis, the temperature on the day before viral challenge. The repeated measure was the dependent variable at each of 5 days following challenge. Although life events were not associated with changes in mucus weights after challenge, those with high numbers of life events had greater increases in temperature after challenge than those with low numbers of events, $F(1, 319) = 6.37$, $p < .02$. Average daily postchallenge temperatures adjusted for prechallenge temperatures are depicted in Figure 3. There was no relation between stressful life events and prechallenge temperatures (36.41 °C for two or fewer events and

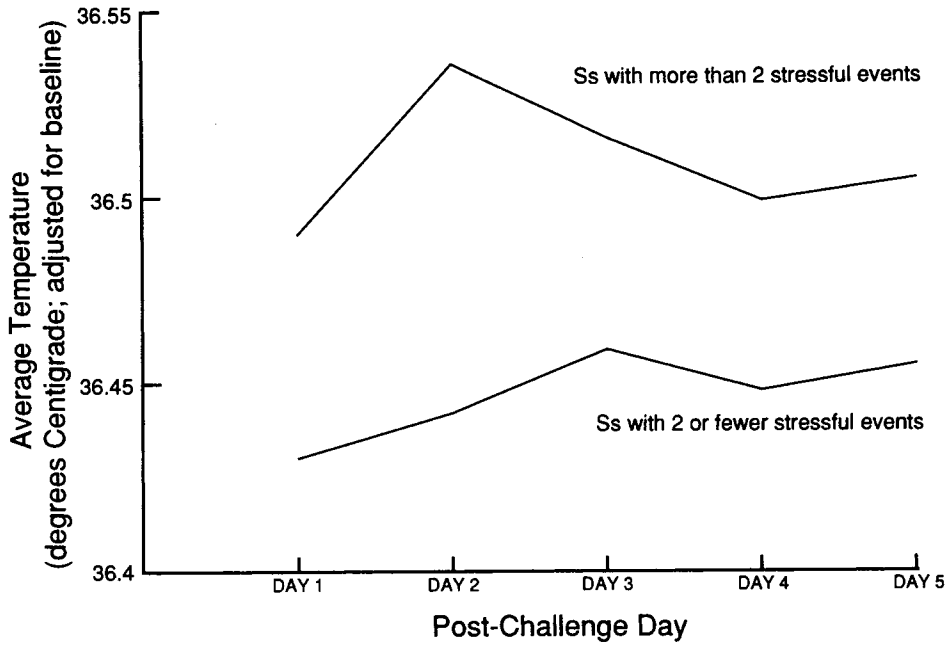

Figure 3. Average postchallenge daily temperature (degrees centigrade, adjusted for baseline) for infected subjects (n = 325) with two or fewer stressful events and subjects with more than two stressful events.

36.48 °C for more than two). An analysis adding the 10 standard control variables as covariates produced similar results, $F(1, 306) = 5.40$, $p < .03$. The interaction between life events and time (repeated measures) did not approach reliability in either analysis. In sum, the relation between life events and clinical diagnosis among infected persons was associated with a biological marker of disease and hence not attributable to stress-elicited biases in symptom presentation.

Analyses of the 91-subject subsample (actually only the 68 who were infected) did not indicate reliable effects of any of the measures on clinical illness for infected persons. This is probably attributable to the substantial loss of power. Although not statistically reliable, the rates of colds among infected people were higher for stressed persons no matter which of the stress scales was used (see Table 1).

Personality or Stress?

In a regression equation predicting colds and including only the three personality measures as predictors, there was a marginal ($b = -.01$, $p = .12$) relation between decreased self-esteem and increased colds. However, this association does not exist when the relation is adjusted for the 10 standard control variables ($p = .42$). There is no association between either personal control or introversion–extraversion and colds in either equation.

In our earlier article, we demonstrated that the association between the psychological stress index and clinical colds was independent of the three personality measures. Because there was some indication that self-esteem might play a role in susceptibility in the disaggregated analyses, we conducted analyses adding self-esteem to the regression equations including the standard controls and health practices to determine whether it could account for any of the relations between stress and illness reported earlier. The regression analyses suggested that the associations between life events and colds ($b = .66$, $p = .12$ for continuous; $b = .47$, $p = .06$ for dichotomous) and negative affect and infection ($b = .05$, $p < .03$) are not substantially affected when the possible effects of self-esteem are removed. However, the relation between perceived stress and infection is substantially reduced ($b = .03$, $p = .31$).

Discussion

There is substantial evidence for similarities among the three stress measures used in this study. The factor analysis and correlations between scales provide support for an underlying common component. The three scales are also similar in that increases in each scale are associated with increases in clinical illness. When the entire sample was included, only stressful life events were reliably associated with increased susceptibility to colds, although similar patterns were found for perceived stress and negative affect. When only those persons without an infectious roommate were studied, both perceived stress and negative affect predicted clinical illness, whereas the association between life events and illness was marginally reliable. 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 slight variations in statistical reliability of the association between each of the scales and colds across analyses is probably attributable to insufficient power. A slightly larger sample (and subsample without the pos-

sibility of person-to-person transmission) would result in a more consistent picture.

As interesting as their similarities, however, are the differences between these scales. Negative life events were associated with greater rates of clinical 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 (a) the negative life events instrument measures something different than perceived stress and negative affect scales and (b) the constructs they tap have somewhat different consequences for the pathogenesis of infectious illness.

Before addressing the possible differences in what the scales measure, it is important to interpret what it means to find elevated rates of infection as opposed to elevated rates of illness among infected persons. Infection reflects whether the virus replicates or replicates enough to be detected. Differences in infection rates may be attributable to associations between stress and the ability of mucosal tissues to block the virus from entering the system (e.g., mucus quality or quantity) or the function of the cilia on the surface of the nasal epithelium that transport the mucus. They may also be attributable to the stress-elicited changes in either secretory or systemic immune processes. This includes the production of secretory IgA and fast-acting systemic immune responses such as the functional ability of natural killer cells that destroy viral-infected cells. It is less clear what drives the production of symptoms among persons who are infected. One possibility is that the mechanism is the same as in the case of infection. That is, clinical illness may merely reflect the extent of viral replication, with symptoms appearing when a threshold number of cells are virally infected. Alternatively, infection and illness may be attributable to very different processes. For example, infection may be attributable to viral replication and illness to an inflammatory immune response to infection: the release of chemicals such as histamines, bradykinins, and prostaglandins that cause symptoms.

Because subjects present their symptoms to physicians, it is also possible that the association between life events and increased illness was due to stress-elicited changes in symptom presentation instead of underlying pathology (see Cohen & Williamson, 1991). However, our analysis of body temperature, a measure of disease manifestation not subject to self-presentation, indicates that persons with greater than two life events had larger illness-induced increases in temperature than those with two or fewer events. Hence the relation between life events and increased illness among infected persons is apparently attributable to pathological change.

What are the differences between the three stress scales that could account for differential relations with infection and symptom development? One possibility is that the perceived stress and negative affect scales are picking up quite a bit of dispositional affect (cf. Costa & McCrae, 1985; Watson & Pennebaker, 1989), whereas the life events scale is primarily assessing a more acute affective response to stressful events. This interpretation suggests that it is affective change (as assessed by life events) that drives symptom development among infected persons and dispositional affect that drives greater susceptibility to infection. Alternatively, it is possible that the perceived stress and negative affect scales are primarily tapping into stress-elicited affect, whereas the life event scale reflects a dispositional style that results in the occurrence of or reporting of stressful life events. We investigated the possibility that three dispositional characteristics, self-esteem, personal control, and introversion–extraversion, might account for the different relations between the various stress scales and disease pathogenesis, but the result did not indicate a pattern that would provide such an explanation. Controlling for these personality measures had little effect on either the associations between life events and colds or negative affect and infection, although they did substantially decrease the association of perceived stress and infection.

The interpretations of our data discussed so far implicate affect as the primary mediator of the relation between stress and illness. Alternatively, it is possible to argue that, at least in the case of life events, affect may not be directly involved. Psychological stress theory assumes that objective events influence disease outcomes through the negative cognitive and affective responses they elicit (Lazarus & Folkman, 1984). In our study, life events predicted illness even when the possible effects of perceived stress and negative affect were controlled for. This occurred even though we assessed only negative-impact events. Moreover, the relation between life events and illness could not be accounted for by differences between low- and high-stressed persons in health practices such as smoking, drinking alcohol, diet, and sleeping. It, of course, is possible that we failed to identify perceived stress, negative affect, or health practices as mediators because we did not measure these constructs appropriately or with sufficient sensitivity. This view isn't terribly persuasive given that negative affect, perceived stress, smoking, and drinking alcohol (see Cohen, Tyrrell, Russell, Jarvis, & Smith, 1992, for health practice data) all predict clinical illness. It is also possible, however, that stressful life events alter other cognitions or behaviors that make infected persons more likely to develop clinical illness. For example, actively and effortfully coping with stressful events may modulate the sympathetic nervous system (e.g., Manuck, Harvey, Lechleiter, & Neal, 1978), consequently suppressing immune response.

Unfortunately, the life events measure in this study was not designed to allow a clean determination of event occurrence outside of respondents' evaluative biases. Future work examining the role of events in infectious susceptibility would benefit from the more elaborate and precise interview measures of life events such as the Life Events and Difficulties Schedule (Brown & Harris, 1978, 1989). Although time consuming and expensive to collect and code, the interview procedure provides a number of advantages over checklists, including strict criteria for whether an event occurs, classification of events on the basis of objectively judged severity of threat and emotional significance, and distinction between events and ongoing difficulties.

The psychological stress index provides a consistent relation with clinical colds and infection, but shows no association in any of the analyses with illness among infected subjects. As reported in our earlier article, this relation is unaffected by the standard controls, by additional controls for health practices, or by personality characteristics. The index is somewhat more strongly related to perceived stress and negative affect than to

negative life events. It may, as a result, merely represent a more reliable measure of the components of stress assessed by these scales.

The differences between the predictive ability of the three psychological stress scales and the stress index are provocative and suggest that life event instruments, even those designed specifically to assess negative impact events, assess an independent and predictive component of psychological stress. It is interesting that a recently completed study (Stone et al., in press) examining the development of symptoms among infected persons also found that those with more life events were more likely to develop clinical colds, although perceived stress and negative affect were unrelated to illness. Their failure to find associations of perceived stress and negative affect with illness are actually consistent with our work as well. This is because their design included only infected persons and hence they could not assess susceptibility to infection where we found relations with these two scales. We hope that future research will identify the components of psychological stress that are responsible for differential effects on pathology. However, a more 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.

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Received January 23, 1992
Revision received June 30, 1992
Accepted July 13, 1992 ■