# PSYCHOLOGICAL STRESS AND SUSCEPTIBILITY TO THE COMMON COLD

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**Abstract** *Background.* It is not known whether psychological stress suppresses host resistance to infection. To investigate this issue, we prospectively studied the relation between psychological stress and the frequency of documented clinical colds among subjects intentionally exposed to respiratory viruses.

*Methods.* After completing questionnaires assessing degrees of psychological stress, 394 healthy subjects were given nasal drops containing one of five respiratory viruses (rhinovirus type 2, 9, or 14, respiratory syncytial virus, or coronavirus type 229E), and an additional 26 were given saline nasal drops. The subjects were then quarantined and monitored for the development of evidence of infection and symptoms. Clinical colds were defined as clinical symptoms in the presence of an infection verified by the isolation of virus or by an increase in the virus-specific antibody titer.

*Results.* The rates of both respiratory infection (P<0.005) and clinical colds (P<0.02) increased in a dose–response manner with increases in the degree of psychological stress. Infection rates ranged from approximately 74 percent to approximately 90 percent, according to levels of psychological stress, and the incidence of clinical colds ranged from approximately 27 percent to 47 percent. These effects were not altered when we controlled for age, sex, education, allergic status, weight, the season, the number of subjects housed together, the infectious status of subjects sharing the same housing, and virus-specific antibody status at base line (before challenge). Moreover, the associations observed were similar for all five challenge viruses. Several potential stress–illness mediators, including smoking, alcohol consumption, exercise, diet, quality of sleep, white-cell counts, and total immunoglobulin levels, did not explain the association between stress and illness. Similarly, controls for personality variables (self-esteem, personal control, and introversion–extraversion) failed to alter our findings.

*Conclusions.* Psychological stress was associated in a dose–response manner with an increased risk of acute infectious respiratory illness, and this risk was attributable to increased rates of infection rather than to an increased frequency of symptoms after infection. (N Engl J Med 1991; 325:606-12.)

STRESSFUL life events are commonly believed to suppress host resistance to infection. When demands imposed by events exceed a person's ability to cope, a psychological stress response composed of negative cognitive and emotional states is elicited.[1] Psychological stress, in turn, is thought to influence immune function through autonomic nerves innervating lymphoid tissue[2,3] or hormone-mediated alteration of immune cells.[4,5] Stress may also alter immune responses through the adoption of coping behaviors such as increased smoking and alcohol consumption.[6]

There is substantial evidence that stressful life events and perceived stress are associated with changes in immune function.[7-9] Although psychological stress is often described as suppressing immune response, the implications of stress-induced immune changes for susceptibility to disease have not been elucidated.[10,11]

There is some direct evidence from previous studies that psychological stress increases the risk of verified acute infectious respiratory illness.[12-14] These studies, however, did not control for the possible effects of stressful events on exposure to infectious agents (as opposed to their effects on resistance) or provide evidence about other behavioral and biologic mechanisms through which stress might influence a person's susceptibility to infection. Moreover, the literature on this topic is not entirely consistent; several studies have failed to find a relation between stress and respiratory disease.[15,16]

We present data from a prospective study of the association between psychological stress and susceptibility to the common cold. Healthy persons were assessed for degree of stress and then experimentally exposed to one of five cold viruses (394 subjects) or placebo (26 subjects). The association between stress and the development of biologically verified clinical disease was examined with use of control for base-line (prechallenge) serologic status, 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. In further analyses we tested the possibility that a relation between stress and susceptibility to illness could be attributed to differences in health practices or differences in base-line white-cell counts or total antibody levels. A final analysis investigated the possibility that differences in personality rather than environmental factors causing stress might account for the association between stress and clinical colds.

## METHODS

The subjects were 154 men and 266 women who were residents of Britain and who volunteered to participate in trials at the Medical Research Council's Common Cold Unit (CCU) in Salisbury. All reported on their applications that they had no chronic or acute illness and were taking no regular medication; all were judged to be in good health after clinical and laboratory examination on their arrival at the unit. Pregnant women were excluded. The subjects' ages ranged from 18 to 54 years (mean [±SD], 33.6±10.6). Sixty-three percent of the subjects were women. Twenty-two percent had not completed their secondary education, 51 percent had completed secondary school but did not attend a university, and 27 percent

had spent at least one year at a university. The subjects were reimbursed for their travel expenses and received free meals and accommodations during the study. The trial was approved by the Harrow District Ethical Committee, and informed consent was obtained from each subject after the nature and possible consequences of the study were fully explained.

## Procedures

During their first two days at the CCU, the subjects underwent a thorough medical examination, completed a series of questionnaires related to behavior, psychological stress, personality, and health practices and had blood drawn for immune assessments and measurement of cotinine (a biochemical indicator of smoking) in serum. Subsequently, the subjects were given nasal drops containing a low infectious dose of one of five respiratory viruses — rhinovirus type 2 ($n = 86$), type 9 ($n = 122$), or type 14 ($n = 92$), respiratory syncytial virus ($n = 40$), or coronavirus type 229E ($n = 54$) — or saline drops ($n = 26$). The viral doses were intended to resemble those common in person-to-person transmission and to result in illness rates between 20 and 60 percent. For two days before and seven days after the viral challenge, the subjects were quarantined in large apartments (alone or with one or two others). Starting two days before the viral challenge and continuing through six days after the challenge, each subject was examined daily by a clinician who used a standard checklist of respiratory signs and symptoms.[17] Examples of items on the checklist are sneezing, watering of the eyes, nasal stuffiness, nasal obstruction, postnasal discharge, sinus pain, sore throat, hoarseness, cough, and sputum. The number of facial tissues used daily by each subject was also counted. Approximately 28 days after the challenge, a second serum sample was collected by the subjects' own physicians and shipped to the CCU for serologic testing. All the investigators were blinded to the subjects' psychological status and to whether they had received virus or saline drops.

## Psychological-Stress Index

Three measures of psychological stress were used: the number of major stressful life events judged by the subject as having had a negative impact on his or her psychological state in the past year, the degree to which the subject perceived that current demands exceeded his or her ability to cope, and an index of current negative affect. The list of major stressful life events contained events that might have occurred in the life of the subject (41 items) or those of others close to the subject (26 items). The events were taken from the List of Recent Experiences compiled by Henderson et al.[18] and were chosen because of their potential negative impact and their relatively high frequency in population studies. The score on this life-events scale was the number of events during the previous 12 months that the subject reported as having had a negative impact on his or her life. The 10-item Perceived Stress Scale[19] was used to assess the degree to which situations in life were perceived as stressful (reliability, $\alpha = 0.85$).[20] Items on the Perceived Stress Scale were designed to measure the degree to which the subjects felt their lives were unpredictable, uncontrollable, and overwhelming. Finally, the negative-affect scale included 15 items from Zevon and Tellegen's list of negative emotions[21]: "distressed," "nervous," "sad," "angry," "dissatisfied with self," "calm" (scored negatively), "guilty," "scared," "angry at yourself," "upset," "irritated," "depressed," "hostile," "shaky," and "content" (scored negatively). Each subject was asked to indicate the intensity of each feeling during the past week on a five-point scale ranging from 0 to 4 (reliability, $\alpha = 0.84$).

All three stress scales formed a single principal component with loadings of 0.66, 0.86, and 0.86, providing evidence that the scales measured a common underlying concept.[22] An index combining the three measures was therefore used as an indicator of the degree of psychological stress experienced by the subjects (stress index). Because life events were not distributed normally, an index based on normalized scores was not appropriate. Instead, the index was created by calculating the quartiles for each scale and summing the quartile ranks for each subject (assigning a value of 1 for the lowest quartile and 4 for the highest); the resulting stress index ranged from 3 to 12. The quartiles divided the subjects into groups with the values 0, 1 through 2, 3 through 4, and

5 through 14 for the life-events scale; 0 through 10, 11 through 14, 15 through 18, and 19 through 33 for the Perceived Stress Scale; and 0 through 7, 8 through 13, 14 through 20, and 21 through 49 for the negative-affect scale. The index scores were approximately normally distributed. In all cases, a higher score indicated a greater degree of stress.

## Viral Isolates and Virus-Specific Antibody Levels

Nasal-wash samples were collected for viral isolation before inoculation and on days 2 through 6 after inoculation. They were mixed with broth and stored in aliquots at $-70°C$. Rhinoviruses were detected in O-HeLa cells, respiratory syncytial virus in HEp-2 cells, and coronavirus in the C-16 strain of continuous human fibroblast cells. When a characteristic cytopathic effect was observed in the tissue culture, fluids were transferred to further cultures and tests were performed to identify the virus. The identity of rhinoviruses and coronaviruses was confirmed by neutralization tests with specific rabbit immune serum, and that of respiratory syncytial virus by immunofluorescent staining of culture cells.

Levels of neutralizing antibodies and of specific antiviral IgA and IgG were determined before and 28 days after the challenge. Neutralizing antibodies (for rhinoviruses only) were determined by neutralizing tests with homologous virus.[23] The results were recorded as the highest dilution showing neutralization, and a fourfold increase was regarded as significant. Suitable neutralizing tests were not available for respiratory syncytial virus and coronavirus.

Specific IgA and IgG levels for rhinoviruses,[24] coronavirus,[25] and respiratory syncytial virus[25] were determined by enzyme-linked immunosorbent assay. This test detects antibody that correlates with neutralization titers, is associated with resistance to infection, and increases in response to infection.[23]

## Infections and Clinical Colds

A subject was deemed infected if virus was isolated after the challenge or if there was a significant increase over base-line levels in the virus-specific serum antibody titer (i.e., a fourfold increase in neutralizing antibody [rhinoviruses]) or an increase in the IgG or IgA level of more than 2 SD above the mean for the unchallenged subjects (all viruses). Eighty-two percent of the subjects who received virus (325 subjects) were infected. Five subjects who received saline (19 percent) were also infected. We attributed infections in the saline (placebo) group to transmission of virus from infected subjects to others housed in the same apartments. Control for person-to-person transmission was included in the data analysis.

At the end of the trial, a physician judged the severity of each subject's cold on a scale ranging from none (0) to severe (4). Ratings of mild cold (2) or more were considered positive clinical diagnoses. The subjects also rated the severity of their colds on the same scale. The clinical diagnosis was in agreement with the subject's rating in 94 percent of the cases. The subjects were classified as having clinical colds if they both had evidence of infection and were given the diagnosis of a clinical cold. Of the 394 subjects who received virus, 38 percent (148) had clinical colds. None of the 26 subjects who received saline had a cold.

Seven subjects with positive clinical diagnoses but no indication of infection were excluded from the sample because we assumed the illness was caused by exposure to another virus before the trial. Analyses including these seven subjects resulted in conclusions identical to those reported here.

## Standard Control Variables

We used a series of control variables that might provide alternative explanations for the relation between stress and illness. These include serologic status for the experimental virus before the challenge, age, sex, education, allergic status, weight, the season, the number of subjects housed together, whether a subject housed in the same apartment was infected, and the identity of the challenge virus.

Serologic status was defined as positive when a subject had a base-line neutralizing antibody titer above 2 for rhinoviruses and a base-line antibody level greater than the sample median for coronavirus or respiratory syncytial virus. Forty-three percent of the subjects were seropositive before the challenge: 55 percent for rhino-

virus type 2, 48 percent for rhinovirus type 9, 20 percent for rhinovirus type 14, 50 percent for respiratory syncytial virus, and 50 percent for coronavirus.

Because age was not normally distributed, it was scored categorically as above or below the median: 18 through 33 years or 34 through 54 years. Education levels were classified on an 8-point scale ranging from no schooling (0) to a doctoral degree (8), as reported by the subjects. Allergic status was determined on the basis of the subjects' answers to questions about allergies to food, drugs, or other allergens. Subjects who reported any allergy were defined as allergic. A ponderal index (the weight divided by the cube of the height) was used to control for subjects' weight. We used the number of hours of daylight on the first day of the trial as a continuous measure of the season. The number of daylight hours is correlated (r = 0.80, P<0.001) with the average temperature on the same day. Control for the possibility that person-to-person transmission rather than viral challenge might be responsible for infections or clinical colds was also included. Because person-to-person transmission would have been possible only if a subject sharing the same housing had been infected by the viral challenge, a control variable indicated whether or not any subject sharing the same housing was infected. Finally, the challenge virus was a categorical variable indicating the experimental virus to which a subject was exposed.

### Measures of Health Practice

Health practices — including smoking, alcohol consumption, exercise, quality of sleep, and dietary practices — were assessed as possible factors linking stress and susceptibility. Cotinine measured in serum by gas chromatography was used as a biochemical indicator of the smoking level because it provided an objective measure of nicotine intake that was not subject to reporting bias.[26,27] We used the base-10 logarithm of the average of the two cotinine measures (before and 28 days after challenge) as an indicator of the level of smoking. (The correlation between the two measures was 0.95 [P<0.001, n = 348].) The correlation between $log_{10}$ average cotinine level and the $log_{10}$ number of cigarettes reported as smoked per day was 0.96 (P<0.001, n = 372).

The remaining health practices were assessed by questionnaire before the viral challenge. The average number of alcoholic drinks per day was calculated on the basis of separate estimates of weekday and weekend drinking. A half-pint, bottle, or can of beer, a glass of wine, and a shot of whiskey contain approximately equal amounts of alcohol, and each was treated as a single drink. The exercise index included items on the frequency of walking, running, jogging, swimming, aerobic exercise, 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 healthful diet and included the frequency of eating breakfast, fruits, and vegetables.

### White-Cell Counts and Total Immunoglobulin Levels

White-cell counts and total immunoglobulin levels were assessed as possible factors linking psychological stress and susceptibility to illness. Assays were performed in blood samples collected before the viral challenge. White cells were counted with an automatic cell counter, and differential counts (lymphocytes, monocytes, and neutrophils) were calculated from 200 cells in a stained film. Total serum and nasal-wash IgA and IgE levels and total nasal-wash protein levels were assessed by enzyme-linked immunosorbent assay.[25] We used the base-10 logarithm of each differential count and immunoglobulin measurement.

### Measures of Personality

Because the degree of psychological stress might reflect stable personality styles rather than responses to environmental factors causing stress, two personality characteristics closely associated with stress — self-esteem and personal control (the expectation that one can control events) — were assessed before the viral challenge. Self-esteem was measured with the self-regard and social-confidence subscales of the Feelings of Inadequacy Scale[28] (reliability,

$\alpha = 0.89$) and personal control with the personal-efficacy and interpersonal-control subscales of the Spheres of Control Scale[29] (reliability, $\alpha = 0.76$). A third personality characteristic, the degree of relative introversion or extraversion, was also assessed because some evidence had suggested that introverts were at higher risk for infection.[30,31] This characteristic was assessed with the Eysenck Personality Inventory[32] (reliability, $\alpha = 0.80$).

### Statistical Analysis

The primary analysis tested whether psychological stress was associated with a higher incidence of clinical colds. Secondary analyses assessed the importance of the two components of the definition of a clinical cold, documented infection and symptoms, in accounting for the association between stress and clinical colds. Specifically, we determined whether the relation between stress and colds was attributable to an increase in infection or to an increase in diagnosed colds among infected persons. The subjects who received saline were not included in these analyses.

Logistic regression was used to predict categorical outcomes.[33] We conducted a series of analyses. In the first stage, only the psychological-stress index was entered as a predictor. In the second, we entered the standard control variables in the initial step of the regression analysis and then tested whether there was a significant change in the log likelihood of a clinical cold when the stress index was added to the equation. Education, weight, the season, and the number of subjects sharing an apartment were entered as continuous variables, and the remainder of the standard controls as dummy (categorical) variables.[33] Because the predictor (the stress-index score) was a continuous variable, we have reported raw regression coefficients (b) and their standard errors.[33] To estimate the sizes of effects, we have also reported odds ratios and their 95 percent confidence intervals, derived from modified regression models in which the continuous stress-index score was replaced with a contrast between the subjects in the bottom and the top quartiles of the stress index. The odds ratio approximates how much more likely it was that the outcome (infection or clinical cold) would be present among those with the highest stress-index scores (top quartile group) than among those with the lowest scores (bottom quartile group).[33]

Additional analyses tested possible roles for immunity, health practices, and personality variables in mediating the relation between stress and clinical colds. In the first analysis, the possibility that white-cell counts, total antibody levels, or five different health practices operated as pathways through which psychological stress influenced the risk of having a clinical cold was assessed by entering these variables along with the standard control variables in the first step of the regression equation and then testing whether adding stress to the equation accounted for a significant change in the log likelihood of illness. In the second analysis, the possibility that the effects of stress might reflect differences in personality rather than reactions to environmental stress factors was assessed by adding first two personality variables associated with stress (self-esteem and personal control) and then another previously associated with susceptibility to infection (introversion–extraversion) to the set of control variables and testing for any additional contribution of stress. All the immune measures, health practices, and personality variables were entered as continuous variables.

## RESULTS

Preliminary analysis indicated that there were no statistically reliable interactions between the standard control variables and the stress index in predicting clinical colds (highest t = 1.62, P = 0.11).[33] The relations we report between the stress index and colds were thus similar for the five viruses and for groups defined by serologic status, age, sex, allergic status, education, weight, the number of subjects sharing an apartment, whether another subject in the same housing was infected, and the season.

There were, however, main effects of three standard

control variables — serologic status (P<0.001), the virus (P<0.001), and whether another subject in the same apartment was infected (P<0.02). The P value for the remaining variables was >0.20. Subjects who were seronegative at base line had more colds (49.3 percent) than those who were seropositive (22.2 percent). The incidence of colds was 61.1 percent for coronavirus, 42.4 percent for rhinovirus type 14, 37.5 percent for respiratory syncytial virus, 33.6 percent for rhinovirus type 9, and 23.3 percent for rhinovirus type 2. Finally, subjects sharing an apartment with an infected subject had more colds (40.9 percent) than those without an infected apartment mate (26.4 percent). Although they were associated with the development of clinical colds, none of these three variables was reliably associated with the stress index (highest F = 1.44, P<0.22).

As is apparent in Figure 1, the rate of clinical colds increased in a dose–response manner with increases in the stress-index score (b [±SE] = 0.10±0.04, P<0.02, n = 394; odds ratio for the comparison of the highest and lowest quartile groups = 1.98 [95 percent confidence interval, 1.10 to 3.56]). Moreover, entering the standard control variables into the equation before the stress index (adjusted rates are shown in Fig. 1) did not alter this association (b = 0.10±0.05, P<0.04, n = 394; odds ratio = 2.16 [95 percent confidence interval, 1.11 to 4.23]).

As is apparent in Figure 2, the rates of infection also increased with increases in the stress index (b = 0.15±0.05, P<0.005, n = 394; odds ratio for the comparison of the highest and lowest quartile groups = 3.45 [95 percent confidence interval, 1.51 to 7.87]). This relation was similarly unaltered by the inclusion of standard control variables in the equation (b = 0.17±0.06, P<0.004; odds ratio = 5.81 [95 percent confidence interval, 2.12 to 15.91]). The level of stress was not, however, reliably associated with the rate of clinical colds among infected persons (b = 0.07±0.04, P = 0.13; including the control variables: b = 0.06±0.05, P = 0.24, n = 325). Hence, the relation between stress and colds was primarily attributable to an increased rate of infections among subjects with higher stress-index scores, rather than to an increase in clinical colds among infected persons with higher stress scores.

The similar effect of stress at the various levels of each standard control variable (i.e., the lack of interaction between stress and each control variable) has already been mentioned. Of special importance in interpreting this study is the fact that stress had the same effects in all the challenge-virus groups regardless of the infectious status of apartment mates or prechallenge serologic status. The consistent effect of stress among the five viruses is illustrated in Figures 3 and 4, which present the rates of colds and infection (adjusted for standard control variables) according to challenge virus for subjects below the median value of the stress index (low stress) and above the median (high stress). That the effects of stress were similar
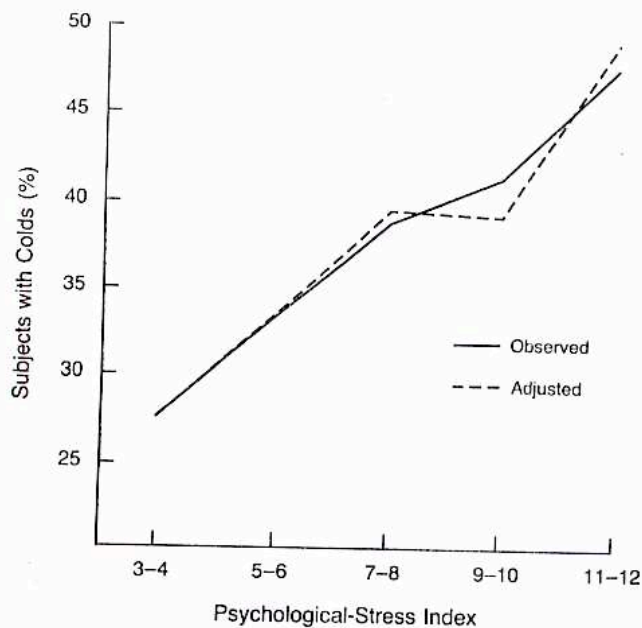


Figure 1. Observed Association between the Psychological-Stress Index and the Rate of Clinical Colds and the Association Adjusted for Standard Control Variables.

For an explanation of the psychological-stress index, see the text. Only the 394 subjects who received virus are included.

for all viruses suggests the biologic generality of the effect. Table 1 presents similar data for base-line serologic status and the infectious status of subjects sharing the same apartment. The data on subjects housed together indicate that greater person-to-person transmission among subjects with higher stress-index scores cannot explain the association between stress
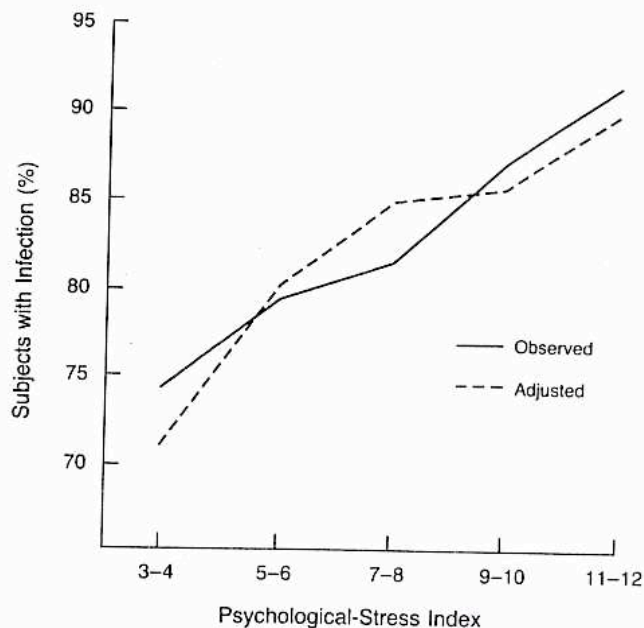


Figure 2. Observed Association between the Psychological-Stress Index and the Rate of Infection and the Association Adjusted for Standard Control Variables.

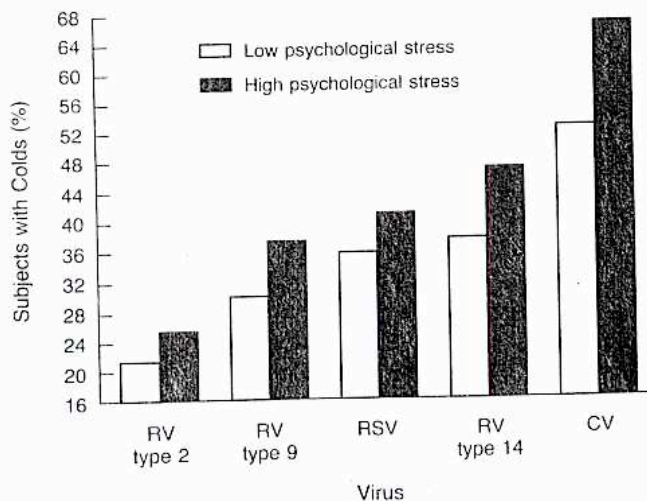Only the 394 subjects who received virus are included.

Figure 3. Subjects with Low Degrees of Psychological Stress (Index Values below the Median) and High Degrees of Stress (Values above the Median) Who Had Colds, According to Challenge-Virus Group.

The rates have been adjusted for the standard control variables. RV denotes rhinovirus, RSV respiratory syncytial virus, and CV coronavirus. Only the 394 subjects who received virus are included.

and colds (such transmission was possible only if the subject had an infected apartment mate). Finally, consistency among groups defined by prechallenge serologic status suggests that if an immune mechanism is the mediator of the relation between stress and colds, it is a primary and not a secondary (immune-memory) mechanism.

Additional analyses tested the possible roles of immunity, health practices, and personality variables in the relation between stress and clinical colds. In the
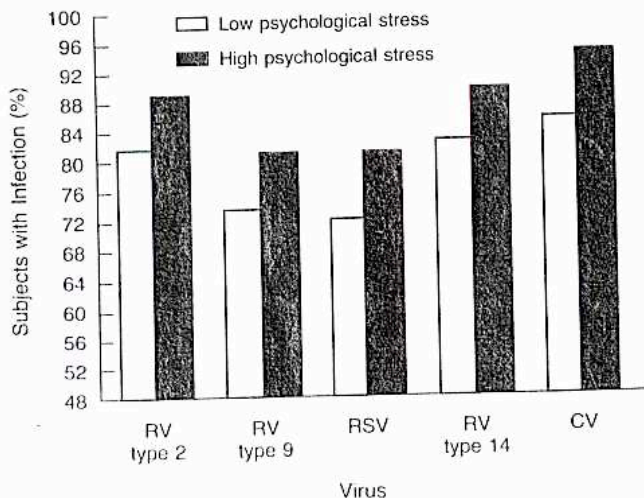


Figure 4. Subjects with Low Degrees of Psychological Stress (Index Values below the Median) and High Degrees of Stress (Values above the Median) Who Were Infected, According to Challenge-Virus Group.

The rates have been adjusted for the standard control variables. RV denotes rhinovirus, RSV respiratory syncytial virus, and CV coronavirus. Only the 394 subjects who received virus are included.

first analysis, we assessed the possibility that measures of white-cell populations (differentials), total immunoglobulin levels, or health practices operate as pathways through which psychological stress is related to clinical illness. These variables were entered together, along with the standard controls, in the first step of a regression equation, with the stress index entered in the second step. The stress index continued to add to the predictive power of the equation even after the additional controls were entered (b = 0.14±0.05, P<0.01). Hence, none of these variables were responsible for the association between stress and illness in this study.

In the second analysis, we assessed the possibility that effects of stress might actually reflect differences in personality rather than reactions to environmental stressors. Two personality variables associated with stress (self-esteem, r = −0.52, P<0.001; and sense of personal control, r = −0.25, P<0.001) and another previously associated with susceptibility to infection (introversion−extraversion, r with stress = −0.04,

Table 1. Rates of Infection and Colds among Subjects with High and Low Stress-Index Scores, According to Prechallenge Serologic Status and the Infectious Status of Apartment Mates.*

| | INFECTION | | COLDS | |
|---|---|---|---|---|
| | LOW STRESS INDEX | HIGH STRESS INDEX | LOW STRESS INDEX | HIGH STRESS INDEX |
| | incidence (%) | | | |
| Prechallenge serologic status | | | | |
| Positive (n = 171) | 67.2 | 79.8 | 18.7 | 25.5 |
| Negative (n = 223) | 86.2 | 92.4 | 43.7 | 55.2 |
| Infectious status | | | | |
| Not infectious (n = 91) | 68.7 | 81.4 | 20.8 | 32.6 |
| Infectious (n = 303) | 81.2 | 88.3 | 37.2 | 44.6 |

*Rates of infection and clinical colds have been adjusted for standard control variables. The categorization of low and high degrees of stress is based on whether the subjects' stress-index scores fell below or above the median value. The infectious status of subjects sharing the same housing is considered "infectious" if any person housed with the subject was infected.

P = 0.46) were added to the first step of the regression (with standard controls, health practices, and immune controls), and the stress index was entered in the second step. The stress index continued to produce a unique contribution to the explanation of colds (b = 0.13±0.06, P<0.04). Thus, none of the personality characteristics we studied could account for the relation between stress and illness.

DISCUSSION

Psychological stress was associated with an increased risk of acute infectious respiratory illness in a dose−response manner; this risk was attributable to increased rates of infection. Although there was some person-to-person transmission of virus in this study, the effect of stress on colds was independent of whether such transmission was possible (i.e., whether a subject shared housing with another infected subject). Moreover, the relation between stress and colds was similar for those with and without infected apartment mates. In short, the stress index was associated with host resistance and not with differential exposure to virus.

The relation between stress and colds also proved to be independent of a variety of health practices. If the increased risk of illness for subjects with higher stress-index scores was not due to associations between stress and exposure to virus or between stress and health practices, what accounts for this relation? Evidence from both human and animal studies indicates that stress modulates immunity.[7-9] Although the immune measures assessed in this study (prechallenge white-cell counts and antibody levels) did not explain the relation between stress and colds, these are quantitative measures; qualitative (functional) measures of immunity were not assessed. Because the effects of stress were the same for both subjects who were seropositive at base line and those who were seronegative, an explanation of the association between stress and illness would need to focus on primary rather than secondary immune responses. Some examples of primary immune functions that could have a role in this association are endothelial or lymphocyte production of interferon, mucus production, and natural-killer-cell activity.[34]

The association between stress and clinical illness was limited (adjusted odds ratio = 2.16), and the detection of the effect required a large sample. The relation between stress and infection, however, is stronger (adjusted odds ratio = 5.81). Moreover, the consistency of the stress–illness relation among three very different viruses — rhinovirus, coronavirus, and respiratory syncytial virus (as well as among rhinovirus types) — was impressive. This observation suggests that stress is associated with the suppression of a general resistance process in the host, leaving persons susceptible to multiple infectious agents, or that stress is associated with the suppression of many different immune processes, with similar results.

Although psychological stress is conceptualized here as a response to environmental events, our measures may also reflect personality characteristics that are independent of environmental factors. However, self-esteem and personal control, two personality characteristics strongly associated with stress, did not account for the effect of stress in this study. Another personality characteristic previously found to predict susceptibility to infection, introversion–extraversion, similarly did not account for the effect of stress. Because the psychological stress index assesses negative cognitive and emotional states rather than environmental stress factors, however, it is possible that it reflects other, individual traits not controlled for in the current study.

The results of research on stress as a risk factor in verified infectious disease have been inconsistent.[10] This inconsistency may be due to insensitive techniques for detecting a relatively small effect on clinical illness. Our data suggest that a relation between stress and susceptibility to illness may be best detected in studies that incorporate control for important demographic and biologic characteristics, reliable and broadly defined indexes of stress, controlled exposure to the infectious agent, and relatively large samples.
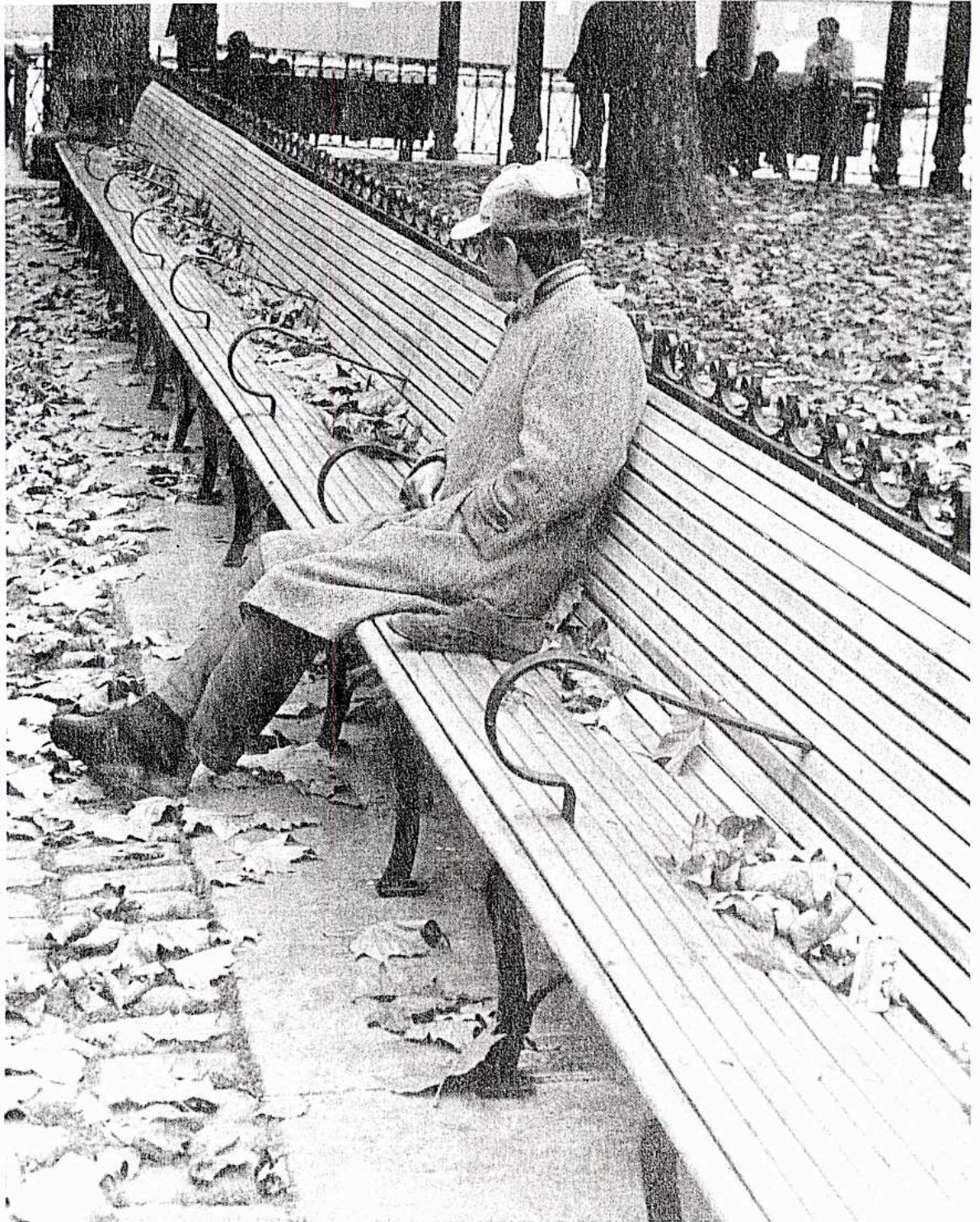
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